CHAPTER 03

Metabolic Alterations in Cancer Cells Exploring the Relationship Between Biochemical and Molecular Events that Drive Tumorigenesis

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SUMMARY

Cancer is reported as an emerging concern, affecting millions of people worldwide. It has harmful effects not only on physical health but also on emotions, social connections as well as finance. The increasing number of cancer-related deaths, challenges faced by healthcare systems and the high-cost treatments highlight the importance of preventing cancer and developing new and effective therapies on a global level. Metabolic alterations, especially associated with changes in cellular energy regulation, play a basic role in the initiation and proliferation of cancer. When metabolic processes are dysregulated, they can cause abnormal cell growth and survival. This dysregulation not only supports the initiation of cancer but also facilitates its progression. Additionally, altered metabolism often leads to synthetic effects, impacting normal physiological functions. Such disturbances may result in abrogated immune responses, enhanced inflammation and augmented oxidative stress (OS), contributing to the complexity of cancer progression. Furthermore, recent research demonstrated the indispensable role of metabolic changes in cancer cells, demonstrating a complex relationship between biochemical and molecular events that drive the development of tumors. In addition to this, understanding and targeting these metabolic vulnerabilities hold the potential for developing new therapeutic strategies to impede cancer initiation and limit its uncontrolled growth. Therefore, in this chapter, we will thoroughly investigate the metabolic alterations in cancer cells as well as the complex association between biochemical and molecular events that drive tumorigenesis.

INTRODUCTION

Cancer is recognized as one of the deadly diseases characterized by complex molecular and biochemical components contributing to its complexity. The fundamental characteristic of cancer is manifested through unregulated cell growth. This abnormal cellular behavior distinguishes cancer from normal physiological processes and culminates in the spread of tumors and the possible dissemination of malignant cells in the body (Du & Elemento, 2015). It is revealed that cancer is not a solitary ailment but rather a collective term for numerous conditions marked by the uncontrolled growth of cells. The complexity of cancer arises from the complex relationship of genetic mutations, signaling pathways and environmental factors that collectively drive the abnormal growth and survival of cells (Ingber, 2002).

Molecular reactions serve as pivotal in the modulation of cancer. Genetic mutations, alterations in DNA repair mechanism and dysregulation of key cellular processes contribute to the aberrant of the cancer cells. Moreover, the biochemical environment surrounding cancer cells, including interactions with neighboring cells and the extracellular matrix, enhances further complexity of the disease (Ingber, 2002).

Cancer cells experience metabolic changes, involving a reconfiguration of cellular metabolism to support their accelerated growth and survival needs. These alterations constitute a fundamental aspect of cancer biology, signifying the transformation in how these cells utilize energy and nutrients. The reprogramming of cellular metabolism is a strategic response to fulfill the escalated necessities of rapid cell propagation and prolonged survival (Agathocles & Harris, 2013).

In other words, cancer modifies their internal metabolic reactions, the molecular processes in a cell, to fuel their abnormal and rapid growth. This adaptation allows them to acquire the necessary resources for continuous and uncontrolled cell division. By redirecting energy and nutrients, cancer cells ensure their sustained proliferation and resilience against the body's normal regulatory mechanisms (Danhier et al., 2017). Therefore, in this chapter, we will thoroughly examine the metabolic modifications in cancer cells as well as we will explore complex associations between biochemical and molecular events that drive tumorigenesis.

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CELLULAR METABOLISM

Cellular metabolism is a complex and highly regulated process that takes place in living cells, providing the energy and building blocks necessary for their survival and function. This complex network of biochemical reactions can be broadly categorized into two main pathways. Anabolism encompasses the synthesis of complex molecules from simpler ones and results in the generation of energy (Morowitz & Smith, 2007) as depicted in Fig 1.

In animals and many other organisms, glucose serves as a central building block for anabolic processes. In the cytoplasm, glycolysis triggers the degradation of glucose, resulting in 2 pyruvate (PRVT) molecules and a limited production of ATP. After this the PRVT can enter the mitochondria, where it undergoes further oxidative processes, generating additional ATP (Chandel, 2021). A key player in anabolism is the molecule of ATP, which acts as an energy currency for the cell. ATP is produced during various metabolic processes and utilized to drive energy-requiring reactions during anabolism, through condensation reactions. Through condensation reactions, simple molecules are linked together to form complex ones i.e., nucleic acids, proteins and lipids (Kaur & Debnath, 2015). Catabolism, in contrast to anabolism, encompasses the dismantling of complex molecules into simpler forms, with the concurrent release of energy. The primary goal of catabolism is to produce ATP which is subsequently used by cells in order to perform their activities (Kaur & Debnath, 2015) as demonstrated in Fig. 2.

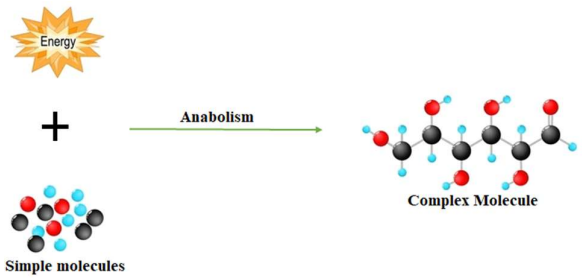

Fig 1. Synthesis of complex molecules from simple molecules

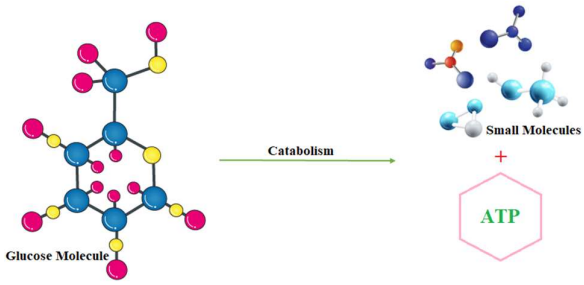

Fig 2. Synthesis of simple molecules from complex molecules

Cellular respiration stands as a major catabolic process situated in the mitochondria. This intricate process results in the breakdown of glucose to yield ATP through 3 primary pathways i.e., glycolysis, TCA cycle and oxidative phosphorylation (OFn). Glycolysis occurs in the cytoplasm, where glucose undergoes conversion into PRVT, resulting in the release of a modest amount of ATP (Kaur & Debnath, 2015; Wikstrom et al., 2015). Subsequently, the PRVT infiltrates the mitochondria, triggering the commencement of the citric acid cycle. This cycle not only generates additional ATP but also produces crucial electron carriers. Finally, OFn harnesses these electron carriers to modulate the production of a substantial amount of ATP (Wikstrom et al., 2015).

Cellular metabolism is efficiently regulated to maintain a dynamic balance between anabolism and catabolism, ensuring that the cell meets its energy and building block requirements. Enzymes serve as indispensable in catalyzing specific reactions and their activity is finely regulated by various regulatory mechanisms (López-Otín & Bond, 2008).

Feedback inhibition is a regulatory strategy commonly employed in biological systems. In this process, the end product of a metabolic pathway functions as an inhibitor for an enzyme situated earlier in the pathway. The purpose of this mechanism is to prevent the overproduction of particular molecules, ensuring a balanced and controlled metabolic response (Shimizu & Matsuoka, 2022). Furthermore, hormones also play a significant role in metabolic regulation. Insulin, for instance, promotes glucose acceptance and storage while glucagon stimulates the release of glucose from storage when energy is needed (Qaid & Abdelrahman, 2016).

HOW CANCER CELLS DEVIATE FROM NORMAL CELLULAR METABOLISM

Metabolic reprogramming in cancer cells refers to the profound alterations in cellular energy and nutrient utilization that distinguish cancer metabolism from normal cellular metabolism. This phenomenon has attracted considerable interest in the cancer research community as it provides insights into the unique strategies that cancer cells employ to sustain their rapid growth, proliferation and survival (Pavlova & Thompson, 2016).

One prominent feature of metabolic reprogramming in cancer cells is the transition from OFn to glycolysis, a shift that occurs even in the presence of oxygen. This transition is commonly referred to as the Warburg effect (Wet) which allows cancer cells to preferentially utilize glycolysis for energy production. Unlike normal cells, which primarily rely on the more efficient OFn in the mitochondria, cancer cells often prioritize glycolysis, producing lactate as a byproduct (Potter et al., 2016). The aforementioned effect is beneficial for cancer cells because it delivers rapid ATP production and generates metabolic intermediates that serve as essential elements for the synthesis of macromolecules obligatory for cell growth and division (Heiden et al., 2009).

Glutamine, an amino acid plays an indispensable role in disturbed metabolic reactions in cancer cells. Cancer cells display augmented utilization of glutamine, a phenomenon known as anaplerosis. Glutamine plays a part in restoring intermediates in the TCA cycle, supporting biosynthetic

pathways and maintaining the pool of molecules required for sustained cellular proliferation (Bruce et al., 2001). Cancer cells often use glutamine to produce Alpha ketoglutarate, a TCA cycle intermediate, promoting anaplerotic reactions that support the creation of nucleotides, amino acids and lipids (Xiao et al., 2016).

Metabolic disturbances in cancer cell extend to lipid metabolism. While normal cells often rely on external sources of lipids, cancer cells frequently exhibit, increased de-novo lipogenesis, synthesizing fatty acids from precursors i.e., glucose and glutamine. This process provides cancer cells with a constant supply of lipids for membrane formation energy storage 7 the formation of signaling molecules (Song et al., 2018). The enzyme fatty acid synthase (FASN) is frequently upregulated in cancer cells, contributing to enhanced de novo lipogenesis. Furthermore, targeting FASN has been recognized as a potential therapeutic strategy to disrupt lipid metabolism in cancer cells (Lin et al., 2016). cancer cells frequently experience OS due to their rapid metabolism and altered mitochondrial function. For the regulation of increased ROS production, cancer cells upregulate antioxidant defense mechanisms. This adaptive response helps maintain redox balance and prevents oxidative damage that could otherwise hinder cancer cells survival and proliferation (Sies & Jones, 2020). NADPH, generated through certain pathways i.e., the pentose phosphate pathway and malic enzyme is indispensable for scavenging ROS and balancing redox homeostasis in cancer cells (Ju et al., 2020).

Metabolic reprogramming in cancer cells extends to amino acid metabolism, which is crucial for supporting the increased demand for protein synthesis during rapid cell proliferation. cancer cells often exhibit altered patterns of amino acid uptake 7 utilization, enhancing the availability of essential amino acids for protein synthesis (Kelly & Pearce 2020). Additionally, certain amino acids i.e., serine and glycine, play key roles in nucleotide synthesis, contributing to the elevated demand for building blocks required for DNA replication and cell division (Amelio et al., 2014).

Mitochondria is the cellular powerhouse that undergoes significant alterations in cancer cells as part of metabolic reprogramming. While OFn is often downregulated in cancer cells still plays an essential role in supporting bioenergetic adaptation. This includes providing metabolites for biosynthetic and participating in redox balance (Raefsky & Mattson, 2017). Mitochondria dynamics, fusion and fission events are also altered in cancer cells, influencing their morphology and function. These changes contribute to the adaptability of cancer cells (Table 1) to varying nutrient and energy availability (Raefsky & Mattson, 2017).

MOLECULAR EVENTS TUMORIGENESIS

Influence of genetic and molecular factors on cancer initiation and progression

Genetic factors serve as a pivotal element in initiating and deriving the progression of this disease. Investigating the genetic factors influencing cancer involves understanding how alterations in the DNA sequence can cause the dysregulation of critical cellular processes, ultimately contributing to the initiation and progression of cancer (Sadikovic et al., 2008).

Genetic mutations are alterations in the DNA sequence that can result from various factors, including exposure to carcinogens, errors during DNA replication or genetic predisposition. This mutation can influence the performance of key genes engaged in the modulation of cell division cell division, growth and repairs. Two major categories of genes are linked with cancer oncogenes and tumor suppressor genes (Basu, 2018). Oncogenes are normal genes that, when mutated, promote cell proliferation and accelerate the growth of cancer. Mutations in oncogenes can result in the formation of hyperactive proteins that drive uncontrolled cell growth. For example, the RAS gene is a well-known oncogene that is frequently mutated in different cancers including lung and pancreatic cancer (Futreal et al., 2004).

Tumor suppressor genes serve as a crucial element in regulating cell division and preventing the formation of tumors. Their primary function is to mitigate abnormal growth of cells, acting as a safeguard against the growth of the cancer. Inactivation or loss of function mutations in tumor suppressor genes can remove the brakes on cell growth, allowing cancer to develop. The TP53 gene, which codes for the p53 protein is a classic tumor suppressor gene. Mutations in TP53 are commonly found in a variety of cancers and are associated with the failure to control cell cycle progression and DNA repair (Lee & Muller, 2010).

Genetic instability refers to an increased tendency for genetic mutations to occur in a cell. This instability can result from defects in DNA repair mechanisms, leading to the aggregation of mutations over time. Lynch syndrome, for instance, is a hereditary condition characterized by a genetic predisposition to colorectal and other cancers due to mutations in DNA repair genes i.e., MLH1 and MLH2 (Huang, 2013). Besides genetic changes, epigenetic variations influence cancer initiation and progression. Epigenetics involves alterations to the DNA molecule or related protein that modulate gene expression without changing the underlying DNA sequence. Aberrant epigenetic modifications can lead to the activation of oncogenes or the silencing of tumor suppressor genes (Gibney & Nolan, 2010). Hypermethylation of CpG islands, which are specific DNA regions with a greater frequency of cytosine and guanine nucleotides, is a common epigenetic alteration in cancer. Methylation of CpG islands in the promoter regions of tumor suppressor genes may silence their expression, promoting uncontrolled cell growth (Esteller, 2002).

Changes in the structure of histone proteins around which DNA is wound, also contribute to cancer progression. Alterations in histone acetylation of methylation can influence gene accessibility and expression, impacting critical cellular processes (Sawan & Herceg, 2010). Some individuals inherit a predisposition to cancer due to specific genetic mutations passed down through their families. Hereditary cancer syndromes are associated with a greater chance of developing different types of malignancies (Fostira et al., 2007).

Furthermore, mutations in the BRCA 1 and 2 genes are linked to an augmented risk of breast and ovarian cancer. These genes are involved in DNA repair and their mutations may cause aggregation of genetic errors, increasing the likelihood of cancer development (Shi et al., 2017) as illustrated in Fig. 3. Familial adenomatous polyposis is a hereditary syndrome characterized by the development of numerous polyps in the colon and rectum, leading to a high risk of colorectal cancer. Mutations in the APC gene are responsible for this condition (Half et al., 2009). Microsatellites are short, repetitive DNA sequences found throughout the genome. Microsatellite instability refers to the accumulation of errors in the length of these repetitive sequences and it is often observed in certain types of cancer (Loeb, 1994).

Fusion genes result from the abnormal joining of 2 separate genes due to genetic rearrangements. These rearrangements can create novel genes with oncogenic potential, contributing to cancer development (Taniue & Akimitsu, 2021). The BCR-ABL fusion gene, generated from the translocation among chromosomes 9 and 22, is prevalent in chronic myeloid leukemia (CML) (Ali, 2016). Genetic mutation can occur in either germline or somatic cells. Germline mutations are present in every cell of an individual and can be passed to offspring, contributing to hereditary cancer syndromes. Somatic mutations, in contrast, arise in individual cells during a person's lifetime and are not passed on to the next generation (Zhang et al., 2015).

The tumor microenvironment, consisting of surrounding tissues, blood vessels and immune cells, significantly impacts cancer growth. Molecular signals from the microenvironment can promote angiogenesis, the formation of new blood vessels, providing nutrients to the tumor. Additionally, chronic inflammation in the microenvironment fosters conditions favorable to cancer development, creating a pro-cancerous environment that supports tumor growth (Anderson & Simon, 2020). Dysregulation of cellular signaling pathways is a hallmark of cancer progression. Complex networks of molecular interactions govern cell functions and disruptions in these pathways contribute to uncontrolled cell growth. Abnormal activation of pathways and certain processes can drive cancer development by promoting cell proliferation and survival (Chappell et al., 2011).

The extracellular matrix (ECM) is a complex network of molecules that provides structural support to tissues. cancer cells can change the ECM via molecular processes i.e., matrix metalloproteinase (MMP) stimulation, allowing them to invade surrounding tissues (Paolillo & Schinelli, 2019). Molecular factors governing immune evasion play a pivotal role in cancer progression. cancer cells can express molecules that suppress the immune response, allowing them to escape detection and elimination by the immune system (Vinay et al., 2015). Furthermore, hormonal factors contribute to the progression of hormone-sensitive cancer. Estrogen, for instance, plays a crucial role in the growth of certain types of cancers (Masi et al., 2021).

ROLE OF ONCOGENESES AND TUMOR SUPPRESSER GENES IN THE REGULATION OF CELLULAR METABOLISM

Oncogenes refer to the genes that, when subjected to mutation or excessive expression, have the potential to stimulate unregulated cell proliferation and play a crucial role in the initiation and growth of cancer. Several oncogenes exert their influence on cellular metabolism, routing it towards pathways that support the high energy demands and rapid proliferation characteristics of cancer cells (Tsatsanis & Spandidos, 2000). The RAS family of oncogenes, including HRAS, plays a central role in cellular signaling and metabolism. When mutated, RAS proteins become constitutively active, resulting in the activation of lowered signaling pathways responsible for cell survival (Zenonos & Kyprianou, 2013). Active RAS promotes increased glucose uptake and enhances glycolysis, even in the presence of oxygen. This metabolic shift allows cancer cells to generate energy rapidly through glycolysis supporting their elevated proliferation (Lv et al., 2016).

RAS activation also influences glutamine metabolism, promoting its increased uptake and utilization in cancer cells. Glutamine serves as a key substrate for the production intermediates in the TCA cycle, facilitating the synthesis of biosynthetic precursors necessary for cell growth (Lukey et al., 2013). The MYC oncogene is a potent regulator of cell growth and metabolism. MYC proteins act as a transcription factor, influencing the expression of genes involved in various metabolic pathways (Stine et al., 2015). MYC enhances glycolysis by upregulating the expression of glycolytic enzymes. This increased glycolytic activity supports the rapid production of ATP and metabolic intermediates required for cell proliferation (Cargill et al., 2021). MYC also stimulates glutaminolysis, promoting the catabolism of glutamine to provide additional carbon sources for the synthesis of lipids and nucleotides, essential for cancer cell growth (Dang, 2013). The PI3K pathway is frequently dysregulated in cancer. Activating mutations in oncogenes such as PI3K or loss of function mutations in the tumor suppressor gene PTEN lead to constitutive activation of this pathway (Yu et al., 2022) as demonstrated in Fig. 4.

The PI3K pathway promotes increased nutrient uptake, including glucose and amino acids, to support the increased metabolic demand of cancer cells. This pathway stimulates anabolic processes i.e., protein and lipid synthesis, promoting cellular growth and proliferation (Nepstad et al., 2020). Tumor suppressor genes are critical for maintaining genomic stability and preventing the uncontrolled growth of cells. Loss of function mutation in these genes leads to the dysregulation of cellular metabolism, contributing to the initiation and progression of cancer (Wang et al., 2019a). The TP53 gene, which codes for the p53 protein, is often referred to as the guardian of the genome. P53 plays a central role in the response to cellular stress, including DNA damage, hypoxia and nutrient deprivation (Royds & Iacopetta, 2006) as demonstrated in Fig. 4.

Table 1. Influence of Metabolic Reprogramming

Metabolic reprogramming aspects	Key influence	Reference
WEt	Shift from OFn to glycolysis.	Pavlova & Thompson, 2016
Glutamine Utilization	Increased usage of glutamine for anaplerosis.	Bruce et al., 2001
Lipid Metabolism	Enhanced de novo lipogenesis in cancer cells, synthesizing fatty acids for membrane formation, energy storage and signaling molecules.	Song et al., 2018
Antioxidant Defense	Upregulation of antioxidant mechanisms in response to increased ROS production.	Sies & Jones, 2020
Amino Acid Metabolism	Altered patterns of amino acid uptake and utilization to support increased protein synthesis and contribute to nucleotide synthesis.	Kelly & Pearce, 2020

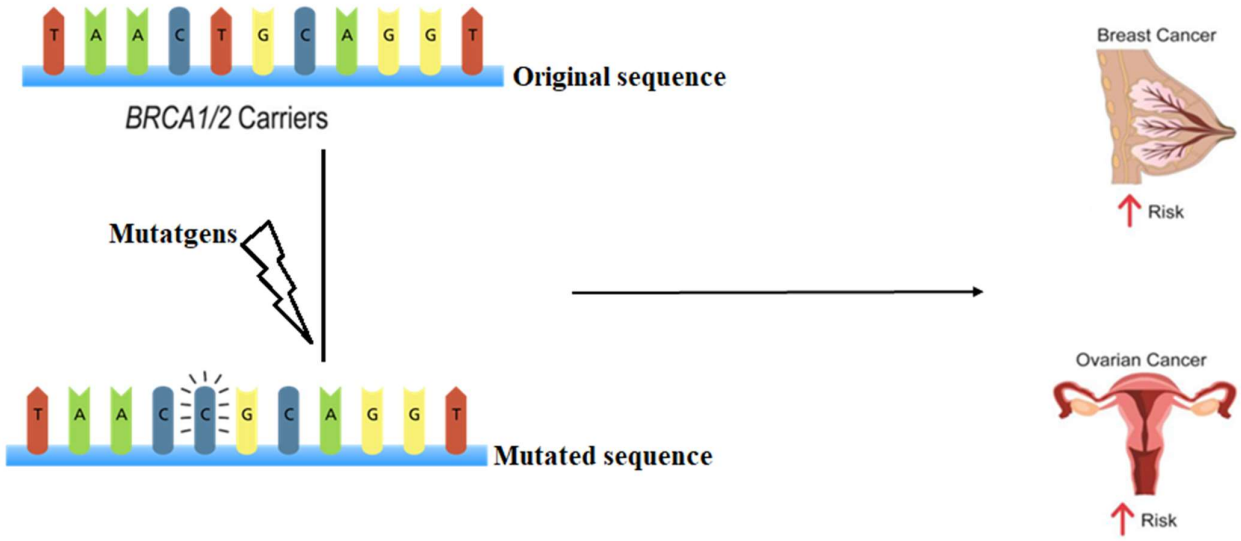

Fig 3. Cancer hazards associated with BRCA1 and 2

Under normal conditions, p53 negatively regulates glycolysis by repressing the expression of key glycolytic enzymes. However, in response to stress i.e., DNA damage, p53 activity is inhibited, allowing for the increased glycolysis to provide energy for cellular repair processes (Zhou et al., 2019). P53 also influences glutaminolysis and its inactivation in cancer cells can result in increased glutamine utilization, supporting the anabolic demands for proliferating cells (Schiliro & Firestein, 2021). Liver kinase B1 is a tumor suppressor that plays a crucial role in cellular metabolism through its regulation of AMPK. LKB1 activates AMPK in response to low energy conditions i.e., glucose deprivation. AMPK in turn regulates cellular metabolism by promoting catabolic processes that generate ATP and inhibiting anabolic processes that consume ATP (Ren & Shen, 2019).

BIOCHEMICAL ALTERATIONS AND MOLECULAR EVENTS IN CANCER CELLS

Biochemical alterations and molecular events in cancer cells encompass a complex range of changes that contribute to the uncontrolled growth, survival and invasive behavioral characteristics of cancer. These alterations occur at the cellular and molecular levels, influencing fundamental processes i.e., cellular signaling, DNA repair and metabolism (Bertram, 2000).

Genetic mutations are fundamental biochemical alterations in cancer cells. These mutations can affect critical genes involved in cellular regulation, leading to dysregulation of cell growth and proliferation. Oncogenes, which promote cell division, can become overactive due to mutations, while tumor suppressor genes, which in normal conditions counteract enhanced cell growth, may be inactivated. These alterations contribute to the loss of normal cellular controls and drive the development of cancer (Plati et al., 2008). Epigenetic modifications, including histone modifications, represent biochemical alterations that affect gene expression without changing the underlying DNA sequence. In cancer cells, these modifications mediate the silencing of tumor suppressor genes or the activation of oncogenes. The resulting changes in gene expression contribute to the malignant transformation of cells and their ability to evade normal regulatory mechanisms (Ilango et al., 2020).

Chromosomal instability is a significant marker underlying the enhanced cancer cells population, categorized by an increased rate of genetic alterations and structural abnormalities in chromosomes. This instability arises from the defects in the cell cycle checkpoints and DNA repair mechanisms. Chromosomal instability contributes to the heterogenicity of cancer cells, allowing them to adapt and survive in different environments (Vargas-Rondón et al.,

2017). Apoptosis is a fundamental process that eliminates damages or unwanted cells. In cancer, there is often a dysregulation of apoptosis, allowing cancer cells to evade cell death signals. Their resistance to apoptosis contributes to the prolonged survival of cancer cells, facilitating tumor growth and resistance to treatment (Plati et al., 2008). Furthermore, angiogenesis is a critical process for supplying oxygen and nutrients to growing tumors. cancer cells stimulate angiogenesis via the secretion of angiogenic factors. The increased vascularization facilitates the sustained growth and survival of cancer cells, contributing to metastasis (Yen et al., 2000). Cancer cells can evade the immune system through various biochemical mechanisms. They may downregulate the expression of antigens that would make them recognizable to immune cells or produce immunosuppressive molecules that inhibit the activity of immune cells. Immune evasion allows cancer cells to escape detection and destruction by the body's immune system (Whiteside, 2006).

Telomerases are protective caps at the ends of chromosomes that prevent them from deteriorating. In normal cells, telomerase shortens with cell division, eventually leading to cell sequence. Cancer cells often maintain their telomerase through the activation of telomerase. This enables cancer cells to undergo unlimited division contributing to tumor growth (Wang et al., 2019b). Cancer cells acquire the ability to invade surrounding tissues and metastasize to distinct organs through a series of biochemical changes. These changes involve alterations in adhesion molecules, enzymes that degrade the extracellular matrix and the acquisition of a more motile and invasive phenotype. Metastasis is a complex process that allows cancer cells to spread and establish secondary tumors in distant sites (Leber & Efferth, 2009).

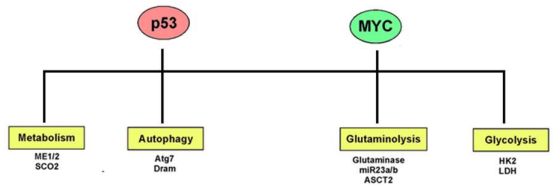

Fig 4. Influence of p53 and MYC

THERAPEUTIC APPROACHES TARGETING CANCER METABOLISM

Therapeutic approaches targeting cancer metabolism have emerged as a promising strategy for developing more effective and selective treatments. Cancer cells exhibit particular metabolic features that distinguish them from normal cells and exploiting these differences provides a unique opportunity to specifically target the vulnerabilities of cancer metabolism (Galluzzi et al., 2013).

Small molecules inhibiting key enzymes in the glycolytic pathway have been investigated as potential anticancer agents. For instance, inhibitors of hexokinase, have shown potential beneficial effects. These inhibitors aim to disrupt the first step of glycolysis, hindering the energy production pathway in cancer cells (Pelicano et al., 2006). Lactate dehydrogenase A (LDHA) is responsible for converting PRVT to lactate, a characteristic feature of the Wet. Inhibiting LDHA disrupts this process, potentially shifting cancer cells towards OFn. Small molecules targeting LDHA are under investigation and early results indicate potential efficacy in inhibiting tumor growth (Miao et al., 2013).

Cancer cells often exhibit an increased dependence on glutamine to support various biosynthetic pathways. Glutaminase is the enzyme responsible for converting glutamine to glutamate, an acritical step in glutamine metabolism. Inhibitors of glutaminase have been developed to limit the availability of glutamate, hindering cancer cell's ability to utilize glutamine to sustain its rapid growth (Matés et al., 2019). In addition to directly inhibiting glutaminase, compounds that act as glutamine antagonists are being investigated. These compounds mimic glutamine and competitively inhibit its uptake by cancer cells, disrupting the biosynthetic processes fueled by glutamine (Xiao et al., 2023).

Altered lipid metabolism is a hallmark of cancer cells and targeting this aspect of cancer metabolism holds therapeutic potential. Fatty acid synthase is a key enzyme in de-novo lipogenesis. Inhibitors of FASN have been explored as potential anticancer agents to disrupt the synthesis of lipids essential for membrane formation and signaling. Preclinical studies have shown promising results and some FASN inhibitors are in early phase clinical trials (Lin et al., 2016). Cholesterol is another critical component of lipid metabolism and inhibitors targeting enzymes involved in cholesterol biosynthesis are being investigated. Disrupting cholesterol metabolism in cancer cells can impair their membrane integrity and signaling processes, potentially hindering tumor growth (Ribas et al., 2016).

Furthermore, NADPH is a crucial molecule for maintaining redox balance and scavenging ROS. Inhibitors targeting enzymes involved in NADPH generation i.e., those in the pentose phosphate pathway and malic enzyme, can disrupt the ability of cancer cells to counteract OS (Hayes et al., 2020). Another approach involves depleting the antioxidants that cancer cells use to neutralize ROS. Compounds that inhibit antioxidant enzymes i.e., superoxide dismutase have shown promising effects by disrupting the cellular defense mechanisms against OS (Battin & Brumaghim, 2009). Compounds targeting mitochondrial metabolism i.e., electron transport chain, aim to disrupt the production of ATP and induce mitochondrial dysfunction in cancer (Pathania et al., 2009).

Furthermore, certain compounds act as metabolic modulators, influencing mitochondrial dynamics and function. For example, metformin has been explored for its potential anticancer effects due to its influence on mitochondrial metabolism (Daugan et al., 2016). Some cancer cells exhibit a dependence on exogenous asparagine for protein synthesis. Asparaginase has been used as a therapeutic agent in certain cancers including lymphoblastic leukemia (Kumar et al., 2014). Furthermore, serine and glycine are essential for nucleotide synthesis and protein production. Inhibitors targeting enzymes involved in serine and glycine synthesis including serine hydroxymethyltransferase, have been

investigated to limit the availability of these amino acids in cancer cells (Lukey et al., 2017).

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