Chapter 7

The Impact of Biochemical Alterations in the Tumor Microenvironment on Cancer Progression and Treatment

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Abstract

The tumor microenvironment (TME) plays a critical role in cancer progression and treatment response. Recent studies have revealed that biochemical alterations within the TME can significantly influence tumor behavior and therapeutic outcomes.

Alterations in the TME, such as changes in pH, hypoxia, and nutrient availability, have been shown to promote cancer cell survival and growth. Acidic pH conditions within the TME enhance tumor invasiveness and metastasis while conferring resistance to conventional therapies. Hypoxia, caused by insufficient oxygen supply, not only promotes genetic instability and immune evasion but also induces resistance to radiation and certain chemotherapeutic agents. Additionally, nutrient deprivation within the TME can activate survival pathways in cancer cells, leading to treatment resistance.

Understanding the biochemical alterations in the TME has led to the development of novel therapeutic approaches. Strategies to modulate the TME, such as targeting angiogenesis, reversing immunosuppression, and normalizing the microenvironment, have shown promise in preclinical and clinical studies. Combining conventional therapies with agents targeting the TME holds potential to overcome treatment resistance and improve patient outcomes.

In conclusion, the biochemical alterations within the TME significantly impact cancer progression and treatment response. Recognizing these alterations and their influence on therapeutic outcomes is crucial for developing effective treatment strategies. Continued research in this area is vital to unravel the complexity of the TME and identify novel therapeutic targets for improving cancer patient outcomes.

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Introduction

The tumor microenvironment consists of various cellular and non-cellular components surrounding the tumor. Biochemical changes in the tumor microenvironment may have important effects on cancer progression and treatment (Arneth, 2020). Biochemical changes in the tumor microenvironment can promote tumor growth and invasion. Factors secreted by tumor cells and stromal cells within the microenvironment can stimulate cell proliferation, angiogenesis, and tissue remodeling, allowing the tumor to expand and invade neighboring tissues (Denton et al., 2018).

Biochemical factors in the microenvironment, such as cytokines and chemokines, can recruit immunosuppressive cells, including regulatory T cells and myeloid-derived suppressor cells, which reduce the anti-tumor immune response (Denton et al., 2018; Wu et al., 2015). The altered composition of extracellular matrix components, increased interstitial pressure, and impaired blood supply can limit the delivery and effectiveness of chemotherapy drugs and radiation therapy (Wu et al., 2015; Multhoff et al., 2012). In addition, the microenvironment may provide survival signals to cancer cells, protecting them from the cytotoxic effects of treatment (Hinshaw et al., 2019).

The tumor microenvironment undergoes angiogenic remodeling, characterized by the formation of new blood vessels to meet the increased nutrient and oxygen demands of the growing tumor (Fukumura et al., 2007). Biochemical factors secreted by cancer cells, such as vascular endothelial growth factor (VEGF), stimulate angiogenesis and aggregation of endothelial cells (Nicosia, 1998; Byrne et al., 2005). This facilitates the establishment of an extensive network of blood vessels within the tumor.

1. Oncogenes and Tumor Suppressor Genes

Oncogenes are genes that, when mutated or activated, promote cell growth and division (Feldman et al., 1991). Tumor suppressor genes normally regulate cell growth and division and may prevent cancer development (Jones et al., 2009). Changes in these genes can upset the balance between cell proliferation and cell death (Ryan et al., 2001).

Proto-oncogenes are the main regulators of biological processes and are found in normal cells. It can act as proto-oncogenes, growth factors, signal transducers, and nuclear transcription factors. The genomes of mammals and birds contain several proto-oncogenes that regulate normal cell differentiation and proliferation (Müller, 1986). Changes in these genes that affect the regulation of their behavior or the structure of their encoded

proteins can emerge as oncogenes in cancer cells. When such oncogenes are produced, they promote cell proliferation and play a crucial role in the pathogenesis of cancer. There are two categories of physical mutations that result in the activation of proto-oncogenes: those that cause differences in the structure of the encoded protein and those that cause dysregulation of protein expression (Jan et al., 2019; Abel et al., 2009). Point mutations of RAS proto-oncogenes and chromosomal translocations producing chimeric genes such as Philadelphia translocation (BRC-ABL) are examples of mutations that affect structure (Abel et al., 2009; Bataille et al., 2017; Kurebayashi, 2001; Klinakis et al., 2006).

Activation of proto-oncogenes results in their conversion to oncogenes; To date, 50 to 60 oncogenes have been identified (Lee et al., 2010). Each proto-oncogene promoter allows the gene to respond to a variety of physiological signals. Depending on the metabolic requirements of the cell, a proto-oncogene may be expressed at very low levels; however, under certain conditions, the expression of the gene can be significantly induced (Lee et al., 2010).

The activation mechanisms of proto-oncogenes are as follows:

a) Chromosomal translocation of a proto-oncogene from a non-replicating location to an adjacent location where it can be replicated (chromosomal translocation of the MYC oncogene in human Burkitt lymphoma).

An example of a chromosomal translocation involving the MYC oncogene is the t(8;14) translocation commonly found in Burkitt lymphoma. In this translocation, a portion of chromosome 8 containing the MYC gene fuses with a portion of chromosome 14, resulting in dysregulation of MYC expression. MYC oncogene plays a crucial role in cell cycle regulation, cellular growth and differentiation. Deregulated expression of MYC due to the t(8;14) translocation leads to constitutive activation of the MYC signaling pathway. This pathway is involved in various cellular processes and is involved in tumor progression. MYC levels are tightly regulated under normal conditions. However, MYC is overexpressed in the presence of the t(8;14) translocation (Quatrin et al., 2021). The displaced MYC gene is now under the control of regulatory elements from the immunoglobulin heavy chain gene (IgH) on chromosome 14, resulting in increased MYC expression. The overexpressed MYC protein forms a heterodimer with its partner protein Max. This MYC-Max complex binds to specific DNA sequences called E-boxes in the promoters of target genes, leading to their activation. Target genes regulated by MYC are involved in cell proliferation,

metabolism and apoptosis (Lüscher et al., 2012; Nie et al., 2012). One of the primary functions of MYC is to promote cell cycle progression from G1 phase to S phase. MYC activates the expression of genes involved in cell cycle regulation, such as cyclins and cyclin-dependent kinases (CDKs), which direct cell division. MYC also supports metabolic reprogramming to support the increased energy demands of rapidly dividing cancer cells. It increases nutrient availability for cancer cell growth by activating genes involved in glucose uptake, glycolysis and glutamine metabolism. Normally, MYC regulates cell death and apoptosis. However, in the context of MYC translocation, its dysregulated expression may impair apoptosis and allow cancer cells to escape programmed cell death. In addition, MYC overexpression can trigger cellular senescence, a state of irreversible growth arrest. The dysregulated MYC signaling pathway promotes uncontrolled cell proliferation, genomic instability, and resistance to cell death mechanisms. These factors contribute to tumor growth, metastasis, and progression in Burkitt's lymphoma and potentially other cancers associated with MYC dysregulation (Rohrberg et al., 2020).

b) Point mutation of a proto-oncogene in which the substitution of a single base by another base results in the substitution of an amino acid in the oncoprotein (a point mutation at codon 12 of the RAS oncogene).

It is a well-known genetic change found in several types of cancer, including colorectal cancer, lung cancer, and pancreatic cancer. This mutation affects the RAS gene, specifically one of three isoforms: KRAS, NRAS, or HRAS. The mutation results in the substitution of a single nucleotide that results in an amino acid change in the protein product of the RAS gene (Miyakura et al., 2002). The most common mutation at codon 12 is the replacement of glycine (G) with valine (V), aspartic acid (D), cysteine (C), or arginine (R). This substitution disrupts the intrinsic GTPase activity of the RAS protein, preventing it from hydrolyzing GTP to GDP, which is essential for normal RAS function and regulation. The mutated RAS protein is locked in its active GTP-bound state, leading to sustained activation of downstream signaling pathways involved in cell growth and survival. RAS is an important upstream regulator of the mitogen-activated protein kinase (MAPK) pathway (Gerber et al., 2022; Farr et al., 1988). The mutated RAS protein lacks efficient GTPase activity and disrupts normal down-regulation of RAS signaling. This leads to sustained activation of downstream effectors even in the absence of growth factor stimulation. Constitutive activation of RAS signaling promotes uncontrolled cell growth, survival, and escape of growth inhibitory signals. It also contributes to increased angiogenesis,

invasion, and metastasis and ultimately promotes tumor progression (Sparmann et al., 2004).

c) Gene amplification by including multiple copies of an oncogene results in increased oncoprotein production (c-MYC in neuroblastoma).

Neuroblastoma is a childhood cancer that arises from immature nerve cells called neuroblasts. It is characterized by abnormal growth of these cells in the adrenal glands, abdomen, chest, or spinal cord (David et al., 1989). Amplification or overexpression of the c-MYC oncogene is commonly observed in neuroblastoma. This can occur through a variety of mechanisms, including gene amplification, chromosomal rearrangements, or dysregulation of transcriptional control elements. Dysregulation of c-MYC contributes to the uncontrolled cell proliferation, survival, and differentiation observed in neuroblastoma. Dysregulated c-MYC in neuroblastoma affects various cellular processes and signaling pathways. Overexpression of c-MYC in neuroblastoma leads to increased cell proliferation and decreased apoptosis, promoting tumor growth. c-MYC also affects the balance between cell differentiation and apoptosis. Normally, c-MYC expression is downregulated during cell differentiation. However, dysregulated c-MYC expression in neuroblastoma inhibits differentiation and contributes to tumor progression by promoting cell survival. c-MYC stimulates the production of pro-angiogenic factors (Hatzi et al., 2002). In neuroblastoma, dysregulated c-MYC can enhance angiogenesis. Similar to other cancers, dysregulated c-MYC in neuroblastoma drives metabolic reprogramming to meet the energy demands of rapidly dividing cells. It promotes glucose uptake, glycolysis and glutamine metabolism, ensuring tumor cell growth and survival. c-MYC dysregulation may contribute to genomic instability by leading to the accumulation of additional genetic changes in neuroblastoma cells. Genomic instability is a hallmark of cancer and can further increase tumor progression and heterogeneity. Understanding the role of dysregulated c-MYC in neuroblastoma is crucial for developing targeted therapies. Efforts are being made to develop drugs that specifically inhibit c-MYC or target downstream pathways affected by c-MYC dysregulation. By targeting c-MYC and its associated signaling pathways, the researchers aim to disrupt neuroblastoma cell growth and improve patient outcomes (Nisar et al., 2020).

d) Combining a gene that promotes transcription (promoter gene) near the proto-oncogene causes overexpression of the gene (mechanism of retrovirus carcinogenicity).

Retroviruses are a family of RNA viruses that have the ability to integrate their viral DNA into the host cell's genome. They can cause carcinogenicity

(cancer development) through several mechanisms. Retroviruses can integrate their viral DNA into the host cell's genome, usually near or within the genes involved in cell growth regulation. This integration can disrupt the normal regulation of these genes, leading to uncontrolled cell growth and potentially their transformation into cancer cells. Viral integration can activate oncogenes or contribute to carcinogenesis by inactivating tumor suppressor genes. Some retroviruses carry oncogenes, which are genes that can induce cancer development. These viral oncogenes are derived from cellular genes captured during previous infections and incorporated into the viral genome. When the retrovirus infects a host cell, the viral oncogene can be expressed and contribute to cellular transformation by altering normal cell growth and survival pathways (Sahu et al., 2022). Retroviral infection can suppress the immune system and allow cells to multiply that would otherwise be eliminated by immune surveillance. This immunosuppression can create a conducive environment for cancer development and progression. Retroviral infection can lead to chronic inflammation, which is known to play a role in promoting tumor growth and progression. Inflammation produces reactive oxygen species and inflammatory mediators, which can damage DNA, promote cell proliferation, and create an environment that promotes cancer growth. Immortalization and Telomere Retroviruses can induce cellular immortalization by activating telomerase, an enzyme that lengthens telomeres, the protective ends of chromosomes. Telomerase activation allows cells to transcend the natural limits in cell division and continue to proliferate, which is a characteristic feature of cancer cells. It is important to note that retroviruses have varying levels of carcinogenic potential. For example, certain retroviruses such as human T-cell lymphotropic virus type 1 (HTLV-1) and human immunodeficiency virus (HIV) have been strongly associated with certain types of cancer, such as adult T-cell leukemia/lymphoma and AIDS (Romanish et al., 2010; Fan, 1994).

2. Genetic Mutations

Mutations in genes play a crucial role in the development of cancer. Oncogenes, tumor suppressor genes, and other genes involved in DNA repair, cell cycle regulation, and apoptosis (programmed cell death) can undergo mutations (Grandér, 1998).

Cancer is a genetic disease while many factors can contribute to cancer development, genetic mutations are the driving force behind the onset and progression of most cancers (Aranda-Anzaldo, 2001).

Driver Mutations: Driver mutations are changes in certain genes that give cancer cells a growth advantage. These mutations directly contribute to the development and progression of cancer. Driver mutations can occur in oncogenes (genes that promote cell growth) or tumor suppressor genes (genes that prevent uncontrolled cell growth). Examples of commonly mutated oncogenes include KRAS, EGFR, and BRAF, while tumor suppressor genes such as TP53 and PTEN are frequently mutated in various cancers (Temko et al., 2018; Li, 2016).

Passenger (Passanger) Mutations: Passenger mutations are genetic changes that occur during cancer development but do not directly contribute to tumor growth. These mutations are a result of the genomic instability and chaotic nature of cancer cells. Although passenger mutations do not drive cancer progression, they can be used to trace a tumor's evolutionary history and provide insight into its cellular diversity (Bozic et al., 2016).

Germline Mutations: Germline mutations are inherited genetic changes found in every cell of an individual's body. These mutations are passed on from parents and may predispose individuals to an increased risk of developing certain types of cancer. For example, mutations in the BRCA1 and BRCA2 genes significantly increase the risk of breast and ovarian cancer (Iau et al., 2001).

Somatic Mutations: Somatic mutations are acquired genetic changes that occur in certain cells throughout a person's life. These mutations are not inherited and are usually caused by exposure to environmental factors such as radiation, chemicals, and tobacco smoke. Somatic mutations accumulate over time and can lead to the development of cancer. For example, exposure to UV radiation from the sun can cause mutations in skin cells, increasing the risk of skin cancer (Martincorena et al., 2015).

Different types of mutations can leave certain patterns or signatures in the cancer genome. These mutation signatures can provide insight into the underlying causes of genetic mutations and help identify potential carcinogens. For example, exposure to tobacco smoke leaves a distinct mutational signature characterized by certain types of DNA changes (Alexandrov et al., 2016).

3. Cell Signaling Pathways

Various signaling pathways control cell growth, survival, and proliferation. Changes in these pathways can lead to uncontrolled cell division and evasion of cell death mechanisms. For example, the Ras-Raf-MAPK pathway and the PI3K-AKT-mTOR pathway are frequently dysregulated in cancer. Cell

signaling pathways play a crucial role in normal cellular processes, including cell growth, proliferation, differentiation and survival. However, when these signaling pathways become dysregulated, it can lead to the development and progression of cancer (Harvey, 2019).

Oncogenic mutations or changes can occur in components of signaling pathways such as receptor tyrosine kinases (RTKs), downstream signaling molecules, or transcription factors. These mutations can trigger uncontrolled cell growth and proliferation, leading to constitutive activation of signaling pathways. Examples include mutations in the EGFR gene in lung cancer or the BRAF gene in melanoma that result in hyperactive MAPK signaling (Lundby et al., 2019). Many cancers take advantage of growth factor signaling pathways, such as the epidermal growth factor receptor (EGFR) pathway, to promote cell survival and proliferation. Dysregulation of growth factor receptors or their downstream effectors can lead to sustained activation of the pathway, promoting tumor growth. Targeting these pathways with specific inhibitors has become a successful therapeutic strategy in some cancers (Yewale et al., 2013). The PI3K/AKT/mTOR pathway is frequently dysregulated in cancer. Activation of this pathway supports cell survival, growth and metabolism. Mutations in components of the PI3K pathway or upstream regulators such as loss of PTEN lead to increased signaling along this pathway, contributing to uncontrolled cell growth and resistance to therapies (Martelli et al., 2011). The Wnt/β-Catenin pathway plays a crucial role in embryonic development and tissue homeostasis. Dysregulation of this pathway can occur through mutations in components of the Wnt pathway or stabilization of β-catenin. Abnormal activation of the Wnt/β-Catenin pathway promotes cell proliferation and is associated with a variety of cancers, including colorectal cancer (Bian et al., 2020). Notch signaling pathway regulates cell fate determination, differentiation and tissue development. Dysregulation of Notch signaling has been associated with numerous cancers, including leukemia, breast cancer, and pancreatic cancer. Abnormal activation of Notch signaling can disrupt normal cellular differentiation, leading to uncontrolled cell growth and tumorigenesis (Yin et al., 2010). The Hedgehog pathway is involved in embryonic development and tissue homeostasis. Mutations in components of the Hedgehog pathway, such as Flattened (SMO) or Patched (PTCH), can cause aberrant activation of the pathway, contributing to a variety of cancers, including basal cell carcinoma and medulloblastoma (Skoda et al., 2018).

4. Metabolism

Cancer cells exhibit altered metabolism compared to normal cells. They often rely on glycolysis (the breakdown of glucose) even in the presence of oxygen, known as the Warburg effect. This metabolic shift provides cancer cells with the necessary building blocks for rapid proliferation. Cancer cells exhibit different metabolic changes compared to normal cells, a phenomenon known as "metabolic reprogramming". These changes in metabolism are essential to support increased energy demands, rapid proliferation and survival of cancer cells.

Cancer cells often rely on glycolysis, which is the breakdown of glucose, even in the presence of oxygen (aerobic conditions); this is a less efficient way of producing energy in mitochondria compared to oxidative phosphorylation. This metabolic switch enables cancer cells to produce ATP and the building blocks necessary for cell growth and proliferation more quickly. Intermediate products of glycolysis can also be directed to support other biosynthetic pathways needed for cell division (Lincet et al., 2015). Cancer cells have an increased demand for an amino acid, glutamine. Glutamine acts as a carbon source for the synthesis of nucleotides, lipids and non-essential amino acids that support the high biosynthetic needs of cancer cells. Additionally, glutamine metabolism contributes to the production of antioxidants and helps cancer cells manage oxidative stress (Desideri et al., 2015). Cancer cells exhibit enhanced lipid biosynthesis to provide membrane building blocks and support cell growth. They regulate de novo fatty acid synthesis and increase lipid intake. Lipids also play a role in signaling pathways and may promote cancer cell survival and migration. Rapidly dividing cancer cells require a large supply of nucleotides for DNA and RNA synthesis. Cancer cells regulate pathways involved in nucleotide biosynthesis to meet this demand. Increased nucleotide synthesis also provides an opportunity for therapeutic targeting of cancer metabolism (Robinson et al., 2020; Mashima et al., 2009). Some cancers rely on glycolysis, while others exhibit enhanced mitochondrial metabolism. This includes increased oxidative phosphorylation, fatty acid oxidation and tricarboxylic acid (TCA) cycle activity. Mitochondrial metabolism is crucial in certain types of cancer to provide ATP, biosynthetic precursors and maintain redox balance. Cancer cells often have increased reactive oxygen species (ROS) levels due to their altered metabolism and high proliferation rate. To manage elevated ROS, cancer cells upregulate antioxidant defense systems such as the glutathione pathway and thioredoxin system to maintain redox homeostasis and promote cell survival (Alberghina et al., 2012).

These metabolic changes give cancer cells a selective advantage that supports their growth, survival, and ability to adapt to the tumor microenvironment. Targeting cancer cell metabolism has emerged as an exciting area of cancer research with the aim of developing treatments that specifically disrupt the metabolic weaknesses of cancer cells while sparing normal cells (Vander Heiden, 2011).

5. Angiogenesis

Tumor growth and progression requires the development of new blood vessels, a process known as angiogenesis. Cancer cells have the ability to secrete various factors that promote angiogenesis to ensure adequate blood flow to support increased nutrient and oxygen demands.

Angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and angiopoietins are produced and released by cancer cells. These factors stimulate the growth and migration of endothelial cells, the blood vessel building blocks (Carmeliet et al., 2011). Angiogenic factors released by cancer cells bind to specific receptors on the surface of endothelial cells, activating signaling pathways that promote cell proliferation, migration and formation of new blood vessels. This process allows endothelial cells to invade surrounding tissue and form capillary shoots (Carmeliet et al., 2011). Remodeling of the extracellular matrix is crucial for the formation of new blood vessels. Cancer cells and stromal cells in the tumor microenvironment secrete proteolytic enzymes such as matrix metalloproteinases (MMPs), which degrade the extracellular matrix, creating a pathway for endothelial cells to migrate and form new vasculature (Gálvez et al., 2001). Endothelial cells proliferate and form sprouts that lengthen and connect with nearby vessels to form a network of new blood vessels. This process is called neovascularization or angiogenesis. Newly formed blood vessels support the growth and survival of the tumor by supplying the growing tumor with oxygen, nutrients, and growth factors (Gálvez et al., 2001).

The tumor microenvironment, composed of stromal cells, immune cells, and components of the extracellular matrix, plays a crucial role in regulating angiogenesis. Cancer cell interactions with surrounding stromal cells, including cancer-associated fibroblasts and immune cells, can modulate the production of angiogenic factors and influence the angiogenic response (Payne et al., 2011). Targeting angiogenesis has been a successful therapeutic strategy in cancer treatment. Drugs that inhibit angiogenesis such as anti-angiogenic antibodies (eg, bevacizumab) and small molecule inhibitors (eg,

tyrosine kinase inhibitors that target VEGF receptors) have been developed and are used in combination with other therapies to limit blood flow to tumors to reduce their growth and improve patient outcomes (Petrovic, 2016).

6. Epigenetic Changes

Epigenetic modifications include changes in DNA and associated proteins without altering the underlying genetic sequence. These modifications can have profound effects on gene expression and play a crucial role in numerous biological processes, such as cancer (Zheng et al., 2008).

DNA methylation is a prevalent epigenetic modification involving the addition of a methyl group to DNA molecules, typically at cytosine residues within CpG dinucleotides. DNA methylation can influence gene expression by preventing transcription factors from binding to regulatory regions of genes, thereby suppressing gene expression. Hypermethylation of tumor suppressor gene promoter regions may result in their inactivation, thereby fostering the development of cancer. In contrast, hypomethylation at particular genomic regions can result in oncogene activation or genomic instability (Kulis et al., 2010). Histones are proteins that DNA wraps around and forms a structure called chromatin. Various chemical modifications such as methylation, acetylation, phosphorylation and ubiquitination can occur in histone proteins. These modifications can regulate gene expression by altering the DNA's accessibility to transcriptional machinery. For instance, acetylation of histones is generally associated with gene activation, whereas methylation may be associated with either gene activation or suppression, depending on the site and degree of methylation. Frequently observed in cancer, abnormal histone modifications cause dysregulation of gene expression and promote tumor growth and progression (Zhao et al., 2019). Non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are emerging as crucial players in epigenetic regulation. miRNAs can bind to messenger RNAs (mRNAs) and block their translation or regulate gene expression by promoting their degradation. Deregulated expression of miRNAs has been implicated in a variety of cancers. On the other hand, lncRNAs can interact with DNA, RNA and proteins by affecting gene expression and chromatin organization. Altered expression of specific lncRNAs has been associated with cancer development and progression (Morlando et al., 2018). Chromatin remodeling complexes can alter the structure and accessibility of chromatin by affecting gene expression. These complexes use energy to reposition, remove or replace histones, allowing for changes in gene accessibility and transcriptional regulation. Dysregulation

of chromatin remodeling complexes can lead to abnormal gene expression patterns and contribute to cancer development (Längst et al., 2015).

Conclusion

Biochemical changes in the tumor microenvironment can affect cancer cell metabolism. Hypoxia, a common feature of solid tumors, leads to altered metabolic pathways, including increased glycolysis and dependence on alternative energy sources. These metabolic adaptations provide survival advantages to cancer cells and support their growth and proliferation.

Understanding the effects of biochemical changes in the tumor microenvironment is crucial to developing effective cancer treatments. Targeting specific components and signaling pathways within the microenvironment has the potential to improve treatment outcomes by inhibiting tumor growth, overcoming therapy resistance, and enhancing anti-tumor immune responses. Treatments that modulate the tumor microenvironment, such as immunotherapies and anti-angiogenic agents, are being actively explored as promising strategies in cancer therapy.

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