Targeting Cancer Cell Signaling Using Precision Oncology Towards a Holistic Approach to Cancer Therapeutics

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Abstract: Cancer is a complex and multifaceted disease having a number of composite problems to be considered including cancer immune evasion, therapy resistance, and recurrence for prevention and cure. Fundamentally it remains a genetic disease as diverse aspects of the complexity of tumor growth and cancer development relate to its genetic machinery and requires addressing the problems at the level of genome and epigenome. Presumably, the mutational changes occurring in the regulatory genes responsible for maintaining optimal cell growth, proliferation, and differentiation gradually lead to cancer progression and metastasis. Importantly, patients with the same cancer types respond differently to cancer therapies, indicating the need for a patient-specific treatment option for cancer cure. Precision oncology is the field of cancer research that focuses on the genetic profiling of individual tumors to identify targetable alterations involved in cancer development for custom-tailored personalized treatment of the disease. It is to rely upon the genomic study of cancer cells to get a clear picture of the prognosis and pathways involved in disease progression and to look for the means to selectively target them to ensure effective treatment of this deadly disease. Thus, precision oncology combines cancer diagnosis and prognosis followed by designing a treatment regimen for precise treatment of cancer at different stages and times. This article aims to briefly explain the foundations and frontiers of precision oncology in the context of technological advances being made in this direction to assess its scope and importance in the realization of a proper cure for cancer.

Key Words: Gene Mutation; Cancer Genomics; p53; K-Ras; C-Myc; Bcl-2, Cancer Stem Cells; Targeted Therapy; Immunotherapy, Precision Medicine

1. Introduction:

Cancer is a devastating disease causing one in six deaths globally with a huge physical, psychological, and economic impact on the people affected by the disease. It continues to be the second most common cause of hospital deaths after heart disease, most of which can be prevented by improving prevention and treatment strategies for cancer. It requires the efficient diagnosis of the disease, the development of efficacious treatment options, and a better understanding of the socioeconomic factors that affect cancer incidence, prevalence, and related deaths worldwide [1,2]. More than 100 cancer types with subtypes have been determined based on location, cell of origin, and genetic variations that influence cancer development and therapeutic response. Most cancers appear in epithelial cells as carcinomas, such as lung, skin, breast, liver, colon, prostate, and pancreas cancer, whereas sarcomas arise from mesenchymal tissues, originating in, myocytes, adipocytes, fibroblasts, and osteoblasts. Tumors can also develop in hematopoietic tissues such as leukemia and lymphoma and in the nervous tissues, e.g., gliomas, and neuroblastomas. They are among the most common cancer types taking a high toll in terms of lives and property all over the world [3,4]. Considering the vast number of cancer incidences, a formal initiative towards fighting the menace of cancer was called for, on the part of government systems across the globe which first appeared in the United States as the National Cancer Act of 1971 signed by President Richard Nixon aimed at promoting cancer research and application of the outcomes for minimizing cancer incidences and mortality rates associated with

the disease. The act was euphemistically described as the "War on Cancer", and the year 2021 marked the 50th anniversary of the signing of the act into law [5]. The National Cancer Program that was borne from this initiative resulted in a concerted effort across the length and breadth of the country to develop the infrastructures required for the treatment, cure, and eradication of cancer. A similar approach was adopted by most other developed and developing nations in the following years to combat the deadly disease, which has succeeded in satisfying the purpose to a good extent since then, despite the fact as feared and the evidence suggests, the demographic factors played a role in cancer development [6,7]. The findings reveal, overall morbidity from cancer has decreased and net survival rates, both short-term and long-term, for all cancers combined have increased substantially in the past decades. The survival rates for cancer types that are responsive to therapy surpass 90% in developed countries, and the prognosis for several other cancer types that were considered the deadliest diseases earlier has improved noticeably in recent years thanks to rapid advances in clinical oncology [8.9]. However, the fight against cancer is far from over, as an estimation by the WHO in 2018 has revealed cancer incidence would be doubled to approximately 37 million new cases by 2040 with no confirmed remedy for most cancer types in the sight [10,11]. While researchers continue the endeavors to identify the exact causes of cancer types and subtypes and develop strategies for prevention, diagnosis, and treatment, cancer remains the leading cause of death and has a major impact on societies throughout the world. There are kinds of therapy available now for cancer, such as chemotherapy, immunotherapy, hormonal therapy, targeted drug therapy radiation therapy, surgery, stem cell transplant, etc., and one can receive a single type of treatment or a combination of therapies, but whatever be the treatment regimen, it must bring the much-needed cure that remains largely elusive till now in reality. It has also been observed that every patient responds differently to particular treatments despite having the same type and stage of cancer. These observations are compelling and have led researchers to look for a patient-specific treatment regimen necessitating the study of genetic features of vulnerable individuals for the most effective treatment of cancer [12].

2. Cancer Genomics and the Emergence of Precision Oncology

Rigorous cancer research in the past few decades supported by ongoing advances in cell and molecular biology has led scientists to clearly understand that there are genetic changes associated with cancer incidences that cause the disease to grow and spread to other parts of the body. Regarded as cancer metastasis that involves the dissemination of tumor cells to new sites in the body resulting in the formation of secondary tumors, is responsible for about 90% of cancer-related deaths. The fundamental abnormality resulting in cancer development is the unchecked proliferation of cells due to an absence of balance between cell divisions and cell loss through cell death and differentiation. Proliferation also requires a balanced rate of cell growth and division to maintain the increase in cell numbers. The division depends on cell cycle regulation that generally involves growth-regulatory signals as well as signaling proteins monitoring the genetic integrity of the cell to ascertain the developments go well in time. It depends on progression through distinct phases of the cell cycle-regulated by several cyclin-

dependent kinases (CDKs) that act in association with their cyclin partners. Alterations in the overall expression pattern of cyclins lead the cellular process to go awry resulting in tumor formation. Most of the related events mainly depend on changes in the concerned genes, and the factors that cause these genetic changes often tend to provoke cancerous development [13,14]. Every single gene in the body is likely to have received mutations on varied occasions in the lifetime while the repair mechanism in place restricts the possible changes. In this way, the generation of cancer must be conclusively linked to the sustained deleterious changes in DNA sequence, i.e., gene mutations brought about by the external agents called mutagens resulting in the appearance of certain somatic variants and/or certain changes that might have been inherited to the body. Yet, a single mutation will not be enough to transform a normal cell into a cancer cell as it requires a number of changes to accumulate in the cells over time for cancerous development to take place. Mutations in the most pronounced cancer-causing genes such as RAS or MYC will not lead to unchecked proliferation until the changes in repressor genes that essentially encode components of the protective mechanisms, such as retinoblastoma gene (RB) or the Tumor protein p53 (TP53) gene have not occurred alongside. Thus, multiple genetic changes will be required for cancer manifestation and so it can be seen as an evolutionary process involving both genetic change and selection [15]. There can be multiple rate-limiting steps working against the development of cancer along with persistent changes accelerating the process. Thus, most cancers are thought to derive from a single abnormal cell or a small group of cells with a few deleterious gene mutations followed by accumulation of additional changes in some of their descendants allowing them to outgrow others in number resulting in tumorous growth in the body [16]. Moreover, cancer can also be driven by epigenetic changes that alter the gene expression pattern of cells without the accompanying alteration in the cell's DNA sequence [17]. It is observed because of some physical modifications in chromatin structure capable of influencing the pattern of gene expression often led by DNA methylation, histone modifications, and miRNA-based alterations inside the cell. Epigenetic regulations of DNA and RNA usually control how genes are turned on or off, and so play important roles in maintaining normal cell behavior whose deregulation causes alterations in gene expression patterns to potentially influence tumorigenesis. The changes are frequently accompanied by sustained exposure of the affected cells to a few stressful external stimuli presented by certain environmental factors and/or lifestyle-related changes that may involve nutrition, toxicants, alcohol, etc. [17]. Although epigenetic changes will not alter the sequence of DNA, the process might cause point mutations and disable DNA repair mechanisms frequently involved in cancer development. Traditionally, epigenetic and genetic changes have been seen as two separate mechanisms participating independently in carcinogenesis which would not be the whole truth associated with cancer development. Recent studies from whole-exome sequencing (WES), the technique for sequencing all of the protein-coding regions of genes in a genome, for thousands of human cancers have revealed the presence of many inactivating mutations in genes that can potentially disrupt DNA methylation patterns, histone modifications, and nucleosome positioning and hence control the epigenome to contribute to cancer progression [18]. Thus, considering both the genome and epigenome regulate cancer progression through mutations, crosstalk between the two is anticipated and can be exploited to bring new possibilities to cancer treatment.

The range of cancer-causing mutations is known to be huge and the totality of cancer-causing mutations, regarded by researchers as the “mutational landscape”, differs from one another, depending on the type of cancer and even people suffering from the same cancer type are found to have considerably different mutation patterns. As routine work, scientists have been analyzing the mutational landscapes of different types of cancer, and the somatic structural variants (SVs) have been shown to account for more than half of all cancer-causing mutations. These are the variants or mutations different from the hereditary or germline variants, that have passed from parents to offspring and become incorporated into the DNA of every cell in the body. The somatic SVs can be noticed in the transformed cells and in their daughter cells that may continue to grow because of errors in DNA copying and their repair mechanisms during cell division thereby altering the genomic structure which will become more numerous with time. Although somatic SVs play a crucial role in cancer development, relatively little has been known about their mode of action in cancer development. Methods to detect and identify the functional effects of these SVs can enable researchers to understand the molecular consequences of individual somatic mutations in cancer. The findings related to the mutation-specific alterations could be used to develop therapies that target the mutated cells, opening up new possibilities in cancer therapy. Furthermore, most of the human genome consists of noncoding regions, and studies on variations in the noncoding regions of the cancer cells are revealing additional mechanisms underlying cancer progression. For example, changes in noncoding regions such as point mutations and complex genomic rearrangements can disrupt or create transcription factor-binding sites or even affect non-coding RNA loci leaving options for unwanted changes in the gene expression pattern of the cell. Oncogenesis typically involves interplay between germline and somatic variants and different modes of action of non-coding variants can further potentiate these developments. Thus, a systematic approach to unraveling the roles of the non-coding genome in cancer progression could help improve cancer diagnosis and therapy. Cancer whole-genome sequencing (WGS) remains the most comprehensive method for identifying variants in non-coding regions as targeted approaches like exome sequencing (WES) may miss certain variants residing outside the coding regions [19,20].

Most importantly, the changes in vulnerable genes involved in cell growth, proliferation, death, or differentiation appear to be the root cause of all the changes in cell behaviors and remain the most fundamental feature of all cancers, so cancer has to be seen essentially as a genetic disease to be treated accordingly for better outcomes. Biometricians since the nineteenth century have been interested in decoding the relationship between genetics and diseases and attempted to understand the roles of "constitutional" and environmental factors in the distribution of diseases. Werner Kalow's 1962 textbook 'Pharmacogenetics' published on the issue of heredity and the response to drugs, emphatically tried to set the agenda of relating the response of therapeutic drugs to their biochemistry and the role of genetics and evolution in shaping individual-level differences in and the idea seems to be of practical use in cancer research. The advances in genetic technologies and consequent understanding of clinically relevant genetic variations over the years are revolutionizing how a range of diseases can be diagnosed and treated in clinics exploiting genetic peculiarities of the individuals and it applies to cancer research adequately. It has been deliberated accordingly in recent years for cancer treatment leading to the emergence of precision oncology as the field of cancer research that takes into

account the genetic specificities of the individuals for a possible cure. [21]. The term, precision oncology has been coined for the specific clinical oncology practice that relies upon genomic profiling of the individual tumors for a complete molecular characterization of the transformed cells and tissues to identify and target specific molecular alterations for efficient cancer therapy [22,23]. Thus, precision oncology intends to bring a perfectly planned cancer therapy by designing a custom-tailored treatment regimen for vulnerable individuals by identifying their unique needs for the best possible results. The proper use of precision oncology in clinics began approximately 25 years ago, but has noticeably enhanced the efficacy of cancer treatment and is on the verge of entering the mainstream of clinical practice [24,25].

3. Molecular Approach to Cellular Reprogramming and Cancer Treatment

Over the years, technological advances in the field of molecular biology have been exploited to fully understand the pathogenesis of human cancer. The emergence of next-generation sequencing (NGS) in 2005 has proved to be massively important in this direction as the technology is used to determine the order of nucleotides in entire genomes or targeted regions of DNA or RNA and has revolutionized biological research, allowing scientists to study biological systems at a level never tried before. It can provide new insights into the nature of genes and proteins thought to be associated with cancer, and the application of evolving molecular techniques to the study of cancer has also provided markers that have led to new advances in tumor diagnosis and proven to be immensely helpful in better assessment of prognosis and disease progression [26]. There are many potential biomarkers in cancer and many prognostic biomarkers are also therapeutic targets for cancer treatment.

The important part of tumorigenesis is that cancers of different tissues utilize somewhat different patterns to finally converge to a common path of cancer development witnessed in the form of tumor growth followed by angiogenesis, invasion, and metastases. All such developments are ultimately guided by genetic and epigenetic changes associated with cancer cells and supported by certain tissue-specific factors that enable the tissue to exploit these changes to its specific needs resulting in reprogramming of the molecular events utilized by different cancer cells, and no gene change is thought to be common to all cancers [27]. Because the realization of uncontrolled cell growth and proliferation remain the most evident cause of cancer, certain alterations in the pattern of cell death and differentiation promoting overall cell survival could further aggravate the gradual transformation of tissue from normal to tumorous and from benign to metastatic. Certain disruptions of the physiologic balance between cell proliferation and cell death prolonging cell survival and proliferation are thought to be an important step in carcinogenesis. Expectedly, pieces of evidence confirm that the evasion of cell death by apoptosis and autophagy is the hallmark property of most if not all cancers actively contributing to cell growth and proliferation. Apoptosis, the process of programmed cell death, also known as type 1 cell death, is mediated through caspase degradation activated by mitochondria. It is employed for removing damaged cells and is crucial to the early development and overall maintenance of tissue homeostasis. Loss of apoptotic control enables cancer cells to survive longer allowing more time for the accumulation of mutations which can deregulate cell

proliferation and differentiation and stimulate angiogenesis and metastasis. Autophagy is the major intracellular degradation system mediated by lysosomes that involve the engulfment of unwanted proteins and damaged organelles in double-membraned vesicles called autophagosomes, for their destruction and recycling. Autophagy can play a protective role to promote cell survival, but excessive autophagy plays a suppressive role by inducing autophagic cell death, known as type 2 cell death. Autophagy has universally been accepted to play a tumor-suppressive role at the early stage, while defective autophagy is associated with tumorigenesis. Deregulation of these essential catabolic pathways contributes to the development of a tumor and is often involved in promoting invasion and metastasis Cancer cells can develop novel mechanisms for evading apoptosis and autophagy and new discoveries direct toward the possible interrelationship between these two catabolic pathways. Evidence suggests that inhibition of apoptosis causes autophagy, while autophagy inhibition induces apoptosis. It may help the key proteins and intermediates involved with these pathways to be exploited in cancer therapeutics successfully. Furthermore, cancer cells maintaining constant proliferative capacity may be guided by their transformation into everlasting non-senescent cells. In this regard, telomeres are the specific repeating DNA structures found at the ends of the chromosome of the cell, which protect the genome against unnecessary nucleolytic degradation, recombination, repair, and interchromosomal interactions. Telomeres are maintained by telomerase which adds nucleotides to telomeres to keep them from getting shorter. Germ cells typically express high levels of telomerase to maintain telomere length. In somatic cells, telomere length usually decreases with the lapse of time, leading cells to undergo senescence with age. Loss of cells in this way generally acts as a barrier to tumor growth which the transformed cells escape as they maintain their telomeres despite repeated cell divisions because these cells are ab;e to express a lot of active telomerase. Telomerase has become a potential target in cancer therapeutics as they are over-expressed in transformed cancer cells and cancer stem cells in diverse forms of malignancies. Telomere maintenance mechanisms (TMM) are used by cancer cells through telomerase activation and sometimes by alternate means called alternative lengthening of telomeres(ALT).to avoid apoptosis. Anti-telomerase therapeutics have been developed to selectively target cancer cells to induce cell death by apoptosis without affecting normal cells [28].

An important feature of cancer is that the population of cells that make up cancer is profoundly heterogeneous at the genetic, and epigenetic levels, mainly because the cancer genome becomes unstable with accumulating numbers of cancer-causing gene mutations. [29]. There are transposable elements (TEs) present in the cells called 'jumping genes', the repetitive sequences of DNA that move from place to place in the genome by different means. and represent almost half of the human genome. They are essential for maintaining genomic stability and regulating the transcriptomic and proteomic profiles of the cell. They represent a powerful means of genetic modification and have played an important role in the evolution of genomes. TEs are typically regulated since the early stage of development and throughout the lifespan by epigenetic mechanisms such as DNA methylation and histone modifications. Dysregulation of TEs has been implicated in different types of human cancers, with the possibility of chromosomal aberrations, oncogenic activation, transcriptional dysregulation, and non-coding RNA aberrations as potential mechanisms underlying the development of cancer. Further, there

are fragile points in every genome where the DNA is more likely to be mutated when the genome is replicated. These breakage points have frequently been linked to genetic and heritable disorders like cancer. Moreover, there can be mutations present in certain genes, known as mutator mutations, that further increase the inherent rate of genomic changes, resulting in even greater genetic instability that leads to the accumulation of multiple oncogenic mutations within a cellular lineage. Not all such changes are "malignant" but the rate of such development could translate into cancer manifestation at different stages in a lifetime. Mutator mutations and genetic instability are generalized concepts in cancer genetics, referred to as mutator hypothesis, that relates to those few mutations that lead to an enhanced rate of the gene mutations leading to chromosomal instability, microsatellite instability, and deregulation of activities related to DNA damage and repair [31]. Furthermore, the gradual accumulation of oxidative damage to critical biomolecules such as DNA, due to persistent metabolic oxidative stress and inflammation also contributes to genomic instability and related diseases, including cancer indicating for relevant measures for prevention and cure. This feature of cancer cells has also guided researchers to kill vulnerable cells by inducing lethal genomic instability in the cells through radiation therapy and chemotherapy. It has been a rather nonselective means of killing cancer cells with associated side effects which could be perfected by devising methods to selectively target the affected cells inside the body. Researchers have begun examining the genomic data of vulnerable individuals to allow clinicians to embark on the path of personalized radiation therapy.

A crucial component of tissue heterogeneity found in tumors is cancer stem cells (CSCs), which are at the forefront of cancer research owing to their potential to induce cancer development. Recent studies have shown that there can be different subpopulations of CSCs within the tumor mass identified by cancer stem cell surface markers on normal stem cells with similar characteristics as normal stem cells, such as self-renewal and multilineage differentiation capabilities, with a much higher half-life than that of most other cells (Table 1) [32]. The intrinsic properties of self-renewal, multipotency, and longevity render stem cells more susceptible to accumulating gene mutations leading to neoplastic transformation, as proposed by the cancer stem cell hypothesis [33,34]. They have been found to be the key driver of tumorigenicity, tumor heterogeneity, recurrence, and drug resistance in many cancer types, and different targeted molecules, including nanoparticles-based drug delivery systems, are being tested for effectively targeting CSC related pathways for cancer treatment [35,36,37.38]. Moreover, the immune cells in the tumor mass could be hugely different, and an emerging finding of tumor heterogeneity is that tumors from different patients show a different degree of immune cell infiltration and immune cell composition. The immunologically "hot" tumors present elevated levels of T -cell infiltration, so these tumors are more susceptible to immunotherapy than immunologically "cold" tumors that don't allow similar T -cell infiltration. This immunogenic heterogeneity simply impacts treatment outcomes and may direct treatment planning [39,40].

Table 1. Representative biomarkers in each cancer cells (Saito, S. et. al. [32])

Cancer Types.	Markers of CSCs
Breast CSCs	CD44/CD24−
Breast Carcinoma	ALDH1
Breast Cancer subtype	CD1333, HER2
Prostate CSCs	CD44
Lung CSCs	CD133, ALDH1, CD44
Epithelial CSCs	ALDH1
Glioblastoma	SSEA-1, EGFR, CD44, ID1
Pancreatic CSCs	CD1333, CXCR4, SSEA-1, CD44
Liver metastatic colorectal cancer	EpCAM, CD44, CD24 CEA-CAM, CDX1
Leukemia	CD34, CD38−
Gastric CSCs	HER2, APC, p53, kRAS, PTEN, LGR5, CCKBR, RHOA, CDH-1, SMAD5, ATP4B, PGA3

Traditionally, cancer treatments such as chemotherapy and radiation therapy have been targeting actively growing cells of the tissue instead of just attacking diseased cells with a variety of side effects. So, the need for a deeper understanding of the molecular events underlying cancer progression was realized decades ago for developing treatments that would selectively target the affected cells alleviating the serious side effects of cancer treatment. The functional roles of many critical players involved in tumor growth, tissue invasion, and metastasis have been described precisely in past decades due to the draft of the human genome and other related developments that took place in the following years [41].. The RB and TP53 are the central tumor suppressor genes that play central roles in regulating the cell cycle and are often found altered in many different cancer types. The RB gene product, i.e., Rb protein, forms complexes with the E2F family of transcription factors and down-regulates several genes that code for key cell cycle regulators. Their transcriptional repression by the Rb-E2F complex can be relieved through phosphorylation of Rb leading to committed cell cycle progression which can be reversed afterward at the level of the cyclin-dependent kinases. TP53 gene that codes the proteinp53, a 53 kDa weighted nuclear protein, mainly acts to ensure genome stability, normal cell growth, and proliferation. It is the key player in the tumor suppressive DNA damage response (DDR). The ATM (ataxia-telangiectasia mutated), ATR (ATM- and Rad3-Related), and other related protein kinases are the initial DDR kinases that help p53sense damage to DNA and activate other genes to repair the damage or suppress cell division to prevent accumulation of oncogenic mutations that often lead to tumor development. The task is supported by p21, the

cyclin-dependent kinase inhibitor (CKI) activated by p53, serving as a cell cycle inhibitor and anti-proliferative effector inside the cell. Stresses like a viral infection or DNA damage, a relatively common oncogenic act, will turn on p53 functions leading to cell cycle arrest for DNA repair, senescence for permanent growth arrest, or apoptosis for programmed cell death. A wide variety of mutations have been identified in the p53 gene which often occurs late during cancer progression. Mutations in the gene not only disable their tumor suppressive function but can also engage in cancer-promoting activities by gaining oncogenic properties or inactivating remaining suppressive elements in the cell. An estimated 40-50% of human cancers carry deleterious mutations in the regulatory p53 gene [42]. The findings have revealed many crucial genes and proteins associated with the pathways of cancer reprogramming which could be taken as attractive targets for precise cancer treatments. These molecules are thought to participate in crucial cellular events in different ways eventually leading to uncontrolled cell growth and proliferation responsible for tumor growth in our bodies. A few common alterations that are frequently implicated in cancer progression with profound effects are detailed below.

MYC genes are a group of related proto-oncogenes that code for Myc proteins, commonly involved in the pathophysiology of human cancer. Myc proteins alone may not cause the transformative effects, and studies reveal changes in the tumor suppressor gene such as TP53 and MYC synergistically induce proliferation, survival, and metastasis. It is also a known target of RB repressor proteins deregulation which may result in enhanced Myc activities. Myc has three family members, C-Myc, N-Myc, and L-Myc, which are essential transcription factors involved in the activation of a large number of protein-coding genes associated with many different biological processes including cell proliferation and differentiation, cell metabolism, and self-renewal of the stem cells. Myc oncoproteins have been shown to mandate tumor cell fate by inducing stemness and blocking differentiation and cellular senescence, the irreversible cell-cycle arrest contributing to cancer progression. Additionally, MYC can influence changes in the tumor microenvironment and induce activation of angiogenesis, and/or suppression of the host immune response. C-Myc oncoprotein forms a very crucial part of a dynamic cellular network whose members interact selectively with one another and with many of the transcriptional coregulators and histone-modifying enzymes supportive to maintain sustained cell proliferation. C-Myc is constitutively and aberrantly expressed in over 70% of human cancers, with many of its target genes encoding proteins that initiate and maintain the transformed state [43].

A series of growth factors and their receptors are involved in cancer development and metastasis. Receptor tyrosine kinases (RTKs) are a class of receptors for many polypeptide growth factors, cytokines, and hormones that can play vital roles in cancer development. RTKs are cell surface receptors with specialized structural and biological features capable of dimerizing with other adjacent RTKs leading to rapidly phosphorylating tyrosine residues on target molecules to initiate several downstream biochemical cascades in the affected cells. RTKs like Fibroblast growth factor receptor (FGFR), Epidermal growth factor receptor (EGFR), Platelet-derived growth factor receptor (PDGFR), and Vascular endothelial growth factor receptor (VEGFR) control vital functions such as cell growth, proliferation, differentiation, apoptosis, inflammation, and stress responses. These cellular processes can be critical for reciprocal interactions between tumors and stromal cells and play a central role in the control of tumor formation, angiogenesis,

and metastasis [44]. The multifaceted role of RTKs makes them suitable candidates for selective targeting in cancer therapy but their involvement with alternate pathway activation often presents serious challenges to anti-RTK therapy.

The trimeric GTP-binding protein (G protein) mediated signaling is critical to many cellular processes and minor defects in the related pathways can cause the pathophysiology of a disease. G-protein-linked receptors (GPCRs), are the serpentine transmembrane proteins that form the largest group of cell-surface receptors where the G proteins, which remain attached to the cytoplasmic face of the plasma membrane, serve as the critical relay center coupling the receptors to different enzymes or ion channels in the membrane. There are different types of G proteins that specifically associate with a particular set of receptors in the plasma membrane to mediate responses to a variety of signaling molecules including hormones, neurotransmitters, and local mediators such as cytokines, chemokines, and growth factors. An activated receptor leads to the dissociation of the trimeric G protein stimulating its components in different ways, the GTP-binding protein subunit serves as GTPase which is crucial to GPCR signaling. Studies reveal they control many aspects of cancer progression including tumor growth, cell survival, invasion, migration, and metastasis [45]. All GPCRs have a similar structure and the same mediator can activate many different receptors enabling them as the most likely targets for drug therapy. Noticeably about half of all known drugs actively target GPCRs and genomic studies continue revealing a growing number of new family members, many of which could prove to be potential targets for cancer therapy.

The small GTPase Ras protein belongs to the Ras superfamily of monomeric GTPases, which is a highly placed target in cancer therapy. They are the products of the most frequently mutated RAS genes in human cancers. Ras proteins are frequently involved in carrying signals from cell-surface receptors to different intracellular targets inside the cell It serves as a transducer and bifurcation signaling protein capable of changing the properties of the signaling process by relaying it along multiple downstream pathways, including the signaling pathways reaching the nucleus to stimulate gene expression for cell proliferation. It is often required in receptor tyrosine kinase (RTK) activated signaling pathways involved in stimulating cell growth, proliferation, and differentiation. Mammalian cells express three different yet closely related Ras proteins, K-Ras, H-Ras, and N-Ras, whose mutational activation effectively promotes oncogenesis. The mutation frequency of different Ras isoforms in human cancers varies, and K-Ras is the most frequently mutated isoform leading to tumor formation, invasion, and metastasis in many cancers [46]. The mutation rate for K-Ras is about 25% for all tumors but is found to mutate up to 80-90% in pancreatic ductal adenocarcinoma (PDAC). The treatment of PDAC, the commonest form of pancreatic cancer and a leading cause of cancer-related death, has so far been sparsely productive because of the tumor microenvironment, which possesses an ample amount of stromal cells and a complicated ECM. Genomic analysis has recently revealed that PDAC harbors frequently mutated genes that include KRAS, TP53, CDKN2A, and SMAD4, which can greatly influence the cellular processes and change the tumor microenvironment, which in turn, affects cancer progression. The drug development to block K-Ras has been partially successful like many other drugs, as the affected cells develop resistance to the inhibitors, a common problem encountered with drugs designed for cancer therapy [47]. The

study of K- Ras resistance mechanisms reveal that researchers may have to try several different drug combinations to overcome resistance, and some of these are in the pipeline. Researchers are tirelessly working to target K-Ras and other signaling intermediates associated with cancer to develop novel therapeutic agents for different cancers.

The nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) belongs to CNC (cap‘n’collar) family proteins, a group of basic leucine zipper (bZip) transcription factors encoded by basic leucine zipper (bZIP) genes, which serves as the master regulator of the cellular antioxidant response. Recent studies have revealed many new roles for Nrf2 in the regulation of essential cellular processes through interacting with other pathways within the cells, thus establishing it as a truly pleiotropic transcription factor involved in carcinogenesis. Originally recognized as a target of chemopreventive agents to help prevent cancer, its protective role is found altered in 6-7% of cancer cases. A growing body of evidence has established the Nrf2 pathway's involvement in the deregulation of cell metabolism, apoptosis, and self-renewal capacity of cancer stem cells, and thus an important driver of cancer progression, metastasis, and cancer drug resistance [48]. S

The insulin-like growth factor receptor (IGF-1R), is an RTK that binds IGF1 with a high affinity and is an important factor in the growth, differentiation, and survival of cells in health and disease. IGF-1R plays an important role in the anchorage-independent growth of cells, which may enable cancer cells to survive and grow in the absence of anchorage to the extracellular matrix (ECM) and the neighboring cells. High gene expression level for IGF-1 and IGF-1R have been associated with the upregulation of pathways supporting cell growth and survival, cell cycle progression, angiogenesis, and metastatic activities during cancer development, and is considered essential in many cancer types [49].

B-cell lymphoma-2 (Bcl-2) oncoprotein is primarily a cell death regulatory protein that controls whether a cell lives or dies by apoptosis. It is a member of a family of regulatory proteins actively involved in the regulation of cell death by all major pathways, including apoptosis, autophagy, and necrosis, serving at the critical junction of multiple pathways with crucial roles in oncogenesis. An aberrant expression of the BCL2 gene may keep cancer cells from dying and is frequently implicated in prolonged cell survival and therapy resistance in human cancer. The Bcl-2 family proteins form subgroups, one of which may inhibit cell death and prolong cell survival by limiting apoptosis while others induce cell death by inducing apoptosis, autophagy, etc. [50]. The gene for the Bcl-2 protein is found on chromosome 18 but can be transferred to different chromosomes as can be seen in many cancer types. An increased expression of pro-survival proteins or abnormal reduction of death-inducing regulatory proteins, resulting in sharp inhibition of apoptosis and other related catabolic activities are frequently seen in many cancers. Resistance to apoptosis is a key development in several hematological malignancies and has been attributed to the upregulation of pro-survival Bcl-2 proteins. The important role played by Bcl-2 family proteins in cancer development renders them as potential targets for the therapy of different cancers, including solid tumors and hematological disorders. Alterations in Bcl-2 activities with concurrent changes in other important regulators such as c-Myc or p53 appear to be great combinations in cancer progression [51]. The recent development

of inhibitors of pro-survival Bcl-2 proteins, termed BH3-mimetic drugs may prove to be novel agents for cancer therapy.

4. Signaling Pathway Deregulation and Prospective Targets for Cancer Therapeutics

Cancer manifestation is mainly the result of uncontrolled cell division. The root cause of cancer is usually genetic or epigenetic alterations in the affected cells leading them to grow and proliferate uncontrollably, although the progression of cancer remains dependent on a complex interplay between the tumor cells and surrounding non-neoplastic stromal cells and ECM present in the tumor microenvironment [52,53]. Cell signaling network as the foremost system of communication between cells and the surroundings that involve a variety of chemical and mechanical signals to regulate different signaling pathways comes into consideration here as all the essentials of cellular behaviors like cell growth and proliferation, cell polarity, cell metabolism, differentiation, survival, and migration can be seen guided by the components of these pathways working in a collaborative manner in the cell.. The signaling pathways together maintain an internal circuitry inside cells guided by external stimuli enabling them to sense whether their state of attachment to ECM and other cells is appropriate and if different growth factors, hormones, and cytokines guide them to proliferate or differentiate, move, or stay put for now, or to commit to cell death by apoptosis or autophagy [54]. Almost all gene modifications can be related to one or more of these signaling pathways that are deregulated in the affected cells to acquire hallmark properties of cancer. Cancer cell signaling displays altered expressions of the components of the signaling network that include many secreted protein receptors, growth factors, protein kinases, phosphatases, different cytoplasmic proteins, and transcription factors leading individual cells to respond to the changes with appropriate physiological behaviors. Cell division is mainly regulated by a group of extracellular growth factors that signal resting cells to divide by exploiting the intrinsic regulatory process of the cell. Cytokines ordinarily signal the immune cells to mount coordinated attacks on invading bacteria, and viruses and play essential roles in cancer prevention. Thus, signals propagated by growth factors and cytokines can simply tell individual cells to divide or not under particular conditions whose alterations could lead to the pathophysiology of cancer.

The earliest information regarding the relationship between cancer and growth factors came from the observation that normal cells in culture often required serum for proliferation, while cancer cells had a much less requirement for serum. The serum is known for providing growth factors among other ingredients needed for the overall regulation of the cell cycle. The other hints came from gene mutations found in cancer cells observed to cause changes in cell behaviors very similar to those related to the activities of growth factors and their receptors. The oncogenic mutations disrupt the cellular circuits that control cell adhesion and signaling, enabling cells that carry them to over-proliferate and invade the other tissues in an uncontrolled fashion. Many of these mutations have been directly linked to the growth factors and their receptor proteins involved with tumor growth, angiogenesis, invasion, and metastases. Oncogenes are the mutated forms of cellular proto-oncogenes, normally involved in the

regulation of cell growth, proliferation, and differentiation, as well as cell death, that translate into activated versions of signaling proteins leading to deregulation of the cell cycle and cell death. Negatively acting tumor suppressor genes mostly act to repress growth and proliferative signals to maintain a balance in product formation and are the actual targets for the action of many signaling molecules [55,56].

A critically important finding of cell signaling is that one kind of cell membrane receptor can mediate many different downstream intracellular pathways and one pathway can also be activated by several of the upstream surface receptors revealing common signaling components in multiple signaling pathways. For example, the RTKs, like EGFR, FGFR, IGFR, VEGFR, PDGFR, and the GPCRs, can all activate the MAPK cascade while the widely studied RTKs such as EGFR/HER family receptor can initiate different signaling pathways including mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K)/AKT, and mammalian target of rapamycin (mTOR) pathways involved in regulations of cell growth, proliferation, differentiation, and survival. This feature of the signaling process evidently presents the option for crosstalk between components of different signaling pathways at different stages of the cellular process. A molecule participating in crosstalk can affect the activation of alternate signaling pathways, and receptors can also have an altered ability to bind to the ligands which can swiftly lead to cancer manifestation. As generally observed, most of the cell signaling pathways contribute to the development of cancer, and seldom does a cancer type arise from the deregulation of a single pathway. Breast cancer can arise due to elevated expression of estrogen receptor (ER), EGFR/HER, or IGFR, but on many occasions, more than one pathway may be involved. Signal transduction leading to tumor growth, cancer cell migration, metastasis, and drug resistance are often complex processes, as cancer cells generally develop abnormalities in multiple signaling pathways or rely on the crosstalk between different pathways and on certain redundant pathways for the maintenance of growth and survival (Fig. 1).

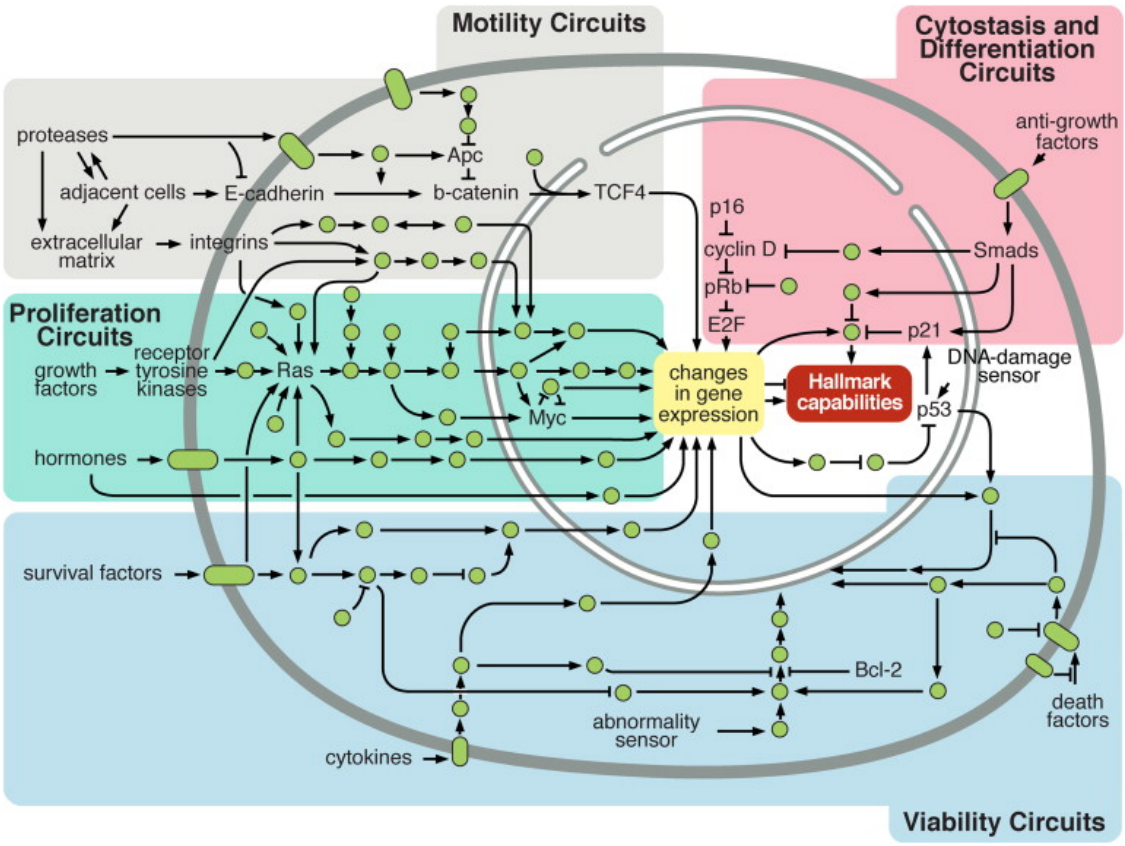

Figure 1. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell.

An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate sub-circuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such sub-circuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these sub-circuits is connected with signals originating from other cells in the tumor microenvironment. (Hanahan and Wienberg [57]. With permission from Elsevier)

As cancer progression involves alterations in signaling pathways due to mutations in the relevant genes, it is satisfying and mechanistically well-founded that a therapeutic intervention taking into account this biology of the affected cells can pave the way for a very effective cancer treatment [58,59]. Therefore, therapeutic substances that can selectively target the cancer signaling processes are being explored as prospective and efficacious agents for cancer treatments. Further, it has been established in clinical practice that targeting a single intermediate or pathway brings considerable results towards recovery, possibly because it impedes the synergistic signaling process of disease progression. Yet, the constitutive activation of a molecular event that contributes to cancer development can be sustained by different

mechanisms, and strategies to inhibit multiple targets or redundant pathways simultaneously with molecular-targeted agents could prove to be an even more effective way to treat cancer and overcome resistance in cancer therapy [60]. It has indeed been tried with anticipated outcomes in some forms of cancer, indicating the need for more research in that direction. The representative signaling pathways involved in cancer cell reprogramming and the scope for therapeutic targeting of the signaling molecules and intermediates for efficient cancer treatment are being discussed here in brief.

Ras/Raf/MAPK signaling pathway: Mitogen-activated protein kinase (MAPK) signaling cascade is an evolutionarily conserved system, and the key signaling pathway to relay extracellular signals through protein phosphorylation, from cell membrane to intracellular compartments and to the nucleus. This pathway is the main route for extracellular signaling molecules like growth factors, to transmit signals to the cell that regulate a wide variety of cellular processes including cell proliferation, differentiation, apoptosis, and stress response and abnormalities in this pathway are common in many cancer types [61]. MAPK cascades comprise the mitogen-activated protein kinases (MAPKs), known as extracellular signal-regulated kinases (ERKs), MAPK/ERK protein kinase (MEK), and rapidly accelerated fibrosarcoma (Raf) kinases. Importantly, the Raf/MEK/ERK signaling pathway is a key downstream effector of the Ras GTPase protein. In this process, ERK is a downstream component activated by MEK followed by its activation by Raf activated by Ras in response to the extracellular signals. Ras acts as a molecular switch that controls the activation and regulation of related cellular pathways responsible for different cell behaviors critical to cancer development [62]. In addition, the mutational activation of Raf in human cancers further supports the important role of this pathway in cancer development. Activated ERK relays the signal downstream to the gene regulatory proteins resulting in the expression of the target genes and it has been the subject of intense scrutiny in the treatment of cancer. Growth factor receptors, such as the TGF-β receptors, EGFR, VEGFR, PDGFR, FGFR, and IGFR, can all activate Ras ultimately leading to ERK activation with consequent response. The study with selected inhibitors against the targets in this cascade has shown positive results, such as growth inhibition, anti-angiogenesis, and suppressed metastasis in cancer cell lines and animal models. These results reveal that this strategy is effective at inhibiting cancer cell proliferation and survival, and more clinical trials and validation is ongoing for efficacious treatment of the disease [63].

PI3K/Akt/mTOR signaling pathway: This pathway can be activated by a variety of factors, such as cytokine receptors, GPCRs, RTKs, and integrins, and regulates several cellular and metabolic activities that lead to cell growth and survival. Phosphatidylinositol (PI) is a unique membrane lipid phosphorylated by activated, PI 3-kinase to generate phosphatidylinositol-3,4,5-triphosphate [PI P3] that works as the docking site for intracellular signaling proteins bringing the proteins together into signaling complexes. The main PI3K effector Akt, also called protein kinase B (PKB) is activated in the process that regulates different downstream targets including mTOR, to relay the signals through the cell. The kinase protein mTOR is of particular interest as

it works as a master regulator of cellular processes involved in cell growth, proliferation, autophagy, and apoptosis, by participating in multiple signaling pathways inside the cell. The canonical pathway of mTOR activation depends on signaling through PI3K/Akt, though alternative non-Akt dependent activation through the MAPK pathway is now recognized as well. Activated mTOR can assemble into a variety of complexes to catalyze the phosphorylation of multiple targets, including Akt), protein kinase C (PKC), components of the insulin-like growth factor receptor (IGF-IR) signaling, and the protein synthesis machinery to influence the cell behaviors accordingly. Persistent mutational activation of the PI3K/Akt/mTOR pathway in the absence of different stimuli has been frequently observed in many cancers. Several mTOR inhibitors have also been developed to treat cancer, and some are being evaluated in clinical trials for approval [64,65]. In addition, Phosphatase and tensin homolog (PTEN)), is a crucial component of this pathway, a potent tumor suppressor that can work independently as a phosphatase against phospholipids and proteins. Its primary target is PIP3, the direct product of PI3K, and mutational deregulations of the PTEN/ PI3K network have been associated with many cancer types including familial cancers. It is a potential means of targeting PI3 K-mediated signaling in cancer therapeutics [66]. Adaptive resistance to the pathway inhibitors is common, and combination therapy, if well tolerated, may produce favorable anticancer results [67].

JAK/STAT signaling pathway: The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, is actively involved in the regulation of essential cellular activities, such as proliferation, survival, invasion, inflammation, and immunity deregulation which has been associated with cancer progression and metastasis. There are seven different signal transducers and activators of transcription (STAT) family proteins in mammals, STAT 1, 2, 3, 4, 5A, 5B, and STAT 6. The Janus kinases (JAK) family comprises four different members, JAK1, 2, 3, and Tyk (tyrosine kinase). This pathway largely involves cytokine signaling which is closely related to the activities of T and B cells and so often linked to the development of hematological malignancies. When a cell is exposed to cytokines such as interleukin-6 (IL-6) or interferon-gamma (IFN-g), JAK kinases associated with the cytokine receptors are activated to phosphorylate and activate STATs. STAT family members, especially STAT3 and STAT5, are involved in cancer progression, whereas STAT1 plays the opposite role by suppressing tumor growth. Target genes of STAT5 may regulate processes such as cell cycle progression, survival, and self-renewal, via binding to growth factors and cytokines, and constitutive activation of the pathway leads to the high-level expression of genes and proteins, resulting in different forms of cancer manifestation [68,69]. It could be finally mediated through the suppression of p53 activities or crosstalk with NF-kB signaling or expression of the Runt-related transcription factors (RUNX) family proteins, leading to inflammation and cancer [70]. Activation of the JAK/STAT pathway can be controlled by suppressors of cytokine signaling (SOCS) family proteins while other inhibitory proteins and phosphatases may also contribute to inhibiting the activated state. The upregulation of JAK/STAT proteins, as well as the reduction of the different SOCS proteins, are associated with different malignancies including solid tumors. This signaling pathway has also been associated with the development of tumor tolerance as hyperactivation of the pathway often leads to an increase in gene expression

resulting in enhanced activity of the regulatory T cells (Tregs), a specialized subpopulation of T cells that work to limit T cell proliferation and cytokine production, thereby resulting in suppression of immune response and maintenance of self-tolerance. These specificities of the signaling pathway provide options for effective drug development against the pathway intermediates with fewer side effects. Many JAK and STAT inhibitors have been tested for their efficacy in cancer treatment and a few inhibitors have shown to be clinically relevant. Targeting the JAK/STAT signaling pathway efficiently remains an intriguing strategy in cancer therapy [71,72].

TGF-β/SMAD signaling pathway: Transforming growth factor beta (TGF-β) superfamily proteins serve as multifunctional secreted cytokines whose activities may be deregulated in many diseases, including cancer. TGF-β signaling is known to control many different biological processes, including cell proliferation, differentiation, migration, and apoptosis, and plays context-dependent roles in carcinogenesis. SMAD proteins are the main signal transducers for the canonical pathway of TGF-β signaling. It comprises a family of structurally similar and well-conserved transcription factors which can relay extracellular signals directly to the nucleus and are critically important for regulating cell development and growth. TGF-β initially functions as a tumor suppressor through the SMAD-mediated pathway when TGF-β/SMAD-dependent p15/p21 induction or c-MYC suppression works well to maintain growth arrest, cell differentiation, and apoptosis. However, the situation could be the opposite if SMAD- dependent suppression became ineffective under the influence of certain oncogenic mutations mediated by many other pathways, and the role of TGF-β could become antiapoptotic, EMT inducer, and carcinogenic. SMAD inactivation under such a circumstance convincingly explains the situation-based role of TGF-β in different malignancies. Furthermore, the classical, SMAD-independent pathway of TGF-β receptors may engage in crosstalks with other signaling pathways, such as Wnt/β-catenin, Ras/RAF/MAPK, and PI3K/Akt/mTOR pathways, to play vital roles in carcinogenesis, and a proper understanding of the TGF- β signaling pathway in cancer progression would resolve controversies related to the signaling pathways [73,74]. The vast range of functionality associated with TGF-β during cancer progression is evidently clear now and it has led to the development of multiple therapeutic agents targeting different intermediates of the signaling pathway, and a combination of drugs may produce even better results against reoccurring and metastasizing cancer [75,76].

The Hippo signaling Pathway: Hippo Pathway is an evolutionarily conserved major signaling pathway originally identified in fruit fly (Drosophila melanogaster) and controls contact inhibition and organ size development. It is a serine/threonine kinase signaling cascade and its dysregulation has been implicated in many cancer types. Contact inhibition enables normal cells to cease growth and proliferation when in contact with each other and an absence of this property can lead the affected cells to proliferate uncontrollably resulting in malignant growth. The canonical Hippo pathway comprises a kinase cascade and related regulators that together work as a repressive system involving phosphorylation and inhibition of the two transcription

coactivators YAP and TAZ, as the downstream effectors to execute its role in the regulation of organ size and tissue homeostasis. Phosphatase and protein ubiquitination modulate the activities of the coactivators in the cascade and can also be regulated by the cytoskeleton for its role in the signaling process. When dephosphorylated, YAP/TAZ translocates into the nucleus and interacts with other transcription factors to induce gene expression leading to cell proliferation and inhibition of apoptosis. The regulation of YAP1/TAZ may be influenced by many other molecular events, including crosstalk with Wnt/β-catenin signaling, and is mostly oncogenic. The core activity of this pathway is controlled by cell density, polarity, and energy requirements as well as ECM stiffness and shear-stress, which together can regulate contact inhibition and related developments, and so its activities can be regulated at multiple levels and widely implicated in angiogenesis and chemoresistance [77]. Cell proliferation and stem cell self-renewal can be directly attributed to contact inhibition governed by this signaling pathway. The noncanonical Hippo pathway operates in tight and adherens junction complexes to control their localization and activity within the cell. Several studies suggest that overexpression of the components of the Hippo pathway contributes to aberrant cell cycle regulation leading to cancer development. The exact role of the Hippo pathway in cell cycle regulation has not been thoroughly understood, but an in-depth exploration of the process could provide effective therapeutic options for cancer treatment. The properties of the extracellular signaling and membrane receptors involved with the pathway remain to be fully known, yet drugs targeting the components of this pathway are under investigation for their efficacy in cancer therapy [78.79].

Wnt/β-catenin signaling pathway: This signaling pathway is one of the key signaling cascades involved in the regulation of cell growth and cell polarity in the developmental process and has been typically associated with stemness, and implicated in carcinogenesis. The signaling pathway begins with a Wnt ligand-protein binding to the extracellular domain of a Frizzled (Fz) family receptor, a distinct family of GPCRs that generally do not involve activation of G proteins, to relay signals through the cell via different paths to influence a variety of cellular mechanisms critical to cancer development. The Wnt pathway has been formally divided into the β-catenin dependent canonical pathway and the β-catenin independent, non-canonical Planar cell polarity (PCP) signaling pathway, and Wnt/calcium pathway. The canonical Wnt signaling is a genetic pathway that promotes normal cell growth requiring meticulous control of a tumor suppressor gene called adenomatous polyposis coli(APC), which functions to limit the activation of β- catenin preventing excessive cell growth and tumor formation. The APC/β-catenin pathway is a highly regulated process that involves many different proteins. APC itself is a negative regulator, a Wnt antagonist that binds to a variety of proteins that include β- catenin. It is an essential component of the cytoplasmic protein complex that targets β-catenin for proteasomal destruction. Furthermore, MYC and cyclins are the important transcriptional targets of this pathway, indicating an overlap with several tumor-promoting pathways. Mutations that prevent the degradation of β-catenin, including certain mutations in β-catenin or the APC component of the β-catenin destruction complex and others, distort the regenerative pathway to contribute to cancer progression and metastasis [80].Deregulation of the signaling pathway results in alterations in cell growth and survival, maintenance of cancer stem cells, metastasis, and immune

control which have been linked to both solid and hematological tumors. The activation of the non-canonical pathway generally involves the recruitment of Rho family small GTPase that leads to enzymatic rearrangements of the cytoskeleton and/or certain transcriptional activation of effector proteins. Both of these pathways essentially require the binding of Wnt proteins to the Frizzled receptors for the execution of the function.

The Wnt/Ca2+ signaling is followed by G-protein-activated phospholipase C activity leading to intracellular calcium fluxes and downstream calcium-dependent cytoskeletal rearrangement and/or transcriptional responses. The Wnt signaling pathway is a crucial mediator in maintaining tissue homeostasis, stem cell populations for tissue repair, and wound healing and is frequently involved in the incidences of many cancer types. Mutations of the APC gene are observed in about 80% of colon cancers where cancer stem cells (CSCs) is thought to play a critical role in metastasis and relapse, indicating the role of this signaling in maintaining CSC. The role of Wnt signaling in cancer immune evasion and drug resistance is well recognized, and identifying tumor-specific signaling intermediates as targets for drug action can be crucial to effective cancer therapy. Many different agents effectively targeting molecules of this signaling pathway are being explored for the efficacious treatment of different cancer types [81,82].

Hedgehog (Hh) Signaling Pathway: Hh is an evolutionarily conserved signaling pathway and one of a few signaling pathways frequently involved in intercellular communication. It is a key regulator of embryonic development that controls cell patterning, proliferation, and differentiation for organs developments in mammals as well as in the regeneration and maintenance of tissue homeostasis This pathway has frequently been associated with birth defects, stem cell renewal, and cancer. Hh signaling depends on three transmembrane receptor proteins. Namely Patched, iHog, and Smoothened. Hh proteins are coded by at least three genes in vertebrates that include Sonic, Desert, and Indian hedgehog. Hh performs its tasks through a signaling cascade in a context-dependent manner to regulate the change of balance between activator and repressor forms of the glioma-associated oncogene (Gli) transcription factors. There are three different forms of the transcription factor, Gli1. Gli2 and Gli3 present in vertebrates which may undergo proteasomal processing similar to that of the Wnt pathway to exert their effects in response to appropriate signals. The activated form of Gli moves to the nucleus to bind to their promoters leading to the transcription of the target genes. Mutational changes that lead to excessive activation of the Hh pathway have been implicated in different malignancies. Communication between Hh and major signaling pathways, such as Wnt, Notch, and TGF-β, play crucial roles in the pathophysiology of the disease. Several Hh signaling pathway inhibitors have been developed for a range of cancers, and a few agents are thought to be highly effective for patients with recurrent and advanced cancers [83].

Notch signaling pathways: It is a contact-dependent signaling pathway that has a major role in controlling cell fate decisions and regulating pattern formation during the renewal and development of most tissues and performs major tasks during the embryonic development of

animals. Signaling is mediated through the Notch receptor protein, a single-pass transmembrane protein that undergoes successive proteolytic cleavage steps upon activation to perform its action. Notch is activated in a contact-dependent manner by the specific signal protein called Delta, present on the neighboring cell that leads to the cleavage and release of its cytoplasmic tail, notch intracellular domain (NCID) which translocates to the nucleus where it regulates expression of the target genes [84]. Notch signaling is associated with the regulation of many cellular processes like cell proliferation, survival, differentiation, and apoptosis through cell-to-cell communication crucial to the development of many tissues. The signaling pathway is a key regulator of self-renewal and differentiation of many cell types and is known to be an important regulator of Hematopoiesis. Notch acts as a context-dependent binary cell-fate-determining pathway and its hyperactivation has been implicated in the oncogenic stimulation of many solid and hematological cancers.

The Hh and Notch signaling pathways are the active regulators of communication between cells and are actively involved in EMT regulation that is critical to organ development, regeneration, stem cell maintenance, and tissue homeostasis. The self-renewal potential of cancer stem cells (CSCs) has been attributed to these signaling pathways crucial to maintaining CSCs in the tumor mass that causes disease progression, recurrence, and chemoresistance. Importantly, the Hippo pathway has been found to repress Wnt signaling stimulation which could induce cancer stems cell activities. In addition to that, the alterations in Wnt signaling is known to influence Hg and Notch pathways alternatively which can be intrinsically related to the maintenance of cancer stem cell properties [85]. Thus, the components of one signaling pathway could influence the performance of the other pathways to synergistically maintain the activities of CSCs involved in cancer development. It presents the option to identify the signaling intermediates with confirmed hyperactivities as potential targets in anti-CSC drug discovery for effective cancer treatment. Selective targeting of these pathways along with other proliferative pathways such as the PI3K/Akt or RAS/RAF/MAPK pathways could prove to be an effective strategy for combination therapy of cancer [86, 87].

The NF-κB signaling pathway: This is initiated by the degradation of IκB proteins via IκB kinase (IKK). IkB binds to the NF-κB dimer in the resting state, preventing it from binding DNA, and its degradation leads to the activation of NF-κB and consequent transcriptional activation. The signaling is mediated via both the canonical (NEMO-dependent) pathway and the noncanonical (NEMO-independent) pathway. The canonical pathway is thought to be involved in immune responses and immunosurveillance, while the noncanonical pathway is associated with developmental activities. Thus, canonical and noncanonical pathways have generally been taken to be distinct, but studies have revealed numerous crosstalk mechanisms that connect them, so both pathways may result in a single NF-κB system [88]. Constitutively activated NF-κB signaling may lead to inflammation-related disorders, and its role in pathological inflammation and cancer development is well recognized now [89]. Furthermore, NF-κB signaling is associated with the epithelial-mesenchymal transition (EMT), which occurs frequently during tumor progression and metastasis. E-cadherin is a well-known tumor suppressor protein, and the

regulation of the adhesive activity of E-cadherin present at the cell surface is important in cancer, and its repression by NF-κB is attributed to EMT induction. NF-kB has been implicated in EMT and metastasis also through the activation of EMT master-switch transcription factors and is highly invasive [90]. Evidence suggests that reversal of EMT is triggered by inhibition of NF-kB signaling, but the activated NF-κB pathway may contribute to antiapoptotic activation, ECM degradation, and E-cadherin-mediated EMT, which results in tumor growth, invasion, and metastasis. NF-κB signaling molecules also communicate with many other signaling pathways as crosstalk can be mediated by intermediates, such as STAT3 and, GSK3-β, p53, p38, PI3K, or the proinflammatory TGF-β proteins which modulate NF-κB transcriptional activity [91,92]. Thus, targeting the NF-κB signaling pathway represents an attractive approach to anti-inflammatory and anticancer therapies, and inhibitors have been developed to block different steps of NF-κB signaling for cancer treatment [93,94].

The cGAS-STING pathway: The cyclic GMP–AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway represents a key cellular process that controls inflammatory responses in the presence of foreign particles based on dsDNA recognition through pattern recognition receptors (PPRs) and thus regulates the overall preparedness for the cell to withstand adversity caused by infection or injury. The binding of cGAS to double-stranded DNA (dsDNA) induces the catalytic activity of the synthase and leads to the production of 2′3′ cyclic GMP–AMP (cGAMP), a second messenger molecule that quickly binds to the stimulator of interferon genes (STING) dimers localized at the endoplasmic reticulum (ER) membrane, which is then released to undergo further processing, finally resulting in the expression of type I interferons, interferon-stimulated genes (ISGs), and several other inflammatory mediators, pro-apoptotic genes and chemokines [95,96]. STING also binds and stimulates IKK, triggering the transcriptional activation of NF-kB that pro- motes noncanonical NF-κB responses. This signaling outcome limits type I interferons and the canonical NF-κB pathway as critical, negative regulators of STING effector mechanisms, which can have important biological consequences related to immune evasion and metastasis [95,96]. cGAS–STING signaling may also induce autophagy and additionally communicate via p53, MAPK p38, and STAT3 signaling in a context-dependent manner [97]. This finding reveals the complex role of this signaling in the regulation of cell behaviors. Mutations associated with the pathway have been implicated in cancer progression. cGAS-STING is an important pathway in cancer immunotherapy, and inhibitors of the pathways are being tried for targeted drug therapy [98,99].

5. Integrating Artificial intelligence (AI) with Multi-Omics in Precision Oncology

Multiomics: High-throughput sequencing technologies, also known as next-generation sequencing (NGS), are a comprehensive term used to describe technologies that sequence DNA and RNA rapidly and cost-effectively. It has revolutionized the field of genetics and molecular biology and aided in the study of biological sciences as never before [100]. Technologies using NGS have been developed that measure some characteristics of a whole family of cellular

molecules, such as genes, proteins, or metabolites, and have been named by appending the term "-omics. Multiomics refers to the approach where the data sets of different omics groups are combined during sample analysis to allow scientists to read the more complex and transient molecular changes that underpin the course of disease progression and response to treatment and to select the right drug target for desired results [101]. It forms the basis of precision medicine in general and is at the core of the development of precision oncology. The breakthroughs in high-throughput technologies in recent years have led to the rapid accumulation of large-scale omics cancer data and brought an evolving concept of "big data" in cancer the analysis of which requires huge computational resources with the potential to bring new insights into critical problems. The combination of big data, bioinformatics, and artificial intelligence is thought to lead to notable advances in translational research in cancer [102,103].

Artificial intelligence: Artificial intelligence (AI) encompasses multiple technologies with the common aim of computationally simulating human intelligence to solve complex problems. It is based on the principle that human intelligence can be defined in a way that a machine can easily mimic and execute tasks from the simpler to far more complex ones successfully [104]. Broadly referred to as computer programming enabled to perform specific tasks, the term may be applied to any machine that displays traits associated with human understanding, such as learning and problem-solving. In regular programming, data are processed with well-defined rules to bring solutions, whereas AI relies on the learning process to devise rules for the efficient processing of data to yield smart results. AI and related technologies have increasingly been prevalent in finance, security, and society, and are now being applied to healthcare as well [105]. It has been widely applied in precision medicine-based healthcare practices and is found to be greatly useful in medical oncology practice. Many artificial intelligence algorithms have been developed and applied in cancer research in recent years. An exact understanding of the structure of a protein remains the first step to knowing all about its roles in cancer progression and therapeutic drugs are also designed using structural information of the target proteins where AI-based techniques can be used for the solutions. The advances in NGS have led multi-omics data on cancer to become available to researchers providing them with opportunities to explore the genetic risk and reveal underlying cancer mechanisms to help early diagnosis, exact prognosis, and the discovery, design, and application of specific targeted drugs against cancer. Thus, integrating multiomics-related studies with artificial intelligence is the need of the hour and is likely to serve the purpose well with time. Taking the help of large datasets from multi-omics platforms, imaging techniques, and biomarkers found and mined by artificial intelligence algorithms, oncologists can diagnose cancer early at its onset and help direct treatment options for individualized cancer therapy for anticipated results. Thus, the advances in AI present an opportunity to perfect the methods of diagnosis and prognosis and develop strategies for personalized treatment using large datasets, and future developments in AI technologies are most likely to help many more problems in this direction to be resolved swiftly. In this way, AI is thought to be the future of precision oncology towards the prevention, detection, risk assessment, and treatment of cancer [106,107].

Machine learning: Machine learning (ML) is a branch of artificial intelligence that aims to develop computational systems with advanced analytical capabilities. It is concerned with the development of domain-specific programming algorithms with the ability to learn from data to solve a class of problems [108]. Therefore, the most common and purposeful application of traditional machine learning in healthcare seems to be in the area of precision medicine and is most suited for the data-driven identification of cancer states and designing treatment options that is crucial to precision oncology-based cancer treatment(Fig. 2) [109].

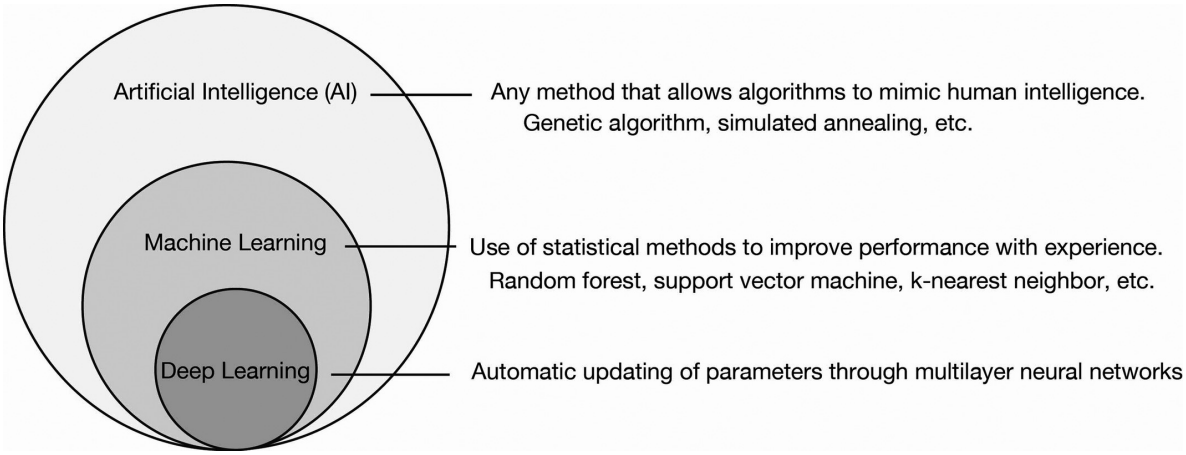

Figure 2. Artificial Intelligence (AI), machine learning and deep learning.

AI refers to a broad range of computational methods that mimic human intelligence. Machine learning is a sub-branch of AI that relies on statistical methods to detect hidden patterns within a dataset. Deep learning is a sub-branch of machine learning that harnesses the power of multilayered networks. ((Shimizu and Nakayama [109])

Deep Learning: Deep learning (DL) is a sub-branch of ML that uses statistics and predictive modeling to extract patterns from large data sets to precisely predict a result. A variety of data have been appearing in modern biomedical research, including electronic health records, imaging, multiomics-based reports, sensor data, etc., which are complex, heterogeneous, and poorly defined and need to be mined efficiently to bring correct results. To meet this end, DL uses a machine learning program called artificial neural networks modeled on the human brain that forms a diverse family of computational models consisting of many deep data processing layers for automated feature extraction and pattern recognition in large datasets to efficiently answer the problems. The human brain consists of neurons arranged together as a network of nerves processing several pieces of information received from many different sources to translate into a particular reflex action. In DL, the same concept of a network of neurons is imitated on a

machine learning platform to emulate human understanding to bring perfect solutions. The neurons are created artificially in a computer system and the data processing layers work together to create an artificial neural network where the working of an artificial neuron could be taken as like that of a neuron present in the brain. Thus, DL is designed to use a complex set of algorithms enabling it to process unstructured data such as documents, images, and text to find efficient results [110].

The effective development of drugs for the treatment of cancer is a major problem in cancer research and DL provides immense help to researchers in this regard. Changes in the genetic composition of tumors translate into structural changes in cellular subsystems that require to be integrated into drug design to predict therapy response and concurrently learn about the mechanism underlying a particular drug response. A proper understanding of the mechanism of drug action can lead researchers to understand the importance of the different signaling pathways, including some new and uncommon pathways associated with tumors to help develop novel drugs for the therapeutic targeting of diverse forms of cancer. Drug combinations targeting multiple pathways are thought to be the answers to the incidences of drug resistance in cancer therapy where computational models could be used to find solutions. Occupation-oriented pharmacology is the dominant paradigm of drug discovery for the treatment of cancer. It relies on the use of inhibitors that occupy the functional binding site of a protein and can disrupt protein interactions and their functions. New advances in AI have enabled researchers to develop DL-based models to predict tumor cell response to synergistic drug combinations to be employed effectively in precision oncology [111]. Researchers continue to discover proteins that may be the key drivers of cancer and need a fuller understanding of the 3D shape, or structure, of these proteins to decide their exact functions in the cell. A recent development in the DL system is AlphaFold, which is being used to predict the structures of different proteins, and the tool has already determined the structures of around 200 million proteins, from almost every known organism on the planet [112,113]. This revolutionary new development in DL is going to be of great use in understanding the roles of suspected proteins in cancer development and in anticancer drug design. A newly developed DL system called PocketMiner is an efficient tool for predicting the locations of bonding sites on proteins. Proteins exist in a state of dynamic equilibrium with their different conformational structures, including experimentally determined structures that may not have targetable pockets. PocketMiner uses graph neural networks to find hidden areas or pocket formation from a single protein and is thought to be 1,000 times faster than existing methods of finding binding sites on proteins. This technology has made researchers understand that around half of proteins that were earlier considered undruggable might have ‘cryptic pockets’ that could be targeted successfully by anticancer agents. The AI-based system finds multiple uses in cancer management like the prediction of treatment response, estimation of survival analysis, risk estimation, and treatment planning, and is becoming the central approach in precision oncology [114].

6. The Cancer Genome Atlas (TCGA) Program and Related Cancer Initiatives

The National Institutes of Health (NIH), has taken the lead role in cancer research and is the largest funder of cancer research in the world. The National Cancer Institute (NCI), the leading cancer research enterprise is part of NIH and is committed to exploiting basic cancer research into efficacious cancer therapies. In this regard, the Cancer Genome Atlas (TCGA) Program is the landmark cancer genomics program initiated by the NIH, and has contributed immensely to realizing the importance of genomics in cancer research and treatment in the last decade and has begun to change the way the disease has been treated in the clinic. It is a joint effort by the NCI and the National Human Genome Research Institute (NHGRI), also a part of NIH, that began working in 2006 and has brought together researchers from diverse disciplines and multiple institutions to work on the characterization and analysis of cancer at the molecular level for a complete understanding of the genetic basis of human cancer [115,116]. The TCGA Research Network has profiled and analyzed a large number of human tumors to discover molecular aberrations at the DNA, RNA, protein, and epigenetic levels and thereby provided reliable diagnostic and prognostic biomarkers for different cancer types since then.

As our understanding of biochemical signaling has grown and the range of possible treatment options expands, it is essentially required to have biomarkers to accurately predict how patients will respond to specific treatment regimens, which is a vital need for precision oncology. Circulating DNA and extracellular vesicles are abundantly released by cancer cells that can be obtained by liquid biopsies and are excellent sources of a variety of molecular markers. Molecular profiling of these markers can be used to gain crucial information regarding cancer development including tumor heterogeneity. Genomic analysis of tumors has certainly become the mainstay in cancer care, and applying it to oncological practice needed a clinical support system that could swiftly predict the clinical implications associated with specific mutations. It led to the development of OncoKB, an expert-guided precision oncology knowledge base developed at Memorial Sloan Kettering Cancer Center(MSKCC), in New York which is among the first to have been recognized as the NCI-Designated Cancer Centers as part of the national cancer program of the federal govt. that started in 1971. OncoKB's curated list of cancer genes with detailed comments is available on its public web resource (http://oncokb.org, which has been incorporated into the cBioPortal for Cancer Genomics (https://www.cbioportal.org/) to provide visualization, analysis, and download of large-scale cancer genomics data sets allowing researchers to gain a thorough understanding of the genomic alterations involved in cancer development. The public cBioPortal site is hosted by the Center for Molecular Oncology at MSKCC and maintained by a multi-institutional team consisting of MSK and others. A vast number of mutations contribute to cancer and the use of next-generation sequencing-based approaches in clinical diagnostics is leading to a tremendous increase in data with an enormous number of variants of uncertain significance requiring further analysis and validation by means of precise techniques to fulfill the purpose involved with the big-data studies satisfactorily [117,118].

Predicting the effects of mutations using in silico tools has become a frequently used approach, but these data cannot be analyzed by simply using traditional tools and techniques that have been available to scientists, but even more advanced computational methods are supposed to be coming to help gain insights into the molecular basis of the origin and evolution of cancer.

To meet this end, a cancer hallmark framework through modeling genome sequencing data has been proposed for the systematic identification of representative driver networks to convincingly predict cancer evolution and associated clinical phenotypes [119,120]. It is based on the consideration that possible observable combinations of those mutations must converge to a few hallmark signaling pathways and associated networks responsible for cancer development. In this way, the proposed framework aims to analyze the available data to explain how the different gene mutations in different patients bring the same downstream effects on the protein networks, ultimately leading to the common path of cancer progression and to direct treatment planning accordingly. In this regard, researchers funded by the NIH have separately completed a detailed genomic analysis of data available through the TCGA program known as the 'PanCancer Atlas', providing an independent view of the oncogenic processes that contribute to the development of human cancer [121,122]. Analyzing over 11,000 tumors from the most prevalent forms of cancer, and focusing on how germline and somatic variants collaborate in cancer progression, the Pan-Cancer Atlas has so far provided a most comprehensive and in-depth understanding of how and why tumors arise in humans [123,124]. Considering the genes and pathways affecting different cancer types and individual tumors vary considerably, a complete understanding of these alterations becomes essential to identify vulnerabilities and discover precise therapeutic solutions. A comprehensive analysis of tumors based on their genomic studies must reveal the alterations in signaling pathways indicating patterns of vulnerabilities and the means to identify prospective targets for the development of personalized treatments and new combination therapies. Analyzing tumors profiled by TCGA to understand mutation patterns in selected signaling pathways reveals that most if not all, tumors possess at least one driver alteration from these few pathways potentially targetable by drugs and some of them with multiple targetable alterations, providing opportunities for combination therapy (Fig. 3) [125].

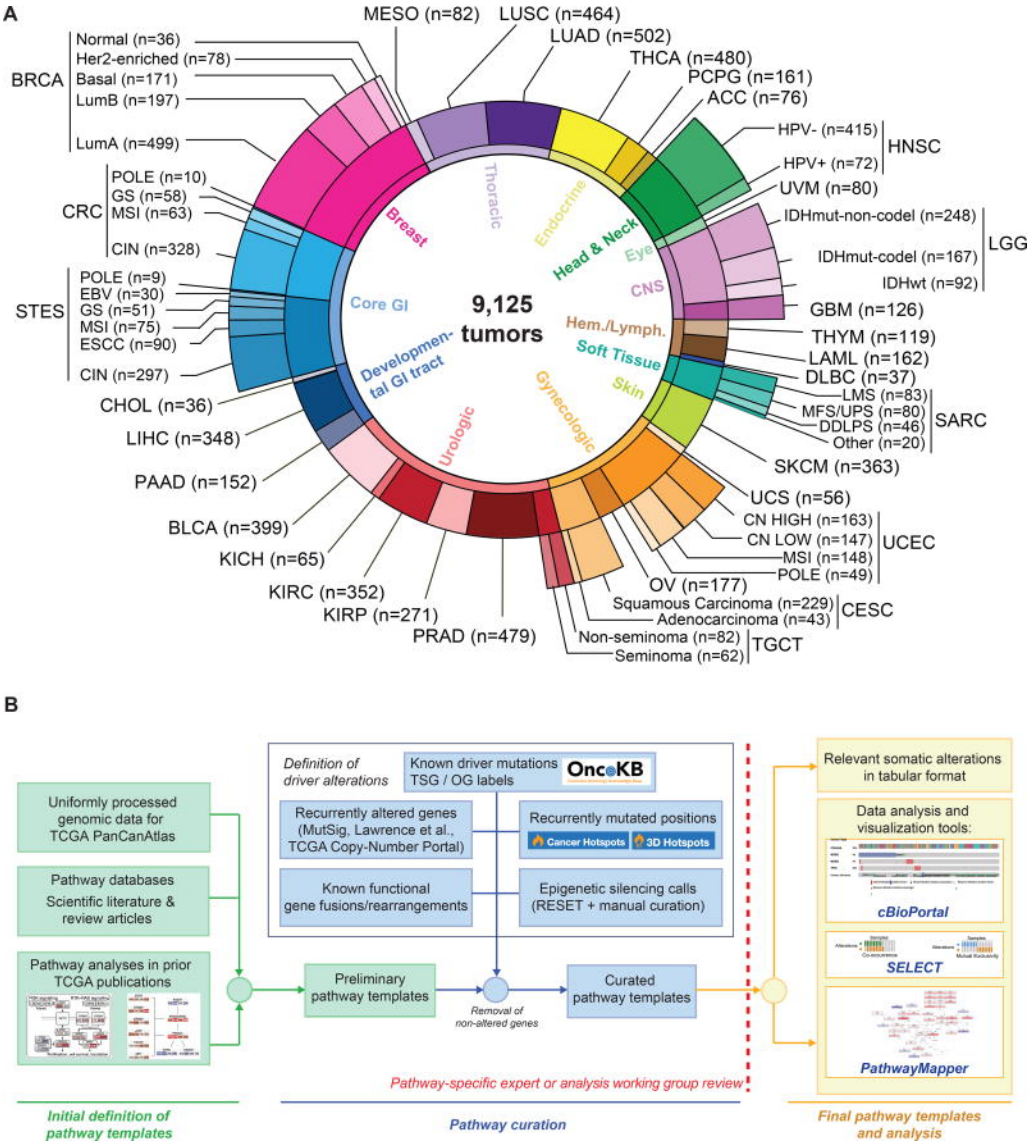

Figure 3. TCGA PanCanAtlas Pathways data set and workflow

(A) Distribution of cancer types in the cohort, including molecular subtypes analyzed. (B) Workflow for pathway curation and analysis.

Genes were curated from previous TCGA efforts and the scientific literature. Only genes with evidence for statistically recurrent or known driver alterations in the uniformly processed TCGA PanCanAtlas data set were included in the curated pathway templates. TCGA disease codes and abbreviations: AML: Acute Myeloid Leukemia; ACC:Adrenocortical carcinoma; BRCA:Breast cancer; CESC:Cervical cancer; KICH:Chromophobe renal cell carcinoma; KIRC:Clear cell kidney carcinoma; CRC: colorectal adenocarcinoma; SKCM:Cutaneous melanoma; DLBC:Diffuse large B-cell lymphoma; GBM:Glioblastoma multiforme; HNSC:Head and neck squamous cell carcinoma; LIHC:Liver hepatocellular carcinoma; LGG:Lower Grade Glioma;

LUAD:Lung adenocarcinoma; LUSC:Lung squamous cell carcinoma; OV:Ovarian serous cystadenocarcinoma; KIRP:Papillary kidney carcinoma; THCA:Papillary thyroid carcinoma; STAD:Stomach adenocarcinoma; PRAD:Prostate adenocarcinoma; BLCA:Urothelial bladder cancer; UCS:Uterine carcinosarcoma; UCEC:Uterine corpus endometrial carcinoma; ESCA:Esophageal cancer; PCPG:Pheochromocytoma & Paraganglioma; PAAD:Pancreatic ductal adenocarcinoma; MESO:Mesothelioma; UVM:Uveal melanoma; SARC:Sarcoma; CHOL:Cholangiocarcinoma; TGCT:Testicular germ cell cancer; THYM:Thymoma; STES:Stomach and esophageal cancer; EBV:Epstein-Barr Virus; HPV:Human Papillomavirus; DDLPS:Dedifferentiated liposarcoma; LMS:Leiomyosarcoma; MFS/UPS:Myxofibrosarcoma/Undifferentiated Pleomorphic Sarcoma; ESCC:Esophageal Squamous Cell Carcinoma; GS:Genomically Stable; CIN:Chromosomal Instability; MSI:Microsatellite Instability. (Sanchez-Vega et al. [125])

The synchronizing view of oncogenic processes based on PanCancer Atlas analyses tries to elucidate the possible consequences of genome alterations on the different signaling pathways involved with human cancers, also reflecting on their influence on tumor microenvironment and immune cell responses, to provide new insights into the development of new forms of targeted drugs and immunotherapies. Further, the stemness features extracted from transcriptomic and epigenetic data from TCGA tumors also present novel biological and clinical insight for cancer stem cell-targeted therapies [126]. The challenge to identify the relevant genes and signaling molecules for different cancer types using cutting-edge technologies will remain an essential part of cancer research and is most likely to help vulnerable people receive precisely designed treatment for cancer. As a singular and unified point of reference, the Pan-Cancer Atlas can be taken as a vital resource to explore the influence of mutation on cancer cell signaling for the development of new treatments in the pursuit of precision oncology.

Besides that, the Cancer Cell Mapping Initiative (CCMI), originally founded in 2015 by researchers from the University of California, San Francisco, and the University of California, San Diego, has been dedicated to generating complete maps of major protein-based genetic interactions underlying cancer progression and attempts to develop computational methods using these maps to identify novel drug targets and patient groups with common outcomes. It has been successful in charting how hundreds of genetic mutations involved in breast cancer and cancers of the head and neck affect the activity of certain proteins that ultimately lead to cancer progression. As there exists a vast amount of sequence data from many different cancer types, efforts are being made to extract mechanistic insight from the available information, and an integrated computational and experimental strategy will have to be employed to help place these alterations into the context of the higher order signaling mechanisms in cancer cells [127]. This is the defined goal of the CCMI and is likely to create a resource that will be used for cancer genome interpretation, allowing the identification of key complexes and pathways to be studied in greater mechanistic detail to gain insight into the biology underlying different types and stages of cancer [128].

Furthermore, the Broad Institute of MIT and Harvard's Cancer Dependency Map (DepMap) initiative, an academic-industrial partnership program formally announced in 2019, is devoting its research to accelerate precision cancer medicine by creating a comprehensive map of tumor vulnerabilities and identifying key biomarkers of cancer. DeepMap initiative is focused on screening thousands of cancer cell lines by the use of RNA interference (RNAi) and CRISPR-Cas9 loss-of-function gene-editing strategies to identify genes whose expression may have been found to be essential for cancer cell development. CRISPR-Cas9 gene editing is an efficient method for genome modification for nearly all cell types. CRISPR editing and screening have emerged as powerful tools for investigating almost all aspects of cellular behaviors and have greatly impacted our understanding of cancer biology and continue to contribute to new discoveries.

A related project called, Cancer Cell Line Encyclopedia (CCLE) project was initiated as a collaboration between the Broad Institute, and the Novartis Institutes for Biomedical Research in 2008 aimed at large-scale genetic characterization of thousands of cancer cell lines to link characteristic genetic alterations with distinct pharmacologic vulnerabilities, and to translate cell line integrative genomics into cancer patient stratification. By access to critical genomic data such as gene mutation, copy number variation, gene expression, and methylation profiles from the CCLE, scientists can now predict novel synthetic lethality and identify new molecular markers whose selective targeting can control cells that possess specific genetic mutations. In this way, the initiative has provided a rigorous foundation on which to study genetic variants, and candidate targets, design anticancer agents and identify new markers-driven cancer diagnoses and therapies [129]. By all such means, the field of cancer genomics can be seen as constantly evolving to help cancer-causing changes be identified to gain a better understanding of the molecular basis of cancer growth, metastasis, and drug resistance, and translate cancer research into new cancer therapeutics.

7. Single-cell Technology to Unmask Tumor Heterogeneity

The tumor is an abnormal mass of tissue that appears due to unregulated growth and division of cells which successfully avoid senescence. A tumor is benign till it is limited to its original position and becomes malignant or cancerous when capable to grow and spread to other parts of the body. Tumor heterogeneity is a hallmark property of cancer development and broadly refers to the differences between tumors of the same type in different patients, the differences between a primary and a secondary tumor, and the differences in genomic and phenotypic profiles displayed by cells within a single tumor. Tumors represent a heterogeneous mass of distinctly differentiated cells that include connective tissue cells, immune cells, cancer stem cells, and vasculature, and these subpopulations of cells can be further distinguished by a variety of features impacting their phenotype that generally involve genetic alterations. Heterogeneity within a single tumor, referred to as genetic intratumoral heterogeneity (ITH), has been documented across most cancers as an outcome of genome instability and clonal evolution [130,131]. Tumor heterogeneity appears to be a critical phenomenon in the history of individual cancers, as its translational significance may reflect on tumor progression, disease recurrence, treatment response, and resistance [132]. Recent investigations on drug resistance and tumor

heterogeneity have confirmed the clonal organization of tumors as the underlying basis for drug resistance, thus indicating the need to fully understand the structure and dynamics of ITH to develop advanced treatment strategies for cancer [133,134]. More precisely the cellular composition of a tumor is known, the underlying mechanism of disease progression is understood, and/or molecules and pathways involved in the process are identified, and more specific therapeutic strategies could be devised to get the desired result. It is the stated goal of precision oncology and the emergence of single-cell technologies for biological analysis has become the crucial tool in this regard as they can carry out accurate single-cell measurements to provide a clear picture of tumor heterogeneity and reveal how structural changes in chromosomes can lead to the complex biological processes involved with carcinogenesis [135,136]. The rapid progress in the development of NGS in recent years has provided many valuable insights into cancer genomics, and NGS-based technologies for genomics, transcriptomics, and epigenomics have enabled laboratories to carry out related single-cell measurements efficiently. Single-cell genomics now facilitates the simultaneous measurement of thousands of genes in thousands of 'single' cells from a single specimen, allowing researchers to compare genomes of individual cells to determine the mutational profile of the affected cells to better understand the molecular consequences of different variants present in the tumor. The single-cell template strand sequencing (Strand-seq), a special single-cell sequencing technology now enables independent and efficient analysis of the two parental DNA strands resolving homologous chromosomes similar in shape and structure but not identical within single cells which is crucial to identifying somatic SVs, understanding genomic rearrangements and unmask tissue heterogeneity. Moreover, single-cell sequencing can also be combined with CRISPR knockout screening that exploits the efficiency and flexibility of CRISPR–Cas9 genome editing to enable large-scale studies regarding how genetic modification can affect cell behavior or gain insights into a specific physiological condition required to fully understand the underlying cellular events [137]. Combining the CRISPR-Cas system with single-cell techniques for studying gene functions with the concurrent use of single-cell resolution techniques, such as flow cytometry, microfluidics, manual cell picking, or micromanipulation, can be exploited in cancer research in many ways, including identifying novel drug targets, studying unknown mechanisms of action of drugs and designing treatment regimen [138].

The importance of epigenetic reprogramming in cancer is well understood, as evidenced by the fact that chromatin regulators are often mutated in the affected cells and the widespread epigenetic, changes throughout cancer genomes can be identified and linked to the activities of different known oncogenes and tumor suppressor genes. Abnormal epigenetic changes are usually influenced by aging, viruses, and dietary and environmental factors that frequently contribute to cancer development. The interrelationship between genetic and epigenetic changes needs to be further examined for the discovery of screening markers to optimize pathways of diagnosis and prognosis and to develop strategies for individualized cancer treatment [139]. For example, DNA methylation is known to be associated with cell differentiation, aging, and diseases including cancer. A considerable amount of understanding exists regarding tissue-specific DNA methylation patterns, but it would reveal much less information about person-specific DNA methylation causing cancer. Thus, the premise of single-cell epigenome profiling holds great possibilities for deciphering the cellular states and characterizing tumor heterogeneity

with an option for therapeutic interventions to pin specific mutations having profound effects on epigenetic pathways. The inclusion of epigenetics in clinical practice would require identifying epigenetic signatures that mediate distinct phenotypical changes of clinical relevance, such as mesenchymal transition, stems, dormancy, and quiescence or therapy resistance.

Single-cell sequencing technologies have largely been successful in leading scientists to understand the cell types and features associated with the tumor yet, the spatial context of this development is essential to better understand how cells organize and communicate across the tissue to fully unlock the repertoire of tumor heterogeneity. It requires a clear understanding of which cells are present, where they are situated in tissue, their biomarker expression patterns, and how they organize and interact to influence the tissue microenvironment. This is an essential part of spatial biology and adds another dimension to single-cell analysis to unmask tumor heterogeneity [140,141]. Spatial biology simply tries to combine whole-slide imaging (WSI), commonly referred to as 'virtual microscopy', at single-cell resolution to visualize and quantitate biomarker expression and reveal how cells interact and organize across the entire tissue landscape. This technique can support research for early biomarker discovery to late-stage translational research and therapy development. The latest development in this direction is spatial transcriptomics which has enabled researchers to visualize and quantify RNA down to the subcellular level and simultaneously compare gene expression in situ. It is a groundbreaking molecular profiling method that exploits multi-omics technologies allowing researchers to measure all the gene activity in a tissue sample and assay the genetic information of single cells within their native tissue environment (Fig. 4) [142,143].

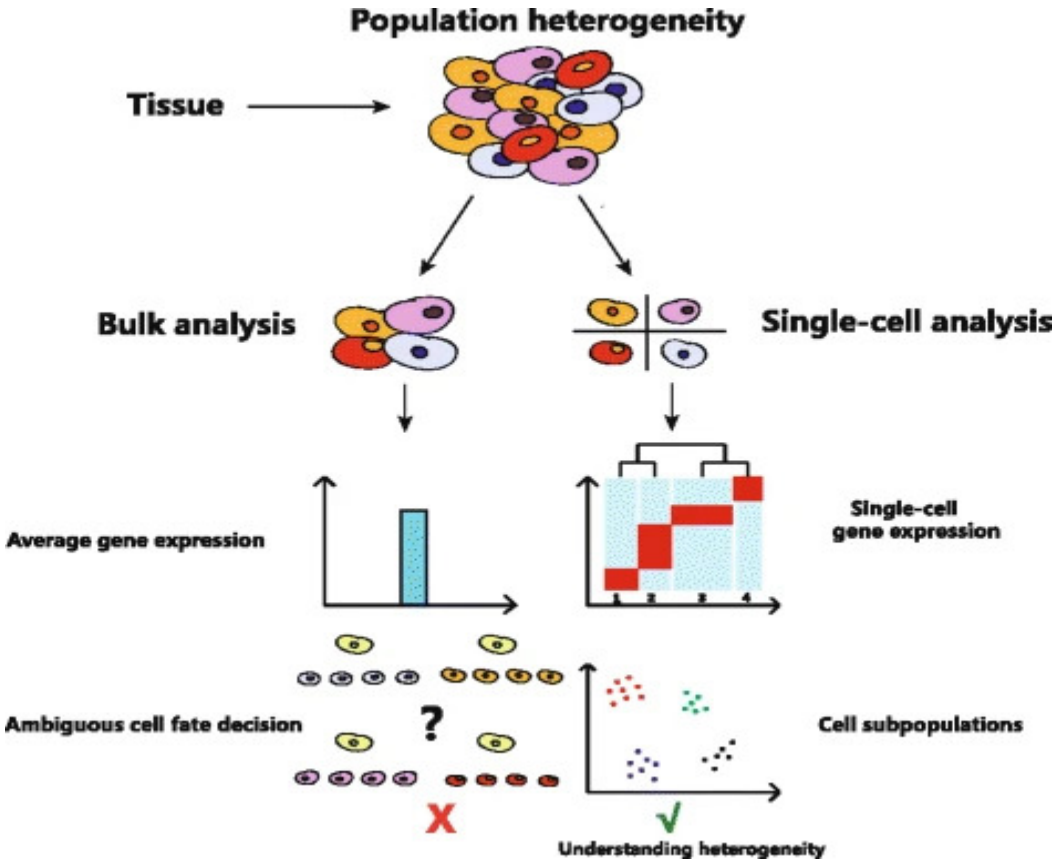

Figure. 4. Single Cell analysis reveals heterogeneity.

Traditional experiments on bulk samples mask the heterogeneity between individual cells. In order to understand the heterogeneity in complex tissue, analysis performed on the single-cell resolution has been used to unveil cell subpopulations and their different gene expressions. (Ye, F., Huang, W. & Guo, G. [143])

The growing ability to demonstrate the role and function of distinct cell types present in the tissue has paved the way for a new understanding of the tissue-specific cellular pathways and interactions that lead to cancer development. The precise molecular analysis of cancer cells based on single-cell technologies now aims to present an accurate picture of the most up-to-date development in the tumor microenvironment and detect changes in the genes and proteins responsible for alterations in cellular processes to better understand the prognosis and pathways of cancer progression and metastasis. New advances in multi-omics techniques powered by AI h now enable researchers to integrate genomic, transcriptomic, epigenomic, and other related data to gain the most accurate information on the activity state of individual genes and proteins to reveal the novel cancer drivers and genetic vulnerabilities for prevention and cure [144,145]. The emerging field of single-cell technology thus provides an unprecedented insight into the complex genetic and epigenetic heterogeneity within individual tumors for advanced precision oncology-based treatment and is likely to streamline future research directions.

8. Precision Oncology and Targeted Drug Therapy of Cancer

Targeted drug therapy is the form of cancer therapeutics that targets specific genes and proteins of cancer cell reprogramming, the signaling molecules, and others in the tumor microenvironment that contribute to cancer development. This contrast with the single-target approach employed in chemotherapy to primarily target and kill actively dividing cancer cells with serious side effects and so the emergence of targeted drug therapy can be seen as a natural outcome of decades of studies on molecular reprogramming of affected cells in different cancers. Some noticeable breakthroughs have come in certain cancers as a renewed understanding of the signaling pathways underlying cancer development has led to the development of specific targeted drugs that have really revolutionized the treatment of cancer. This form of cancer therapy can be thoroughly optimized by means of precision oncology that enables taking advantage of genomic profiling of patient samples for insights into the mutational changes underlying pathway alterations responsible for cancer initiation and progression (Fig. 5.) [146]. Precision oncology-based treatment strategies pledge to diagnose and prognosis the disease by the use of specific molecular-level information about a patient's tumor to treat the ill with desired results. In this way, it qualifies to be a theranostic approach to cancer treatment satisfactorily. The term, theranostics literally means a combination of diagnosis and therapeutics and refers to the pairing of diagnostic methods such as the proteogenomics approach to biomarker discovery, with appropriate therapeutic interventions for effective management of the disease. Theranostics focuses on patient-centered care and thus provides a transition from conventional to personalized medicine for targeted, efficient and safe pharmacotherapy relevantly applicable in precision oncology [147,148].

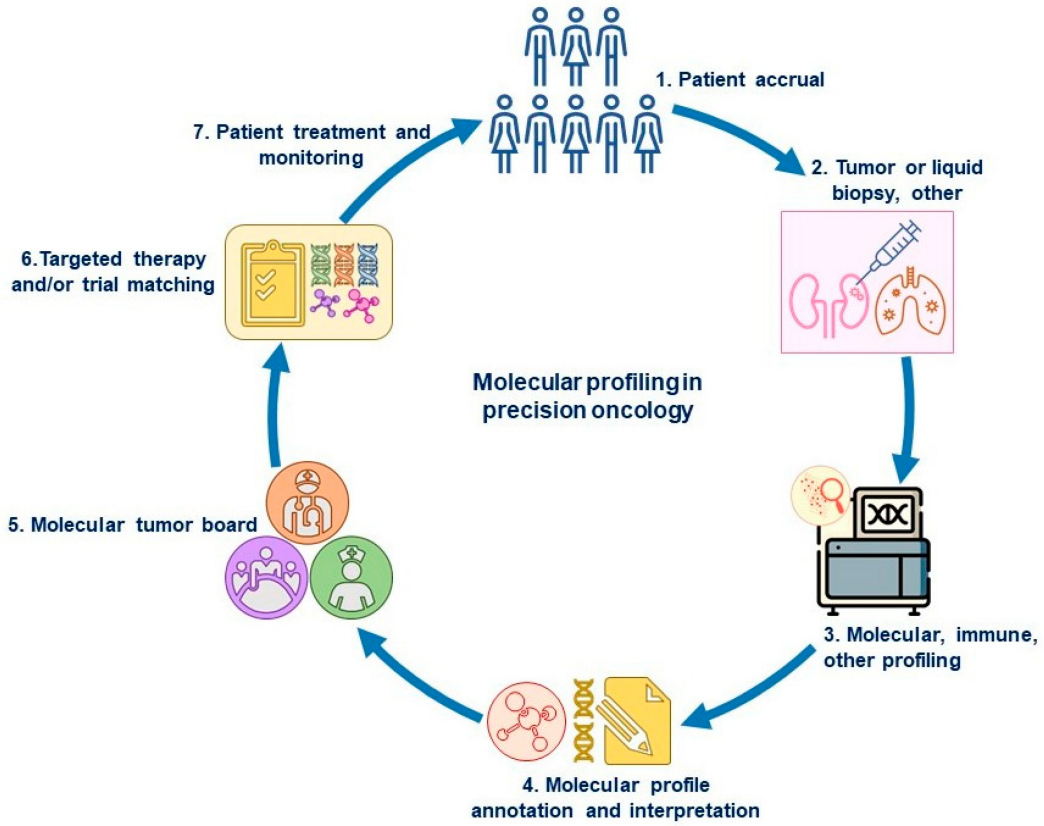

Figure 5. Overview of molecular profiling in precision oncology.

In the screening phase of a biomarker-driven trial, patients (1) undergo a tumor biopsy or blood draw (liquid biopsy) (2) that is used for tumor molecular profiling (3) to determine the drivers of carcinogenesis (genomic or protein level), if any (4). The molecular profile report is often discussed at a molecular tumor board (5) for the interpretation of tumor alterations and for matching with a targeted therapy or clinical trial (6). The patient is then treated with the assigned therapy (FDA-approved or investigational drug after screening for clinical trial) and monitored for anti-tumor effects and toxicity (7). If the disease progresses, the next treatment can again be selected from a new round of tumor or blood analyses to identify evolving biomarkers. (Song I-W. et. al. [14])

The anticancer drugs employed in targeted therapy are mainly designed to target selected molecules directly involved with cancer cell signaling or those in the tumor microenvironment essentially required for tumor growth and cancer manifestation [149]. They are broadly classified as monoclonal antibodies (mAbs) and small-molecule drugs. The small molecule drugs are designed to directly approach the cell membrane and interact with targets inside the cell and usually inhibit the enzymatic activity of target proteins such as the proteasome complex, tyrosine kinases, or cyclin-dependent kinases. A type of targeted therapy, called tumor agnostic therapy uses drugs and other substances to target cancer-specific genetic changes or markers to treat the problem without requiring focusing on the cancer type or where the disease may have started in

the body. Therapeutic targeting of DNA damage response (DDR) signaling is another emerging field of targeted cancer therapy that exploits the options of targeting cancer cells with exceeding deficiencies in homologous recombination (HR) signaling which includes BRCA-mutated cancers. Poly(ADP-ribose) polymerase (PARP)and Inhibitors of poly(ADP-ribose)glycohydrolase (PARG) are the most important DNA repair enzymes that work synergistically in many different DDR pathways, including base excision repair, non-homologous end joining, nucleotide excision repair, homologous recombination (HR), maintenance of replication fork stability and nucleosome remodeling. These enzymes are essentially involved in the process of single-strand break (SSB) repair whose failure leads to the conversion of SSB into double-strand breaks(DSB) requiring repair by HR to prevent cell death. Such lethal genetic interactions, known as synthetic lethality, can be exploited to develop anticancer therapeutics and the enzymes of DDR signaling fit the needs satisfactorily. Overexpression of these proteins has been witnessed in different cancer types such as pancreatic, prostate, breast, ovarian, and oral cancers, providing scope for inhibiting PARP activity as an effective therapeutic strategy. PARP and PARG inhibitors have shown improved results in different forms of tumors, and are under investigation for being used in combination therapy safely. [150,151].

The therapeutic mAbs are modified monoclonal antibodies that target antigens found on the cancer cells or cytotoxic T-lymphocytes in targeted cancer therapy. mAbs are important in cancer treatment as they may be exploited for potentiating the natural immune system by successfully mutualizing changes in immunogenicity of the affected cells during oncogenesis. The mAbs may be designed to coat the cancer cells to be opsonized and destroyed by the immune cell, block the activity of different cancer-specific antigens called neoantigens, generated by cancer cells, or inhibit the activities of immune checkpoint proteins that promote immune evasion in cancer development [152,153]. Several immune checkpoint proteins are expressed by immune cells, such as T cells, and cancer cells capable of binding with other partner proteins to help cancer cells escape immune responses. Their activation limits vital immune cell activities like T-cell infiltration and other effector cell functions resulting in tumor formation. CTLA-4 is a checkpoint protein present on the T-cell surface that binds to another protein called B7, preventing T cells from killing other target cells, including cancer cells. Certain mAbs, also called anti-CTLA4 monoclonal antibodies, are used to block CTLA-4 and are widely used as immune checkpoint inhibitors in a variety of human cancers. Different forms of monoclonal antibody-based therapy have proven to be efficacious in cancer treatment and are becoming increasingly important tools in targeted cancer therapy [154,155]. Importantly, cancer cells express a number of protein antigens that can be recognized by cytotoxic T lymphocyte (CTL) T cells, thus providing means for CTL-mediated cancer therapy. Targeting transformed cells by CTL may be crucial to the prevention of both hematological and solid tumors and its roles are being explored in cancer immunotherapy. T-cell transfer therapy, also called adoptive immunotherapy or immune cell therapy is a new form of cancer treatment designed to exploit enhanced anti-tumor immune response of the tumor antigen-specific CTL found in the tumors, and has been tried against neoantigen-possessing cells effectively in recent times. Two types of T-cell transfer therapy, tumor-infiltrating lymphocytes or TIL therapy and CAR T-cell therapy are in use and both involve harvesting autologous T cells infiltrated into the tumor, growing large

numbers of these cells in vitro, and administering to the patient for desired results. CAR T-cell therapy is similar to TIL therapy except that the T cells are designed to express a type of protein known as CAR (CAR for chimeric antigen receptor) to target specific antigens expressed in cancer cells in the body. Although CAR T cells have significantly improved the landscape for hematological malignancies, it has shown limited results in solid tumors as the solid tumors present certain obvious barriers to adoptive T-cell transfer and localization, but a variety of approaches are being deliberated to overcome these barriers to increase its specificity, efficacy, and safety in the treatment of different malignancies. The development of CAR T cell therapy for solid tumors has been impaired also because most target antigens are common with normal cells. Research is being directed to develop a 'toolbox' of novel chimeric antigen receptors (CARs) that could be programmed to use logic to discriminate between normal and cancerous cells to prevent toxicity. This development could help to overcome some of the barriers to the application of CAR-T cells against solid tumors.

Furthermore, therapeutic cancer vaccines, such as the dendritic cell (DC) vaccine, peptide vaccine, and RNA-based neoantigen vaccines have been developed for inducing CTLs against the antigens in cancer patients and have shown encouraging results. These vaccines can be designed to induce the production of biomolecules capable of targeting the shared antigens expressed by cancer cells through appropriate immune response and, are being investigated for their efficacy as neoantigen-targeted individualized cancer vaccines. Dendritic cells (DCs) are specialized Antigen-presenting cells (APCs) known for their ability to present antigens to T cells, and this property of DCs has been exploited for their application in therapeutic cancer vaccines which have been shown to induce protective anti-tumor activities. [156,157]. Besides that, the transposable elements(REs) usually present in the tumor microenvironment are of potential therapeutic importance to create a pan-cancer vaccine that can aid in the prevention of a range of cancers. There is an enumerable number of regions with TEs involved with the expression of proteins in the cancer cell. Many of these are shared across tumors of the same type and could provide means for destruction by the immune system. The goal of immunotherapy remains to activate the individual's own immune system against the evolving tumors to successfully target the transformed cells with high selectivity, low toxicity, and appropriate results (Fig. 6). . Immunotherapy is the frontline area of cancer research, and precision oncology will be focused on immunotherapy accordingly.

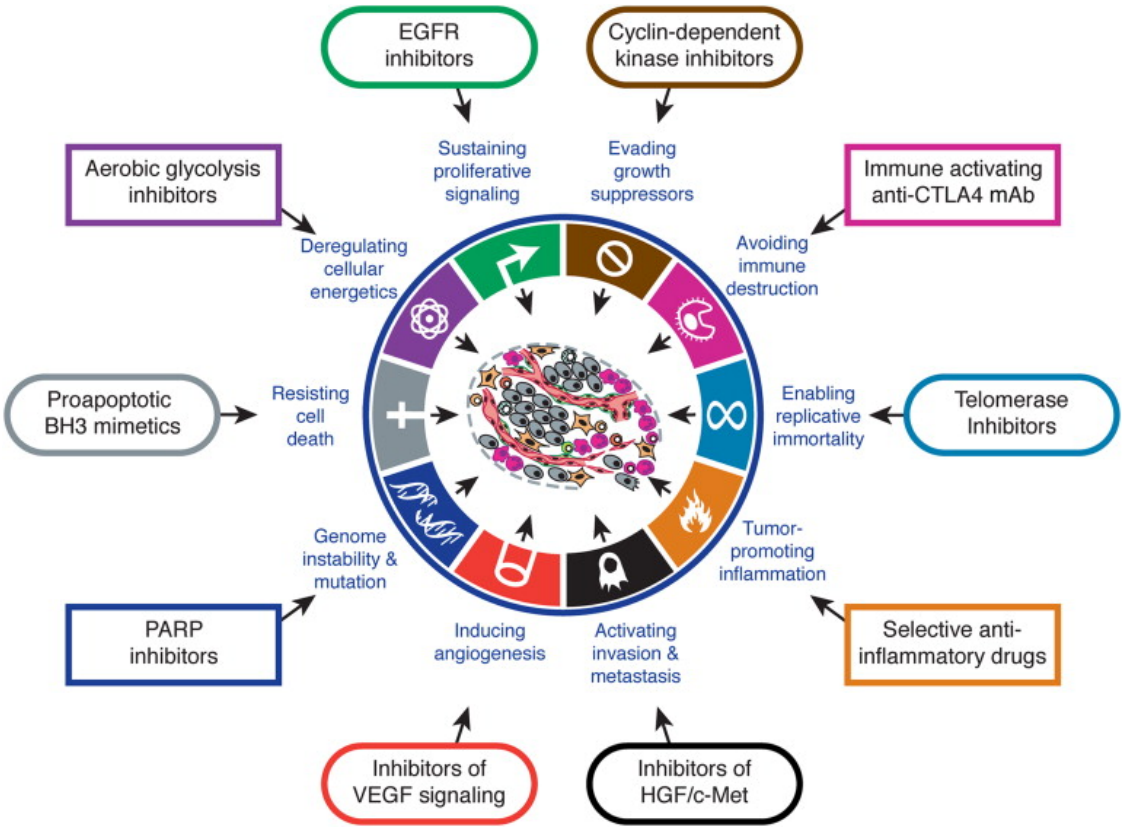

Figure 6. Therapeutic Targeting of the Hallmarks of Cancer

Therapeutic agents that can mitigate the acquired capabilities necessary for tumor growth and cancer progression are being developed for clinical use in treating different cancer types. These drugs are being developed in clinical trials to target each of the emerging neoplastic characteristics and the enabling hallmarks capabilities towards effective cancer therapy. The listed drugs are just illustrative examples; there is a deep pipeline of investigational drugs in development to target different signaling molecules that lead to the hallmark capabilities. (Hanahan and Wienberg [57]. With permission from Elsevier)

As discussed earlier, the major concern in cancer therapeutics remains proper drug delivery to the affected cells and tissue for the desired outcomes. Conventional chemotherapeutics may possess some serious side effects due to nonspecific targeting or inability to enter the core of the tumors, resulting in impaired treatment and a low survival rate. Researchers have been trying to address the issue with more specific methods of drug delivery including the use of nanotechnology in cancer therapeutics. Nanoparticles(NP)-based systems can be programmed to recognize cancerous cells for selective and accurate drug delivery with increased drug localization, cellular uptake, and bioavailability, avoiding encounters with healthy cells. The newly developed quantum dots (QDs) are the class of heterogeneous fluorescent nanoparticle, nanoscale materials with sizes ranging from 1 to 10 nm, with unique optical properties and

optimal surface chemical properties to link with targets such as antibodies, peptides, and other small molecule drugs. Named so as the photoluminescent nanostructures can have fully quantized energy states with superior fluorescence characteristics, they are thought to be more specific and effective methods with wide applications in the diagnostics and molecular targeting of the transformed cells. The NP-based drug delivery system, in general, displays better pharmacokinetic and pharmacodynamic profiles including efficient targeting of cancer cells and reduction in side effects, they are sure to serve the needs of precision oncology-based therapy satisfactorily [158,159]. Further, antibody-drug conjugates (ADC) are a fast-expanding therapeutic strategy designed to selectively deliver drugs to cancer cells. ADCs are monoclonal antibodies linked with small molecule cytotoxic drugs through a chemical linker capable to approach the cancer cells and attach to the specific tumor antigens on the cell surface for direct drug delivery sparing healthy cells in the surroundings. They are designed to exploit the features of antigen-antibody specificity for efficient drug delivery and are considered to be the magic bullets in targeted cancer therapy. In this way, precision oncology seems to be the best fit for strategizing effective means of targeted drug therapy by exploiting the genomic peculiarities of individuals or a cohort of patients for effective personalized cancer treatment (Table 2) [160]. It will remain dedicated to studying the genetic profile of cancer cells to gain a thorough understanding of the alterations in key signaling pathways and related molecular events during cancer progression, therapy resistance, and recurrence to help improve cancer therapy [161].

Table 2. List of FDA-approved Protein Kinase Inhibitors for cancer treatment

(Dupont CA. et al. [160])

Protein kinase inhibitor	Approval year	Indications	Primary targets
Abemaciclib	2017	Breast cancer	CDK4/6
Acalabrutinib	2017	Lymphoma	BTK
Afatinib	2013	Lung cancer	EGFR; ERBB2; ERBB4
Alectinib	2015	Lung cancer	ALK; RET
Avapritinib	2020	Gastrointestinal cancer	PDGFR; KIT
Axitinib	2012	Kidney cancer	VEGFR
Binimetinib	2018	Melanoma	MEK1/2
Bosutinib	2012	Leukemia	BCR-ABL

Brigatinib	2017	Lung cancer	ALK; EGFR
Cabozantinib	2012	Thyroid cancer; kidney cancer; hepatocellular carcinoma	VEGFR2; MET; RET
Capmatinib hydrochloride	2020	Lung cancer	MET
Ceritinib	2014	Lung cancer	ALK
Cobimetinib	2015	Melanoma	MEK1/2
Crizotinib	2011	Lung cancer	ALK; MET
Dabrafenib	2013	Melanoma; lung cancer; thyroid cancer	BRAF
Dacomitinib	2018	Lung cancer	EGFR
Dasatinib	2006	Leukemia	BCR-ABL
Encorafenib	2018	Melanoma; colorectal cancer	BRAF
Entrectinib	2019	Lung cancer; solid tumors	TRKA/B/C; ROS1
Erdafitinib	2019	Urothelial carcinoma	FGFR
Erlotinib hydrochloride	2004	Pancreatic cancer; lung cancer	EGFR
Everolimus	2009	Breast cancer; kidney cancer; neuroendocrine tumors	mTOR
Fedratinib	2019	Myelofibrosis	JAK2
Gefitinib	2003	Lung cancer	EGFR
Gilteritinib	2018	Leukemia	FLT3
Ibrutinib	2013	Lymphoma	BTK
Imatinib mesylate	2001	Leukemia; gastrointestinal cancer	BCR-ABL; KIT; PDGFR

Lapatinib ditosylate	2007	Breast cancer	EGFR; ERBB2
Larotrectinib	2018	Solid tumors	TRKA/B/C
Lenvatinib	2015	Thyroid cancer; kidney cancer; hepatocellular carcinoma; endometrial carcinoma	VEGFR; FGFR; PDGFRA; RET; KIT
Lorlatinib	2018	Lung cancer	ALK
Midostaurin	2017	Leukemia	FLT3
Neratinib	2017	Breast cancer	ERBB2
Nilotinib	2007	Leukemia	BCR-ABL
Osimertinib	2015	Lung cancer	EGFR T790M
Palbociclib	2015	Breast cancer	CDK4/6
Pazopanib hydrochloride	2009	Kidney cancer; soft tissue sarcoma	VEGFR; PDGFRA/B; KIT
Pemigatinib	2020	Cholangiocarcinoma	FGFR
Pexidartinib	2019	Tenosynovial giant cell tumor	CSF1R; KIT; FLT3
Ponatinib hydrochloride	2012	Leukemia	BCR-ABL
Pralsetinib	2020	Lung cancer	RET
Regorafenib	2012	Colorectal cancer; gastrointestinal cancer; hepatocellular carcinoma	VEGFR; RET; KIT; PDGFRA/B; FGFR1/2; RAF1; BRAF
Ribociclib	2017	Breast cancer	CDK4/6
Ripretinib	2020	Gastrointestinal cancer	KIT; PDGFRA
Ruxolitinib phosphate	2011	Myeloproliferative disorder	JAK1/2
Selpercatinib	2020	Lung cancer; thyroid cancer	RET
Selumetinib	2020	Neurofibroma	MEK1/2

sulfate			
Sorafenib tosylate	2005	Kidney cancer; hepatocellular carcinoma; thyroid cancer	BRAF; RAF1; VEGFR; PDGFRB; KIT; FLT3; RET
Sunitinib malate	2006	Gastrointestinal cancer; kidney cancer; pancreatic cancer	VEGFR; FLT3; RET; KIT; PDGFRA/B; CSF1R
Temsirolimus	2007	Kidney cancer	mTOR
Trametinib	2013	Melanoma; lung cancer; thyroid cancer	MEK1/2
Tucatinib	2020	Breast cancer	ERBB2
Vandetanib	2011	Thyroid cancer	EGFR; VEGFR2
Vemurafenib	2011	Melanoma; histiocytic sarcoma	BRAF
Zanubrutinib	2019	Lymphoma	BTK

The recent advances in cancer genomics and single-cell technologies have certainly made targeted therapy the accepted form of cancer treatment, and yet a huge amount of investment will be needed for future research, drug discovery, and diagnostics to fully unlock its potential and for their application in the management of cancer. Let us not forget that the socioeconomic burden of cancer remains high as the treatment options for most common cancers have been limited so far and is an indication for a renewed approach to expedite drug development to bring effective anticancer agents from bench to bedside in a cost-effective manner. The lack of understanding of the genetic heterogeneity of individual cancers has traditionally been limiting the search for efficacious agents for cancer treatment and missing a wide range of possibly suitable agents from other disease areas. The use of molecular characterization of different cancer types through cancer genomics can help resolve drug-related issues to a reasonable extent by repurposing the use of certain existing drugs as anticancer agents for a wide range of applications, and it will remain at the forefront of precision oncology [162,163]. Moreover, the move from tissue-based cancer-specific treatments to genome-based targeted treatments entails the reuse of anticancer drugs prescribed for one type of cancer to treat other cancer types as well. It is envisaged that, with the ever-greater understanding of cell signaling mechanisms and genetic alterations in carcinogenesis, considerable progress in cancer treatment will be realized in the near future. Considering that academia, industries, and civil society will be working in tandem to cater to the contemporary needs of the system, it is hoped that a wide range of people with cancer will benefit from this new development in cancer research in the future to benefit the system as a whole [164,165].

9. Conclusion

Precision oncology-based cancer therapeutics propose to develop treatments that target the specific molecular characteristics of an individual's tumor instead of targeting the common features of certain cancer for a cure. Considering the way, a thorough understanding of the genetic composition and heterogeneity of the individual's tumor is now becoming possible through single-cell technologies, it is poised to help individuals get the right treatment at the right time rather successfully without requiring them to go through more generalized treatment that would prove not very effective in the end. Further, cancer research has traditionally been focused on common cancers for obvious reasons leaving therapeutic options for less frequent tumor types largely limited, and such anomalies are likely to be addressed with the new development successfully. Besides that, precision medicine approaches to treat inherited diseases have been in use for directly targeting associated pathways and proteins, and such methods can be employed in the treatment of inherited cancers as well. In this way, precision oncology as the emerging field of cancer research that relies on identifying specific mutations in the cancer genome to selectively target the most specific pathways involved with disease progression is best suited to ensure accurate treatment for the disease. It appears to be the natural outcome of the cancer genome project, and, considering the level of support coming from multi-omics platforms, it looks destined to satisfy the intended purpose of the cancer initiative satisfactorily. The success of this form of treatment is sure to further strengthen our belief in the possibility of a proper cure for cancer and it needs to be accessible to a larger number of people with cancer towards the realization of the goals with time.

Declarations:

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Supplementary File 1: New FDA-Approved Oncology Drugs (2021–2022) (https://ascopost.com/issues/june-3-2022-narratives-special-issue/new-fda-approved-oncology-drugs-2021-2022/#.ZDUJRrQ2lAE.)

Supplementary File 2: Ongoing/Cancer Accelerated Approvals (https://www.fda.gov/drugs/resources-information-approved-drugs/ongoing-cancer-accelerated-approvals)