Review Article

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The hallmarks of cancer and their therapeutic targeting in current use and clinical trials

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Abstract:

Cancer represents one of the most up to date issues worldwide because of the increasing number of affected people and the impact of it on the families and health system. It is one of the new challenges that face scientists and health worker and for many years lots of research and trials were trying to help in fighting this killer. The main aim of this review is to get a general look at the new understanding of cancer pathways and possible causes of resistance and their application in trails and clinical works, this piece of work aims to highlight the importance of pathophysiology of cancer in producing an effective treatment through targeting them. This review depended mainly on reviewing articles in the PubMed and Google Scholar, through writing (The hallmark of cancer, Hanahan and Weinberg) in the PubMed, around 14 articles had been emerged and only articles produced by the same authors in the years 2001 and 2011 had been selected as they were talking about the hallmark of cancer and resistance in details. Then, each pathway was followed as we searched according to a specific pathway and its targeted therapy in the PubMed and Google Scholar. Around 60 articles and trials had proved that targeting these pathways at different levels and even trying to stop these pathways with different targets can help to control cancer, and the new studies showed very promising results and they opened the door for future studies. For long time it was believed that cancer cells share six characteristic between them to develop and growth, however the same researchers who developed the initial hallmark of cancer had added new hallmarks which are : (1) abnormal metabolic pathways, (2) evading the immune system and two enabling characteristics: (1) genome instability, and (2) inflammation. Targeting these pathways has improved survival dramatically in most of cancers.

Keywords:

Cancer, hallmark, targeted therapy

Introduction

Cancer was and continues to be one of the challenges that face scientists around the globe. Hundreds, if not thousands, of theories have tried to answer and explain the strange behavior and nature of cancer cells, or at least to understand the underlying mechanism of its occurrence and progression. In 2000, Hanahan and Weinberg published an article, and they claimed that malignant cells in all types of cancers share six traits that allow normal cells to become cancerous ones, namely sustaining proliferative signaling, evading growth suppressors, avoiding immune destruction, enabling replicative immortality, tumor-promoting inflammation, and activating invasion and metastasis.[1] This work opens new avenues for the understanding and knowledge about some hidden secrets of this aggressive disease.

In 2011, the same scientists updated their work and added four new traits. These are inducing angiogenesis, resisting cell death, deregulating cellular energetics, and genome instability and mutation.[2] These new advances in knowledge about cancer

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mechanisms have been accompanied by the development of targeted therapy. Nowadays, with the understanding of these ten hallmarks of cancer mechanisms, and the main changes that occur in the normal cell growth pathways, the treatment of cancer cells with specific therapies has become possible in a high number of cases [Figure 1].

In this review, we will discuss the concept of the hallmarks of cancer that facilitated the development of targeted therapies and how this approach has been successful in improving patient survival. Therefore, the big question is "with this significant progress in understanding the cancer biology, is there any clinical benefits."

Hallmark 1: Sustaining Proliferative Signaling

Normal cells need external stimuli for division and growth. This mechanism is modified or dysregulated in cancer cell growth.[2] The mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (ERK) pathway (sometimes called RAS-RAF-MEK-ERK pathway) plays a crucial role in this hallmark.[2] MAPK pathway includes cascades of signals that control many cellular processes, such as cell proliferation and growth and differentiation and transformation with cellular apoptosis.[3] Dysregulation of the MAPK pathway or its components can lead to tumorigenesis, and cancer cells will be able to sustain proliferative signals and evade apoptosis, angiogenesis, and even metastasis. For the importance of this pathway, lots of works have been done to inhibit this pathway. BRAF is an essential part of this pathway.[4] BRAF mutations occur in 8% of all cancers; they occur in nearly 50% of advanced melanoma cases, 40% of papillary thyroid cancer, around 10% in colorectal cancers, and in less percent in lung cancer. Moreover, BRAF mutation occurs in many hematological malignancies, such as hairy cell leukemia and plasma cell myeloma.[5,6]

Inhibitors of oncogenic kinases

Vemurafenib and dabrafenib are both inhibitors of mutant BRAF, and they are the main drugs used in the management of melanoma. Vemurafenib improved the progression-free survival and overall survival in patients with advanced melanoma. Dabrafenib is another inhibitor of mutant BRAF; it demonstrated a progression-free survival (PFS) advantage with less toxicity.[7] BRAF mutation is associated with poor prognosis in cancer. It is associated with the proved poor prognostic factors in colorectal tumors, such as old-age patients, female sex, and poor response to chemotherapy and epidermal growth factor receptor (EGFR) inhibitor drugs.[8] In papillary thyroid cancer, vemurafenib demonstrated an objective response rate (ORR) of up to 38.5% for patients with radioactive iodine-refractory cases with BRAF V600E mutation.[9]

Understanding the downstream signaling and its relation with the hallmark (sustaining proliferative signaling)

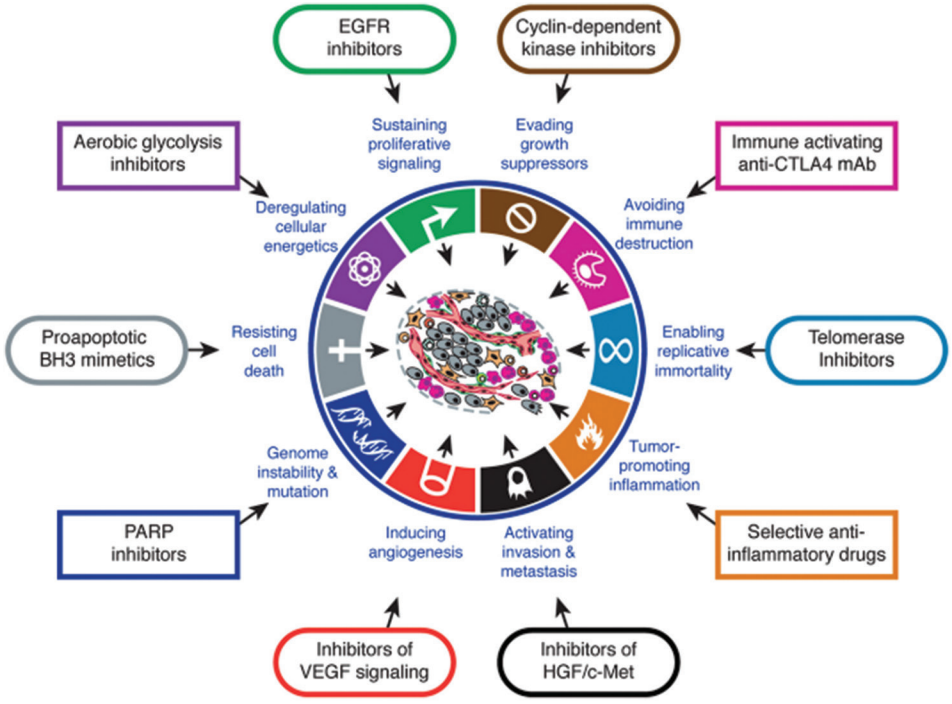

Figure 1: Therapeutic targeting in the hallmarks of cancer[2]

increased scientists' knowledge about the possible role of downstream pathways in the development of drug resistance. Trametinib is an MEK inhibitor that combined with BRAF inhibitors, using this treatment can help to target two different mutations in the same time. It revealed a longer overall survival compared with BRAF inhibition alone and a higher response rate with longer PFS with a significant decrease in dermatological side effect.[10] This drug helped to treat drug resistance with a great success; Figure 2 shows the possible mechanisms for resistance in this pathway. One of the breakthroughs in medicine was the introduction of imatinib, a tyrosine kinase inhibitor, in the management of chronic myeloid leukemia. Imatinib acts against BCR-ABL fusion gene, which forms Philadelphia chromosome; Figure 3 shows the mechanism of action of imatinib. Imatinib is one of the success stories in the management of cancer; it changed the outcome of chronic myeloid leukemia and patients got prolonged overall survival with this targeting therapy.[11,12]

Hallmark 2: Evading Growth Suppressors

Normally, the cell growth and proliferation are under the control of a much-organized mechanism in the body, which includes a balance between growth suppression and growth stimulation signals. Tumor cell needs to dysregulate this process to grow and survive.[2] Antigrowth signals are under the control of two proteins, namely, retinoblastoma (pRb) and P53. pRb is active when it is not phosphorylated, which occurs when it is attached to E2F transcription factor to form an RB/E2F complex, and this complex prevents the cell from transformation to the next S stage (DNA replication phase in normal cell cycle); also, it inhibits the cyclin-dependent kinases (CDKs) in G1, but under external stimuli, the accumulated CDKs can phosphorylate pRb by detaching it from E2F, and this will promote cell division, making cells unresponsive to antigrowth signals.[13,14]

P53 gene is one of the interesting genes in cancer, mutation or loss of this gene can be found in different types of cancers, such as head-and-neck tumors, esophageal cancer, colorectal cancer, and other different types. Uncontrolled cell division can be caused by a mutation or loss of these genes after exposure to different types of risk factors, such as radiation and chemotherapy.[14,15] The other important protein in this process is transforming growth factor-β (TGF-beta) which works as a negative regulator of cell growth. It controls pRb signaling by the prevention of RB phosphorylation, which can lead to inhibition of cell proliferation. If cell gets transformed to a cancer cell, this system will be out of normal cell control.[16]

Cyclin-dependent kinase inhibitors

Palbociclib is one of the drugs that target CDKs (CDK4 and CDK6) by controlling the CDK–RB–E2F pathway. It is used in metastatic hormone-positive breast cancer. There was a 10 months' improvement in the PFS when the drug was added to hormonal therapy, despite the insignificant overall survival result. The main adverse effects of this drug are hematological such as neutropenia, but they are tolerable and manageable at most of the time.[17]

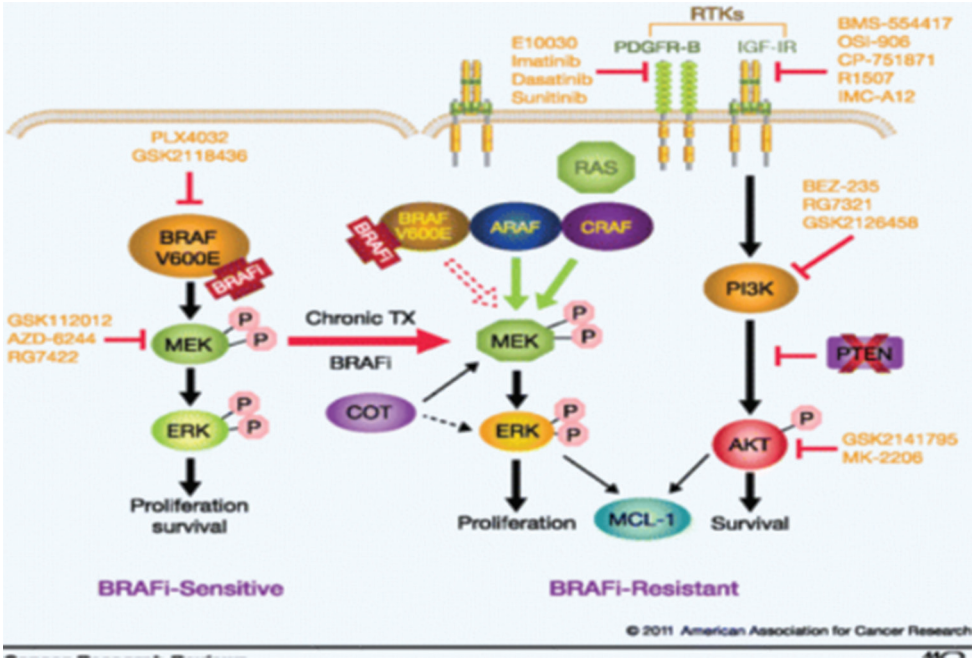

Figure 2: Mechanisms of BRAF inhibitor resistance. RAF isoform switching, activation of receptor tyrosine kinases such as insulin-like growth factor-1 receptor and engagement of the PI3K pathway to promote cell survival. PTEN loss leads to activation of the PI3K pathway

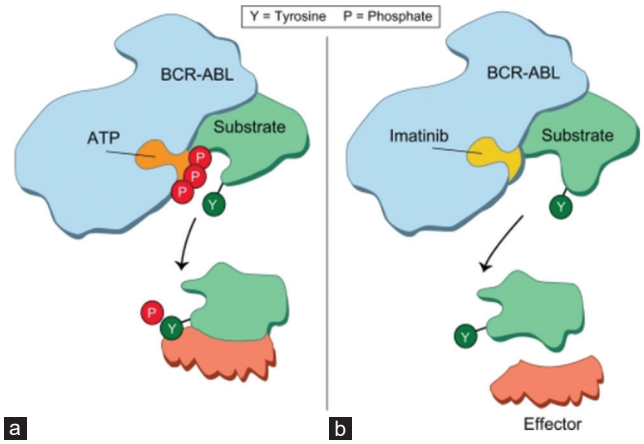

Figure 3: Mechanism of action of imatinib in chronic myelogenous leukemia, (a)It binds to the amino acids of the BCR/ABL tyrosine kinase adenosine triphosphate binding site and stabilizes the inactive, nonadenosine triphosphate binding form of BCR/ABL. (b) How imatinib preventing tyrosine autophosphorylation and, in turn, phosphorylation of its substrates

Hallmark 3: Avoiding Immune Destruction

The immune system plays a vital role in the protection of our bodies against cancer cells through different mechanisms. However, this system can be abused by cancer cells to cause damage to the human being. Figure 4 shows the steps of avoiding immune destruction by a cancer cell.[18]

The use of immunotherapy represents a huge leap in the modern treatment of cancer. These drugs can work on the body immunity with fewer side effects in comparison with chemotherapy, and the initial results showed a significant decrease in the tumor's volume with the use of these drugs in practice.[19]

Programmed cell death-1 (PD-1) is a checkpoint protein expressed on the surface of activated T cells; it works with another protein called cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which is also expressed on the surface of T cell to prevent attacking tissues by its immune cells. Both work as checkpoint receptors that downregulate immune responses, and PD-1 binding with the programmed death-ligand 1 (PD-L1) will trigger a cascade of signals that inhibit T-cell activation and then slow immune response.[19] Most cancer cells express a large amount of PD-L1 so that they can evade the immune system.[19] Targeting CTLA-4 and both PD-1 and PDL-1 is an attractive issue as blocking these pathways may help to stop cancer cells escaping from the immune system.

Immune checkpoint inhibitors

Ipilimumab is a human monoclonal antibody; it blocks CTLA-4 and then promotes the body's immune response against cancer cells. The drug has dramatically changed the management of melanoma.[20] However, immune-related adverse events are the main side effects

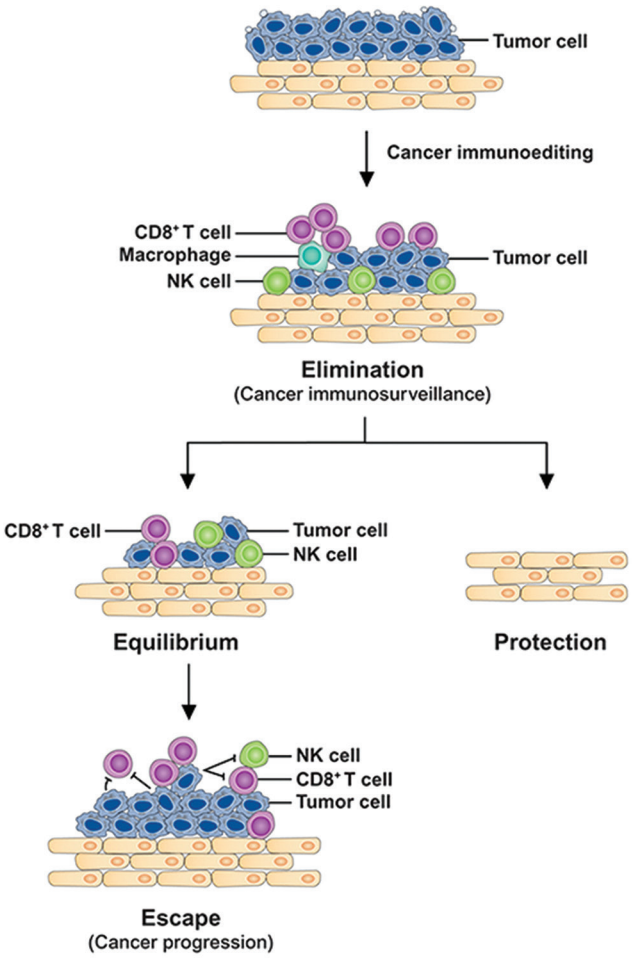

Figure 4: Avoiding immune damage. Cancer immunoediting, which is composed from three steps: elimination, equilibrium, and escape[18]

associated with the drug, such as diarrhea and hepatic toxicity.[20,21]

Pembrolizumab and nivolumab are both monoclonal antibodies that inhibit PD-1 checkpoint. Both drugs added a significant survival and have been approved in different types of cancers, such as non-small cell lung cancer (NSCLC), melanoma, Hodgkin's lymphoma, and renal cell carcinoma.[22,23] The resistance emerged for these drugs raised the issue of the benefit of the combination of the drugs. Nowadays, ipilimumab has been used in conjunction with other PD-L1 inhibitors as they show a better response than ipilimumab alone in melanoma.[24] The biggest problems with these drugs are skin reactions, gastrointestinal manifestations, and lung inflammation, which can be in the form of severe pneumonitis.[24]

Hallmark 4: Enabling Replicative Immortality

Telomerase is a specialized reverse transcriptase enzyme attached to the chromosome ends. Its primary function

is protection of these critical ends from damage during normal cell division, and it is responsible for the *de novo* synthesis of telomeric DNA. It shortens with each cell division, and this will restrict the proliferative capacity of cells where the enzyme plays a key role in enabling replicative immortality.[25] In cancer, this function is dysregulated leading to uncontrolled cell growth, which is a hallmark of cancer cells.[25] While normal cell has limited number of divisions and this process is controlled by an organized intrinsic cellular pathway, cancer cell can pass this limit through re-expression or overexpression of more telomerase.[2] The fact that nearly 90% of cancer cells express telomerase, unlike normal cells where it is absent or reduced in expression, encouraged scientists looking at this interesting enzyme as a target for treatment.[26,27] Immunotherapy, gene therapy, and small-molecule inhibitors are the main ways to target telomerase enzyme, and the key role is the inhibition of its subunit (hTERT) or the RNA template (hTER), both can stop cell proliferation. G-quadruplex stabilizers and HSP90 inhibitors, which can target the enzyme subunit indirectly causing cell death, constitute another effective inhibition.[26]

Telomerase inhibitors

GemVax & KAEL (GV1001) / RIAVAX™ inj. (Tertomotide HCl, code name GV1001™, Korea) is one of the telomerase inhibitor drugs, which has been used in many trials; it is a therapeutic vaccine that helps the immune system to recognize telomerase in cancer cells. The drug showed a durable T-cell memory-associated prolonged progression-free survival in NSCLC and good tolerability, but it did not go further beyond Phase 2, so it needs further trials for more confirmation.[28,29] The drug was also used in metastatic melanoma and hepatocellular carcinoma with a good immune response, but all these trials were only Phases I or II. In pancreatic and breast cancers, there were no survival benefits with the use of the drug.[30]

There is less possibility of resistance with this hallmark because of the rare mechanism of alternative lengthening of telomeres (evidence for an alternative mechanism for maintaining telomere length in human tumors and tumor-derived cell lines).

Hallmark 5: Tumor-Promoting Inflammation

Inflammatory cells are present in the microenvironment of tumors; this truth has been proven since 1863 by Rudolf Virchow.[31] Hanahan and Weinberg (2011) supposed that this tumor-associated inflammatory process might fortify cancer cells to survive and progress. Most of the studies have been linked between chronic inflammation and cancer occurrence, where inflammatory cells can provide the malignant cells with growth factors and other hallmark-facilitating mechanisms, such as cytokines and proteases. In addition to this, the inflammatory cells can produce chemical substances that can cause genetic mutations in the tumor microenvironment. As a result, all these factors can aid malignant cells to proliferate and survive and even to metastasize.[32]

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs showed activity in different types of cancer, such as breast and colorectal cancers and, in a less extent, lung cancer. Most of the studies showed a significant decrease in the relative risk with the use of aspirin for colon cancer and breast cancer.[33] The indirect anticancer activity of these drugs is supposed to be through the ability of these drugs to induce apoptosis and inhibition of the proliferation.

Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor that inhibits the release of prostaglandin as shown in Figure 5.[34] Polyps are well known as a risk factor for colorectal cancer, and several trials addressed the relationship between polyps and the use of a COX-2 inhibitor, especially for the premalignant polyps.[35] These drugs showed a considerable decrease in the number and size of polyps in familial adenomatous polyposis syndrome and other colorectal polyps when used at a dose of 400 mg twice daily for more than 6 months, and there was a 31% reduction in the number of polyps.[36] In breast cancer, a COX-2 expression is usually associated with aggressive features, such as large tumor size and HER2-positive tumor. Many trials are trying to assess the combination of these drugs and hormonal therapy in patients with breast cancer, especially after the significant results that have been seen with the use of celecoxib and aspirin in the reduction of breast cancer risk by 20% in females.[37] The serious cardiac side effects of COX-2 inhibitors that have been seen in patients halted their further use in clinical practice.

Hallmark 6: Activating Invasion and Metastasis

The ability of cancer cells to grow and metastasize was one of the puzzles to scientists for many years. The understanding of this mechanism is a key to the understanding of the management of many cancers. Malignant cells by changing their shape and losing or downregulating cell–cell adhesion glue, E-cadherin, and losing the adhesion within the extracellular matrix can invade the surrounding tissues and even metastasize.[38] This downregulation or losing of E-cadherin is one of the features of epithelial-to-mesenchymal transition (EMT).[2] EMT is a process that regulates changes in cell morphology and function during embryogenesis and tissue development. EMT plays a significant role in cancer progression and metastasis. Cells undergoing EMT can

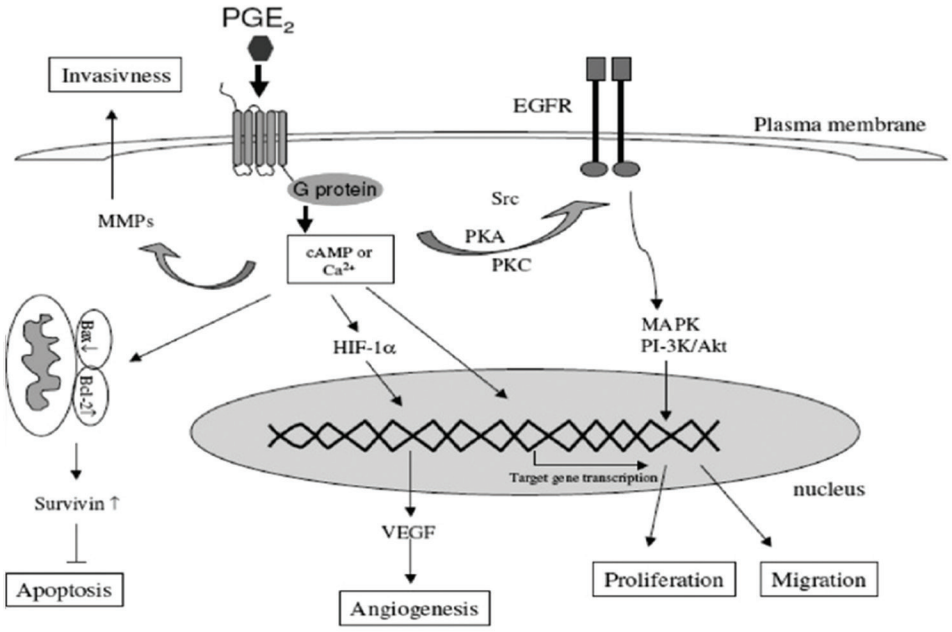

Figure 5: Mechanisms of carcinogenesis produced by cyclooxygenase-2-derived prostaglandin[34]

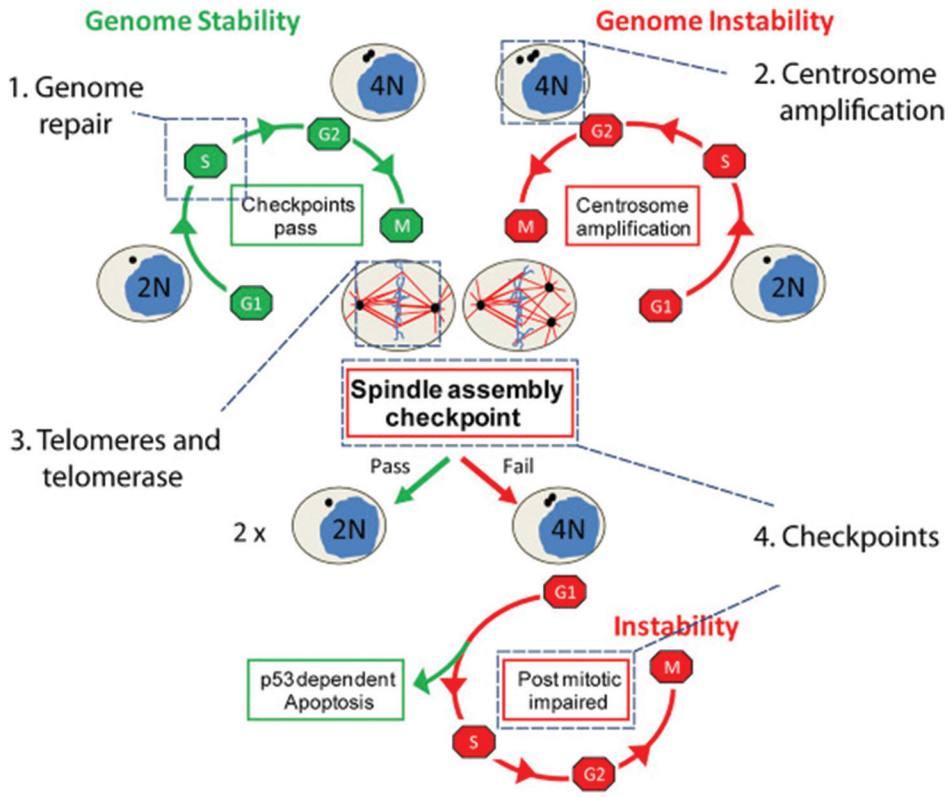

Figure 6: Genomic instability in human cancer: Molecular insights

invade surrounding tissue and disseminate far from the primary site.[39]

There is a central role for hepatocyte growth factor (HGF)/c-Met pathway in cancer invasion and metastasis in animal models; human cell lines that overexpress HGF and c-Met become tumorigenic and metastatic when implanted into nude mice.[40,41] The dysregulation of HGF/c-Met signaling has emerged as a key player in the invasion and metastasis in human malignancies,

where HGF can induce EMT. HGF/c-Met pathway is essential during embryo life as it participates in the development of placenta and many other organs such as the central nervous system, and in adult life, it takes part in organ regeneration as in wound healing.[41] The MET pathway is abnormally regulated in a wide range of human cancers, such as lung cancer in nearly 50%, breast cancer; colorectal tumors; pancreatic cancer; ovarian malignancies; pediatric tumors such as medulloblastoma, lymphoma, and papillary cell carcinoma; and bone tumors, which are characteristic for this pathway, as MET is expressed in osteoblast and osteoclast cells.[42,43] Dysregulated MET signaling can result from several molecular mechanisms, such as c-MET gene mutation, c-MET chromosomal rearrangement, and c-MET amplification.[44] The MET (c-Met) receptors need the ligand HGF for activation, of this pathway. This pathway also plays a role in chemoresistance and radioresistance as in lung cancer, colorectal cancer, and breast cancer.[45,46]

Inhibitors of hepatocyte growth factor/c-Met

Rilotumumab (AMG102) is a monoclonal antibody target HGF (IgG2) which prevents the binding of HGF to its receptor; this can stimulate the induction of apoptosis in cells expressing (c-Met). Clinical studies on this drug had been terminated because of increase in the number of deaths in the rilotumumab and chemotherapy treatment arm when compared to the chemotherapy treatment-only arm.[47] Cabozantinib is a multikinase inhibitor acting on MET, VEGFR2, FLT3 mainly, and other pathways; the drug is approved for the treatment of medullary thyroid cancer but has no clear role in renal cell carcinoma.[48-51] The drug showed longer overall survival and PFS in patients with hepatocellular carcinoma.[22,23,52]

Hallmark 7: Inducing Angiogenesis

Angiogenesis is the process of new blood vessel formation and one of the supposed mechanisms by which malignant cells can grow and metastasize.[2] Vascular endothelial growth factor (VEGF) family and its receptors (VEGFR) are the main players in neoplastic vascularization, and their expression can be triggered by hypoxia. Then, the balance between the pro-angiogenic factors, such as VEGF, angiopoietins, essential basic fibroblast-like growth factor, and TGF-β and the anti-angiogenic factors, such as thrombospondin-1, angiostatin, and endostatin, are believed to be pivotal elements in the process.

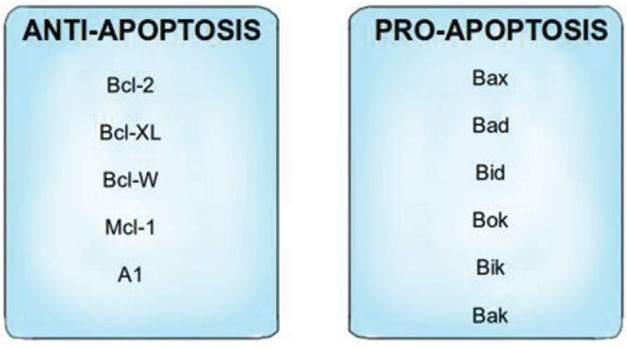

Figure 7: BCL2-family showing pro-apoptotic and pro-apoptotic proteins

Inhibitors of vascular endothelial growth factor signaling

Targeting this pathway was a very attractive issue, as it means inducing the death of malignant cells by cutting their blood supply, and such type of treatment does not need particular histology type to work on (unlike in the case of chemotherapy). It works on tumor microvasculature; in addition to that, it has a fewer side effects in comparison with chemotherapy.

Bevacizumab (Avastin) is a humanized monoclonal antibody that blocks angiogenesis by inhibiting VEGF-A; it is used in different cancers, such as metastatic colorectal cancer, breast cancer, lung cancer, and brain tumors. The drug proved to improve the PFS by 1.4 months and survival in colorectal cancer patients.[53] This unclear benefit delayed its approval in National Institute for Health and Care Excellence guideline (cancer guideline in the UK) for many years, as the cost-effectiveness was small for the adoption of the drug. On the other hand, it is not clear which chemotherapy combination is the best with it is, and all the trials gave conflicting results. The other issue is the serious side effects, such as hypertension and poor wound healing, which are important issues in cancer patients.[54] In breast cancer, its indications have been changed lastly and its use lost some of the enthusiasm after the disappointing results with its safety in patients is it does not improve the quality of life or extend the survival.[55] In lung cancer, the nonsquamous type of the drug was used as the squamous type can cause bleeding and there are certain limitations for its use such as any history of bleeding and the performance status of patient.[56]

The survival benefits of targeting this hallmark are disappointing in clinical practice, and drugs could not show any significant progress in any clinical data. In addition, one of the issues with angiogenesis inhibitors is that they often end up promoting another hallmark, i.e., invasion.

Hallmark 8: Targeting Genome Instability and Mutation

Genomic instability (GI) refers to multiple DNA damage and chromosomal abnormalities, such as rearrangement and gain or loss as in aneuploidy [Figure 6]. Microsatellite instability and chromosomal instability

are the most common form of GI. Poly (ADP-ribose) polymerase (PARP) plays a vital role in repairing single-strand DNA damage in the stabilization of the genome. If PARP is inhibited, this will halt DNA correction, leading to cell death.[57,58]

Poly-ADP-ribose inhibitors

Olaparib is an oral PARP inhibitor used in recurrent ovarian cancer, with or without BRCA mutation. Other indications are mainly in breast cancer, especially in triple-negative type and BRCA mutation because of high upregulation of PARP.[59] Treatment with the PARP inhibitor olaparib in patients whose prostate cancers were no longer responding to standard treatments and who had defects in DNA repair genes led to a high response rate.[60,61]

Hallmark 9: Resisting Cell Death

Apoptosis in normal cells is regulated through two pathways: intrinsic (or mitochondrial), which needs internal stimuli from inside the cell to activate the process, and extrinsic, which requires external signals for activation. It is believed that the intrinsic one is more important in cancer and the primary regulator of apoptosis in this pathway is BCL-2 family proteins.[62] There are two types of this family, as shown in Figure 7, anti-apoptotic (inhibit apoptosis) and pro-apoptotic (trigger apoptosis when they are activated). Each group can bind to the other one to control the process of apoptosis. BCL-2 has four BCL-2 homology or BH domains.[63] BH3-only member is a subclass of BCL2-family that interacts with both pro-apoptotic and anti-apoptotic types to decide for cell behavior. It has a significant role in the death signal's transition between intrinsic and extrinsic pathways. BH3-only proteins work through interfering with anti-apoptotic Bcl-2 proteins or stimulating the pro-apoptotic proteins directly.[63] Cancer cells that increase the expression of anti-apoptotic BCL2 or downregulation of pro-apoptotic proteins by this tumor can dysregulate BCL2-family and then evade apoptosis.[2]

BH3 mimetics

ABT-737 is a BH3 mimetic inhibitor, used in chronic lymphocytic leukemia (CLL) and follicular lymphoma, but it was ineffective in solid tumor.[64]

BCL2 inhibitors

Venetoclax (Abt-199) was subsequently developed as a highly selective, orally available small-molecule Bcl-2 family protein inhibitor that binds with high affinity to Bcl-2 and with lower affinity to other Bcl-2 family proteins (Bcl-XL and Bcl), and venetoclax has recently received approval for relapsed/refractory CLL.[65,66]

Hallmark 10: Deregulating Cellular Energetics

Cancer cells mainly depend on anaerobic glycolysis to adjust their high requirements for energy for growth and replication, which produce less energy, so to compensate for that, cancer cells upregulate glucose transporters, mainly Glut-1, to increase glucose transportation to the cytoplasm.[2] In addition, cancer cells increase the expression of most of the glycolytic enzymes. Another way is activated oncogenes, such as RAS, Myc, and HIF-1afa, and mutated P53 can also induce glycolysis.[2,67]

Aerobic glycolysis inhibitors

Targeting this metabolic pathway is interesting because of its role in tumorigenesis. Targeting multiple levels in this path including enzymes shows a promising result, as in the inhibition for glutaminase 1, which is highly upregulated in malignancy.[68] Inhibition of HIF, MCT1, and MCT4 can interfere with lactate transfer causing cell death by starvation.[69,70] The inhibition of mutant isocitrate dehydrogenase 1 and 2 is another way of management. Metformin (the great antidiabetic drug) decreases the blood glucose level by reducing adenosine triphosphate production through the inhibition of mitochondrial liver cells, but the results are still in their original stages.[71] This hallmark played a huge role in the development of breakthrough investigation in cancer, which is positron emission tomography-computed tomography scan (^{18}F-fluoro-2-deoxyglucose), through understanding the high uptake of glucose by malignant cells, which differentiate it from other normal cells.[72,73]

Conclusions

With this significant development in the understanding of cancer biology, is there any clinical benefits. Yes, is the answer for the initial? These benefits can be seen clearly through the new drugs that improved the survival and the response rate. By contrast, there are some disappointing results, but the future looks promising with these drugs, with more understanding for more proteins involved in pathways, and individulization of treamtent according to specific biomarkers or receptors may help to overcome many obstacles. Resistance is one of the major issues with these pathways and combination of multiple targeted pathways inhibitors may be the solution in future. In addition, the discovery of the relationship between these different channels and different proteins in the hallmarks, such as P53 which has a role in many hallmarks, can help stop multiple pathways by targeting one protein.

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Conflicts of interest

There are no conflicts of interest.

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