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Metabolic Reprogramming and Mitoepigenetic Alterations Crosstalk on the Path to Cancer

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Abstract: Cancer cells exhibit profound metabolic reprogramming to support uncontrolled growth, survival, and therapy resistance. In addition to a shift toward aerobic glycolysis, tumors display increased dependence on amino acids such as glutamine, serine, methionine, and cysteine, essential for biosynthesis, redox balance, and epigenetic regulation. Lipid metabolism, particularly fatty acid oxidation and lipolysis, is also upregulated, with key enzymes like ATP-citrate lyase (ACLY) and acyl-CoA synthetase short-chain family member 2 (ACSS2) facilitating acetyl-CoA production, which fuels histone acetylation and chromatin remodeling. Importantly, mitochondrial metabolism plays a pivotal role in supporting both bioenergetic and epigenetic demands, linking mitochondrial function with gene regulation. Nucleotide synthesis, both de novo and salvage, is enhanced in tumors and influenced by oncogenes and stress responses, contributing to genomic instability and metastasis. These integrated metabolic and epigenetic adaptations present promising therapeutic vulnerabilities. Targeting key metabolic enzymes and mitochondrial-epigenetic interfaces may function with gene regulation. Nucleotide synthesis, both de novo and salvage, is enhanced in tumors and influenced by oncogenes and stress responses, contributing to genomic instability and metastasis. These integrated metabolic and epigenetic adaptations present promising therapeutic vulnerabilities. Targeting key metabolic enzymes and mitochondrial-epigenetic interfaces may provide effective strategies to suppress tumor progression and overcome chemoresistant.

Keywords: *Cancer Metabolism, Mitochondrial Epigenetics, Amino Acid Reprogramming, Fatty Acid Oxidation, Nucleotide Biosynthesis, Chemoresistance, Mitochondrial Epigenetics.*

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I. INTRODUCTION

Cancer is a condition where body tissue is destroyed by uncontrolled dividing aberrant cells. It is anticipated that 20% of people worldwide will have cancer at some point in their lives[1]. With comparable risk levels for men and women, this corresponds to about one in five individuals. According to recent research, epigenetic reprogramming and changes in cellular metabolism are closely related and play key role in the development and spread of tumors. The study of epigenetic changes that take place inside mitochondria or have an impact on mitochondrial function is known as mitoepigenetics[2]. Once thought to constitute the cell's powerhouse, mitochondria are now recognized as dynamic controllers of signaling and cellular homeostasis. In addition to meeting bioenergetic and biosynthetic needs, they also produce metabolites that act as cofactors for enzymes that alter chromatin, which contributes to oncogenesis. Through this metabolic interaction, mitochondria can modify gene expression patterns that promote carcinogenesis by exerting epigenetic control over both the nuclear and mitochondrial genomes[3]. At the same time, important molecules including acetyl-CoA, NAD^+, and α-ketoglutarate become unavailable due to the rewiring of cancer cell metabolism, which is often known as the Warburg effect and includes more extensive metabolic reprogramming[3]. These metabolites serve as essential substrates or cofactors for enzymes that change DNA and histones, so connecting the cell's metabolic status to its epigenetic environment[3]. Understanding how metabolism, epigenetics, mitochondrial function, and crosstalk between the nucleus and mitochondria interact, it offers a fresh insight in cancer biology. It also identifies weaknesses that could be used for therapeutic intervention, like reversing aberrant epigenetic marks, targeting oncometabolites, or interfering with mitochondria-epigenome signaling networks[4].

II. CROSSTALK BETWEEN THE NUCLEUS AND MITOCHONDRIA

In addition to generating energy through oxidative phosphorylation, mitochondria are crucial for practically every facet of cellular physiology, including acting as signaling hubs to control cellular homeostasis. As essential metabolic centers where catabolic and anabolic cellular activities meet and are integrated, mitochondria have a particular function in controlling metabolism, reactive oxygen species creation, calcium homeostasis, osmotic

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balance, apoptosis, steroid production, cell cycle, proliferation, differentiation, innate immune signaling, epigenetics, and aging processes[5]The growth and spread of cancer are significantly influenced by the crosstalk between the mitochondria and nucleus, which is necessary for cellular activity. Energy production, stress response, and DNA repair are all impacted by this connection, which involves signaling pathways and metabolite exchange[6]. Oncogenic processes, such as alterations in cell metabolism, DNA damage, and oncogene activation, can be facilitated by dysregulation of this interaction. In cancer theranostics, nuclear-mitochondrial cross-talk is a crucial facilitator. It serves as the foundation for communication between the mitochondria, which have their own tiny genome, and the nucleus, which has the majority of the cell's genetic information. The presence of mitochondrial proteins in the nucleus and the availability of mitochondrial metabolites for epigenetic alterations provide evidence of the crosstalk between the mitochondria and nucleus. It's interesting that several proteins linked to metabolism have been shown to go into the nucleus. circumstances that impact cell anergy and metabolism, such as the transport of substrates utilized for his tone modification and mitochondrial proteins in the nucleus[7]. The nuclear membranes' nuclear pore complexes (NPCs) facilitate the transfer of signals to the nucleus and the interchange of macromolecules with the cytoplasm. Similar to this, the mitochondria communicate with the nucleus and other cell compartments through a variety of signaling pathways. For instance, mitochondria produce metabolites from the tricarboxylic acid cycle (TCA) that regulate chromatin and, consequently, gene expression through the acetylation and methylation of DNA and histones. Moreover, studies have shown that the disruption of mitochondrial membrane potential and the generation of reactive oxygen species (ROS) within mitochondria play a key role in signaling pathways between the mitochondria and the nucleus [8].

III. MITOCHONDRIAL DNA

Mitochondria is the powerhouse of the cell and is responsible for the oxidation of glucose thereby leading to the production of energy in form of ATP molecules. Mitochondria was once a freeliving bacteria that were engulfed but not digested by eukaryotes hence there exists a symbiotic relation between the bacteria and the larger cell wherein the bacteria is responsible for providing the food while the larger cell provides it a protective covering all around[9]. Endosymbiotic theory being one of the stepping stones in the development of mitochondria has led to the fact that mitochondria resemble the bacteria in a number of ways[10]. They both are circular and the mitochondrial chromosome is 16,549 base pairs long. It is tightly packed without the presence of introns it thereby making it unique and different to the nuclear chromosome which has the presence of both coding (exon) and non-coding (introns) region present in it[11]. Human mitochondrial chromosomes have been vastly reduced over the period of time and many of its functions particularly including that of respiration as well has been transported to the nuclear DNA[12]. The structure of mitochondrial chromosome has the presence of a control region comprising signals for DNA and RNA synthesis. This forms the basis of mitochondrial DNA replication due to the presence of D loop in this region[13]. However, the non-coding region has the presence of a hypervariable portion which can accumulate mutations as good as ten times more compared to the nuclear DNA. One of the most prevalent reasons for mutations in mitochondrial DNA exists considering the fact that it lacks any proofreading and repairs mechanisms when DNA is not replicating. Mitochondrial DNA does not recombine with other chromosome and is only inherited from maternal side as the sperms mitochondria are discarded as soon as the sperms penetrates the ova thereby providing a significant evidence for maternal inheritance in the progeny, this makes mitochondrial the most unique as far as its inheritance is concerned[14]. Mitochondria have the presence of several complexes which are responsible for storage and production of energy molecules and these complexes specifically code for particular genes thereby forming the backbone of mitochondrial DNA to function efficiently. Complex I also well known as NADH dehydrogenase transporter encodes 7 subunits of protein complex. Complex III also called, cytochrome c oxidoreductase is responsible for encoding cytochrome b protein which forms a crucial part of inner mitochondrial membrane. On the similar grounds the complex IV and V also named as cytochrome c oxidase and ATP Synthetase respectively assist in electron to be transported and energy being produced effectively[15]. There is also the presence of ribosomal RNA mitochondrial genes encoding mRNA which later on translates to protein. It mainly involves the translation of 16s and 12s rRNA for gene expression. 22 genes encode transfer RNA molecule which helps in delivering specific amino acids and making them get associated with ribosomes for incorporation of a long chain of peptides[16, 17].

➢ *Mitochondrial DNA Replication*

Mitochondrial DNA consists of heavy and light strands that vary in their base composition. The heavy strand is rich in guanine and begins replication at the origin located in the D-loop or control region, whereas the light strand, which is cytosine-rich, initiates replication near a tRNA-coding gene situated about 11,000 base pairs downstream from the heavy strand's origin. It is acted upon by the TWINKLE DNA helicase opens up the two strands of mitochondrial gene[18]. Small proteins attach to the single stranded DNA structure which are also known as single stranded binding proteins or mt SSB proteins. These proteins in the mitochondria are further subjected to attachment of primers through the enzyme POLRMT which popularly named as single subunit RNA polymerase. Mitochondria, however has its own DNA polymerase present in it known as POLγ[19]. POLγ comprises three subunits one catalytic and other two are beta subunits thereby which acts as a helper to the catalytic subunit denoted by A. POLγ plays an quintessential role in replication as it is responsible for the polymerase activity, 3'-5'exonuclease activity and lyase activity as well [19]. It attaches nucleotide strand to the loop while the TWINKLE helicase opens up the mitochondrial DNA strand[20, 21]. This intensifying opening in loops causes stretch and leads to the formation of a displacement / D loop as herein the double

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stranded DNA gets displaced by the single stranded DNA in the heavy chain. Since the light chain remains unconstrained, the SSBP attaches to it and the POLRMT along with as POLγ attaches the nucleotides thereby forming a hairpin loop kind of structure on the inner side of the light chain[21]. The mitochondrial replication will however stop when both the heavy and light chains come across the termination associated sequence. One of the very prominent proteins RNASEH1 thereby removes the RNA primers and change them into the DNA nucleotide strand post the termination encounter signal is accomplished. The mitochondrial DNA so replicated however are further acted upon by Topoisomerase3γ so as to prevent hemicantenation and prevents any further coiling to take place [22].

IV. DNA METHYLATION

DNA methylation is among the most extensively researched epigenetic modifications in mammals and plays a crucial role in maintaining normal cellular functions. In eukaryotes, the most prevalent type of DNA methylation is 5-methylcytosine (5mC), formed by the addition of a methyl group to the C-5 position of cytosine. Another form, N6-methyladenine (6mA), results from methylation of the exocyclic NH_2 group at the N-6 position of adenine. Methylation and hypermethylation of gene promoters are key mechanisms leading to gene silencing. DNA methyl-binding proteins (MBPs) specifically recognize methylated cytosines and prevent transcription factors from binding to the promoter region, thereby repressing gene expression[23]. DNA methylation of cytosines is carried out by a group of enzymes called DNA methyltransferases (DNMTs), which catalyze the transfer of a methyl group from S-adenosyl-methionine to cytosine. In mammals, five DNMT family members have been identified: DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L [24]. But as far as we are aware, the global cytosine methylation pattern is exclusively produced by the interaction of DNMT1, DNMT3a, and DNMT3b. Unlike the methylation of nuclear DNA (nDNA), which predominantly occurs at CpG islands, mitochondrial DNA (mtDNA) methyltransferases can modify both CpG dinucleotides and non-CpG sites. Moreover, the level of N6-methyladenine (6mA) in mtDNA is over 8,000 times greater than that found in nDNA [24]. This data suggests that adenine is the main methylation target in mtDNA, even though the enzymes causing mtDNA adenine methylation have not yet been found [25]. The process of DNA methylation is reversible. DNA demethylation has been reported as both passive and active. While active DNA demethylation involves multiple processes, beginning with the removal of methyl groups and the breaking of carbon-carbon bonds, passive demethylation is linked to inhibition of the DNMT enzyme[25]. TET1 and TET2 protein involvement is necessary for the active oxidation-mediated process of demethylation of mtDNA bases. In order to maintain the methylation status of CGIs throughout several cell generations, In the newly synthesized DNA daughter strand, DNMT1 seems to play a role in restoring the parental DNA methylation pattern[26]. DNMT1 is characterized by a predilection for hemi-methylated substrates and a domain that targets replication foci [26].

V. MITOCHONDRIAL EPIGENETICS (MITOEPIGENETICS)

The term "mitoepigenetics" was initially introduced to describe the epigenetic regulation of mitochondrial genome sequences. However, its scope has since expanded to encompass the complex interactions between mitochondrial function and epigenetic patterns. Nearly all key metabolites required for epigenetic regulation, such as β-nicotinamide adenine dinucleotide (NAD^+), ATP, α-ketoglutarate, and acetyl coenzyme A, are generated within the mitochondria and transported to the nucleus [27]. The changes in mtDNA haplogroup sequence and removal of mtDNA have been linked to variations in nuclear DNA methylation patterns which suggest nuclear and mitochondrial genomes follow an important epigenetic interaction [28]. Some studies have reported the presence of non-coding RNAs (ncRNAs) within mitochondria, suggesting that these nuclear- and mitochondria-encoded molecules play a role in regulating communication between the nucleus and mitochondria through both anterograde and retrograde signaling pathways [29][29]. Although mitochondrial DNA (mtDNA) is not packaged with histones, its organization into nucleoids is facilitated by proteins such as TFAM, mitochondrial single-stranded DNA-binding protein, and the Twinkle helicase. These nucleoids may be subject to epigenetic regulation through modifications like acetylation and phosphorylation. Additionally, mtDNA methylation and hydroxymethylation have been investigated in several studies as key components of mitoepigenetic regulation [30].

- *Mitochondrial DNA Methylation:*

The expression of several transcription factors alongside inhibitors becomes regulated through epigenetic mechanisms when tumorigenesis occurs to control both cell differentiation and apoptosis and DNA damage response (DDR). Gene expression changes resulting from epigenetic modifications do not become inherited because they do not modify the actual DNA sequence of affected genes[30, 31]. Epigenetic regulation involves not only DNA and RNA modifications—such as methylation and the action of long and short non-coding RNAs, but also various histone modifications, including acetylation, phosphorylation, methylation, SUMOylation, ubiquitination, and poly ADP-ribosylation (PARylation), which influence the structure and function of chromatin and other associated proteins [30]. Different environmental elements and other factors impact epigenetic modifications that produce specific cell- and tissue-specific modifications to cellular processes. The distinct features of disease pathophysiology including cancer find an explanation through these modifications of the genome. Research into mitochondrial epigenetic patterns remains limited and diagnostic field has excluded mitochondrial epigenetics from investigation despite reporting various genetic abnormalities linked to cancer development.

Cell proliferation occurs through ATP generation by aerobic glycolysis which results in differentiation prevention [32]. Onco proliferative cancers along with pluripotent cells maintain low mtDNA copy numbers and dense DNA

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methylation. These conditions are controlled by fusion/fission activity which distributes mtDNA evenly across the cell [33]. Research shows that defects in fusion act as a positive factor for mtDNA depletion [34]. Since the early hypothesis researchers determined that mitochondria possessed no DNA methylation components of their own. Researchers measured and predicted that mtDNA methylation exists at fractionated levels lower than those found in nuclear DNA within a range of 1 to 20%[28]. The circular nature of mtDNA structure and its secondary structures potentially resulted in false positive DNA methylation signal identification according to bisulfite sequencing analysis and mtDNA methylation assessment [35].

Recent scientific findings demonstrate that methylation alterations take place in mtDNA thus supporting its significance for genome replication as well as gene expression control. Proof of greater mtDNA methylation occurs following DNA replication treatments thus suggesting that feedback control mechanisms through methylation regulate mtDNA copy number [35].

- *Hypomethylation –*

Early research into the link between hypomethylation of protooncogenes failed to produce conclusive evidence among 23 investigative studies [36]. Scientific research at a global scale demonstrates how hypomethylation exists within cancer cells while controlling the overexpression of essential genes and growth factors connected to uncontrolled cell proliferation and metastasis. DNA hypomethylation is started by several events involving tumor genes, including calcium-binding protein, PLAU, and S100A4[36]. Through functional modulation of the extracellular matrix, the hostile phage of cancer cells generates protease that harms extracellular matrix and stimulates cancer metastasis [37]. Proliferation of cancer cells depends on the insulinlike growth factor 2 (IGF2). The cancer cell divisions grow faster when tumour cell hypomethylation modifies the IGF2 gene allele inside tumour cells [37]. Hypomethylation of retrotransposons, such as long interspersed nuclear elements (LINEs), promotes genetic instability in cancer cells. However, the exact causes of DNA hypomethylation remain unclear to researchers [37]. Researchers observed a methylation-related connection between the BCL-2 gene and human

Bcell chronic lymphocytic leukemia yet subsequent evidence for hypo-methylation activating protooncogenes has not emerged. While reduced gene methylation at C-MYC and other genes occurs in human tumors, convincing evidence has not emerged which demonstrates that hypomethylation causes gene activation over secondary changes commonly observed in cancer cells [38].

The mitochondrial genome consists of approximately one to two thousand genes that are encoded by nuclear DNA, alongside numerous copies of mitochondrial DNA (mtDNA). This mitochondrial DNA (mtDNA) shows a significantly increased mutation rate, causing the appearance of new mutations that create a diverse mixture of mutant and normal mtDNA within cells, a phenomenon known as heteroplasmy [39]. As the ratio of mutant mtDNAs escalates, the cell's energy production capacity diminishes, ultimately reaching a point where energy levels are inadequate to maintain cellular functions, known as the bioenergetic threshold. Additionally, mitochondria are subject to continuous processes of fusion and fission, which facilitate the complementation of mtDNAs in a trans manner. The mitochondrial genome (mtDNA) encodes several critical elements, such as 13 proteins, 22 tRNAs, and the 12S and 16S rRNAs. This DNA is packaged within nucleoids and is replicated by the enzyme DNA polymerase-γ (pol-γ) [40]. Transcription is carried out symmetrically from both strands by mitochondrial RNA polymerase (RNA pol), producing large polycistronic transcripts that contain tRNAs interspersed throughout [41]. The cleavage of tRNAs from these transcripts results in the formation of mature rRNAs and mRNAs, which are subsequently translated by ribosomes that are specific to mitochondria and sensitive to chloramphenicol [42]. mRNAs corresponding to these nDNA-encoded subunits undergo translation on cytosolic ribosomes, after which the resultant proteins are transported into the mitochondria via the outer (TOM) and inner (TIM) membrane complexes. Mitochondrial transcription factor A (TFAM), also known as mtTFA, mtTF1, or TFAM, is a crucial protein that interacts with mitochondrial DNA (mtDNA) in a sequence-specific and non-sequence-specific manner to modulate the initiation of mitochondrial transcription and the replication of mtDNA [42]. Mitochondrial DNA (mtDNA) levels generally correspond to the amount of TFAM present, although the precise mechanisms behind this association remain unclear. Research suggests that TFAM dosage affects the regulation of mitochondrial promoters, which in turn influences gene expression and the initiation of RNA synthesis for the first strand of mtDNA replication. Moreover, TFAM possesses a non-specific DNA binding activity that is characterized by combined behavior and high affinity. Evidence from in vitro experiments indicates that TFAM can effectively compact plasmid DNA, which suggests that its non-specific DNA binding activity may play a crucial structural role in genome packaging [43]. A rising perspective sees TFAM as a multifunctional coordinator of mtDNA processes, and interactions between TFAM and mtDNA support this, with major consequences for the preservation of gene expression and control of genome copy number [47].

- *Hypermethylation-*

When DNA hypermethylation affects various activated genes it results in epigenetic silencing which produces genetic instability in cancer cells 38. Researchers have shown that the promoter region of the retinoblastoma tumor suppressor gene (RB1) can undergo primary epigenetic modifications. Large sections of tumor suppression genes become silenced through hypermethylation events that control various human cancer tumorigenic features 44. The cellular signaling process gets influenced by activities which occur within cells. The G1 phage of the cell cycle becomes regulated by two p15 and p16 cell cycle-related genes that show hypermethylation in various cancers. Cells manage DNA repair activities poorly because of dishabituated DNA methylation. DNA mismatch repair mechanism-based

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hypermethylation causes gastric cancers and simultaneously breaks DNA strands in breast and ovarian cancers44. The development of metastatic cancer cells occurs through silencing CDH1 gene (E-cadherin) expression while deathassociated protein kinase 1 (DAPK1) gene silencing causes cancer cell apoptosis escape. Researchers have discovered that every type of cancer along with each cell displays its own distinctive DNA methylation pattern 44. Statistics demonstrate the human genome contains only one percent CpG dinucleotide pairs while the available combinations theoretically amount to six percent. The observed prevalence stands at 1 percent whereas statistical calculation projects an expected prevalence of 6 percent (1/16). Many common genes and especially those related to tumor suppression contain CpG repeat sequence islands existing within their promoter regions at densities ranging from hundreds to thousands of base pairs 45. Methylated DNA regions usually stay in an unmethylated state until they become methylated which results in downstream gene silencing. The hypothesis can be verified through pharmaceutical DNA methyltransferase inhibitor medications or gene mutation that restores expression to suppressed genes. Research indicates that localized promoter hypermethylation serves as a cause of gene inactivation instead of being a consequence of tumor development through observations on experimental animals along with cell cultures and human cancer specimen analysis 45. For example- Hypermethylation at CpG promoters of the mismatch repair gene MLH1 represents an example of epigenetic change in microsatellite-unstable human colorectal cancers. Short DNA regions called microsatellite sequences occur between 1 and 4 base pairs in length throughout the genome. DNA repair defects lead cells to develop irregular microsatellite patterns because of their natural polymorphic nature. During methylation of the MLH1 gene cells stop producing vital proteins which make genome mutation repair impossible thus increasing the mutation rate up to100 times more than normal cellular levels 46.

VI. INTRODUCTION TO NUCLEAR TRANSCRIPTIONAL REGULATION OF MITOCHONDRIAL CONTENT

➢ *Regulation of TFAM–DNA Binding*

The exploration of nuclear transcriptional regulation concerning mitochondrial content introduces the role of TFAM as a critical player in this domain. As a multifunctional protein, TFAM's activities necessitate meticulous regulation to ensure an appropriate equilibrium between compaction, transcription, and replication processes [47]. However, the mechanisms that modulate TFAM activity are not yet fully elucidated. While it may be intuitive to link TFAM's functional capacity to its mRNA expression levels, it is essential to recognize that TFAM transcripts do not always correlate with the actual protein levels. Experimental findings illustrate a significant example of a possible regulatory mechanism that could affect TFAM activity [47]. The ability of cells and tissues to adjust their mitochondrial content in response to energetic demands is a critical adaptive mechanism. Nutritional deficiencies or dysfunctions within the mitochondria can lead to an upregulation of nuclear-encoded mitochondrial gene transcription, a compensatory process referred to as mitochondrial biogenesis [48]. This process, which results in an increase in mitochondrial numbers, is primarily governed by changes in nuclear transcriptional activity. The complexity inherent in mitochondrial biogenesis, which includes feedback amplification, pathway interactions, and tissue-specific responses, is beyond the scope of this review; nonetheless, specific transcriptional regulators are essential to its execution. The PPARγ coactivator-1 (PGC-1) family, consisting PGC-1α, PGC-1β, and PPRC1, interacts with various transcription factors to influence nuclear gene expression[49]. Notably, PGC-1α is essential for stimulating the expression of Nuclear Respiratory Factors (NRF)-1 and -2, which jointly control many genes encoding proteins targeted for import into mitochondria, including TFAM [49]. TFAM is a well-conserved basic protein with around molecular weight of 25 kDa. The mature forms of TFAM in mice and humans (designated as mTFAM and hTFAM, respectively) exhibit a 77% similarity and a 63% identity in their amino acid sequences [50]. Both forms possess a comparable isoelectric point (pI) of around 10, which can be attributed to the presence of basic amino acids that constitute 23% of the protein's structure [50]. The transcriptional upregulation of TFAM is typically associated with an increase in mitochondrial DNA (mtDNA), indicating that TFAM serves as a crucial link between the nuclear transcriptional response and mtDNA levels, thereby facilitating the coordination of mitochondrial biogenesis across both genomes [43]. Mitochondrial transcription factor A (TFAM) is a protein encoded by nuclear DNA that plays an important role in the metabolism of mitochondrial DNA (mtDNA). TFAM interacts with mtDNA in both sequence-specific and non-specific ways. The sequencespecific interaction with mtDNA promoter regions is essential for the initiation of mitochondrial transcription, which may also function as an RNA primer for the commencement of replication[43]. Furthermore, TFAM engages with mtDNA in a sequence-independent manner, facilitating the compaction of the genome. It is probable that both binding modes of mtDNA influence TFAM's effect on the copy number of mtDNA. Given its significant role in the regulation of mtDNA copy number, it is pertinent to explore the relationship between TFAM and neurodegeneration. Investigating this association could provide insights into the potential role of TFAM-related mitochondrial mechanisms in both neurodegenerative processes and neuroprotection [51]. Cancer cell survival relies on functional mitochondria. While mitochondrial gene mutations frequently occur in these cells, they do not disrupt mitochondrial energy production; instead, they modify the mitochondria’s bioenergetic and biosynthetic landscape [57]. These modified states communicate with the nucleus through mitochondrial "retrograde signaling," which regulates signal transduction pathways, transcriptional networks, and chromatin structure in order to match the metabolic and nuclear requirements of the cancer cell [57]. Consequently, cancer cells reprogram surrounding stromal cells to enhance their microenvironment. These alterations activate developmental, stress response, wound healing, and

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nutrient-related pathways that are frequently specific to the local context [58]. Depending on the amount of calories and oxygen available as well as the needs for cell maintenance and reproduction, the mitochondrion serves as a very complex mechanism for energy production and distribution [59]. Bioenergetic reprogramming in many cancer cells reflects a shift from relying primarily on maximal ATP production via oxidative phosphorylation (OXPHOS) in quiescent, differentiated cells to balancing energy generation with the synthesis of substrates required for cell growth and division in proliferating cells [60].

➢ *Role of TFAM in Cancer*

Beyond its essential role in the functionality of normal cells, TFAM is significantly involved in tumorigenesis. Notably, the expression of TFAM in various tumor cells can manifest in two contrasting ways. On one side, elevated level of TFAM have been associated with the advancement and progression of specific malignancies. For instance, TFAM is found to be upregulated in prostate cancer, glioma, and breast cancer, correlating positively with unfavorable patient outcomes [52]. Additionally, in drug-resistant liver cancer cells, increased TFAM expression has been observed, and its inhibition has been shown to improve the sensitivity of these resistant cells to chemotherapy [53].

Loss of the TFAM gene causes mitochondrial dysfunction and reduces tumor development in a Kras-driven lung cancer mouse model. In colorectal cancer cells, increased calcium uptake activates phosphodiesterase 2 (PDE2), which inhibits mitochondrial protein kinase A (PKA). This inhibition stabilizes TFAM levels within the mitochondria, promoting colorectal cancer cell proliferation [54]. A related study showed that increased mitochondrial Ca^{2+} uptake boosts TFAM expression, leading to enhanced mitochondrial biogenesis and elevated production of mitochondrial reactive oxygen species (ROS). This sequence of events activates the NF-κB signaling pathway, which in turn accelerates colorectal cancer cell proliferation [55]. Mutations in TFAM are linked to higher cell proliferation rates and increased tumorigenicity in xenograft models. In colorectal cancer, reduced TFAM expression promotes metabolic reprogramming that suppresses the Wnt/β-catenin signaling pathway through α-ketoglutarate (α-KG), thereby preventing tumor initiation [56]. Furthermore, silencing TFAM in non-small cell lung cancer inhibits tumor cell growth by triggering the ROS-driven JNK/p38MAPK signaling pathway, leading to a reduction in cellular energy production [57]. Reduced TFAM expression increases tumor cells' sensitivity to ionizing radiation [67], and induces G1/S phase arrest. This arrest enhances the interaction between p53 and MDM2, resulting in decreased levels of p53 and its downstream target gene TIGAR.

In contrast, some studies suggest that decreased TFAM expression may be associated with tumor progression. Lower levels of PGC1α and TFAM have been recognized as potential markers of chemoresistance in epithelial ovarian cancer. Suppression of TFAM in ovarian cancer cells increases resistance to chemotherapy by reducing mitochondrial reactive oxygen species (mtROS) and lessening cisplatin-induced apoptosis [58]. Additionally, reduced TFAM levels promote the release of mitochondrial DNA (mtDNA) into the cytoplasm, causing cytoplasmic mtDNA stress and activating the cGAS-STING pathway. This activation stimulates autophagy and supports the progression of esophageal squamous cell carcinoma. In breast cancer, TFAM knockdown decreases mtDNA copy number, triggers Calcineurin-dependent mitochondrial retrograde signaling, elevates mesenchymal gene expression to initiate epithelial-mesenchymal transition (EMT), and fosters the development of cancer stem cells [58].

In the context of head and neck cancer, there is a notable reduction in the expression of TFAM and mtDNA within tumors when compared to their normal counterparts, and this reduction is inversely related to the advancement of the disease [59]. The silencing of TFAM promotes cellular proliferation and resistance to chemotherapy. Conversely, a marked reversal of these phenotypic alterations occurs with elevated TFAM expression, which is linked to metabolic reprogramming in cells and the activation of the ERK1/2-Akt-mTORC-S6 signaling pathway [59].

VII. MITOCHONDRIA AND HISTONE MODIFICATIONS

Beyond DNA methylation, mitochondrial metabolism plays a crucial role in regulating histone tail modifications. The regulation of chromatin structure and function is largely dependent on posttranslational modifications (PTMs) of histones, which include methylation, succinylation, acetylation, SUMOylation and ubiquitylation [60]. These histone PTMs modify the interactions among nucleosome components, such as histones and DNA, thereby impacting chromatin architecture. The dynamic nature of histone modifications is maintained through stringent regulation by histone modification enzymes and their substrates, which are also closely controlled by mitochondrial activity [61].

VIII. EPIGENETICS IN NORMAL DEVELOPMENT AND TUMORIGENESIS

A cell's fate is largely determined by the genes it expresses, which are predominantly controlled through epigenetic modifications. These changes are heritable and result in stable yet reversible alterations in gene activity without modifying the underlying DNA sequence [62]. Epigenetics is a fundamental mechanism that influences the early programming of critical cellular activities such as proliferation, differentiation, programmed cell death, and the development of diseases. It plays an essential role in normal developmental processes, including embryonic development and the differentiation of stem cells [63]. Disruption of epigenetic regulation can lead to a range of diseases, including cancer. Two main models have been proposed to explain tumor development: the clonal evolution model and the cancer stem cell (CSC) model. CSCs drive cellular heterogeneity by displaying stem cell-like characteristics, including self-renewal and modified differentiation potential [64]. This hierarchical organization can be reversible under specific circumstances. The characteristics associated with

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stemness in cancer cells arise from both genetic and epigenetic modifications. The onset and advancement of cancer, driven by oncogenic mutations, are often accompanied by profound epigenetic changes. The regulation of cancer cell states is influenced by epigenetic dynamics, including patterns of DNA methylation, histone modifications, and nucleosome remodeling [65]. These epigenetic alterations are linked to the repression of tumor suppressor genes and differentiation genes across various cancer types, and they may disrupt essential signaling pathways that govern self-renewal and differentiation, such as the Wnt, Notch, Myc, and Hedgehog pathways. Epigenetics extends its regulatory influence beyond stem cells to encompass a variety of other cell types. Comprehensive reviews have examined the epigenetic pathways that contribute to the stability and adaptability of T cell fate [65]. Additionally, the epigenetic control of gene expression is vital for the differentiation, activation, and operational capabilities of innate immune cells. The process of determining cell fate relies on the accurate execution of gene expression programs, which are subject to modifications in the genome and epigenome, both of which are acknowledged for their sensitivity to metabolic factors. Metabolites such as acetyl-CoA, α-ketoglutarate (α-KG), S-adenosylmethionine (SAM), NAD+, and OGlcNAc are instrumental in influencing cell fate by modulating epigenetic changes and gene expression 65.

IX. MITOCHONDRIAL METABOLITES PLAY A VITAL ROLE IN REGULATING EPIGENETIC PROCESSES THAT INFLUENCE BOTH NORMAL DEVELOPMENT AND THE INITIATION OF TUMOR FORMATION

Cofactors required for histone acetylation are key determinants of cell fate. For example, αketoglutarate (α-KG), a byproduct of glutaminolysis, is essential for M2 macrophage activation, supporting their function through integrated metabolic and epigenetic reprogramming 66. Glutamine metabolism supports M2 macrophage activation by facilitating the removal of H3K27 methylation, a repressive epigenetic mark that suppresses the transcription of M2-associated genes 67. Acetyl-CoA, serving as both an acetyl group donor for acetylation and a cofactor for deacetylase enzymes, is crucial for the proper differentiation and function of macrophages and dendritic cells 68. Administration of acetate, a precursor of acetyl-CoA, increases H3K9ac and H3K27ac levels and postpones the early differentiation of human pluripotent stem cells (PSCs) and mouse embryonic stem cells (mESCs) 69. This suggests that lowered acetyl-CoA levels may promote early differentiation in PSCs by reducing histone acetylation. Therefore, acetyl-CoA plays a critical role in regulating differentiation via histone-dependent gene expression in adult stem cells. Key cofactors involved in histone acetylation significantly influence the determination of cell fate 69. Intracellular metabolite levels are influenced by the cell's metabolic processes as well as by external environmental factors like nutrient availability. Importantly, nutrient supply, whether tissue-specific or systemic, can influence stem cell fate by modulating α-KG-dependent dioxygenases, thus connecting external signals to cellular fate decisions 70.

X. METHODS TO DETECT MITOCHONDRIAL EPIGENETICS

Investigating the epigenetics of the mitochondrial genome in cancer cells is considerably more complex than similar studies involving the nuclear genome. Careful attention is required during the isolation of purified mitochondria to facilitate accurate epigenetic assessments[70]. Furthermore, the mitochondrial genome's limited size, which features a reduced number of CpG sites and lacks histones and introns, poses additional challenges. Nonetheless, there are multiple techniques that can be employed to examine the epigenetic modifications induced in mitochondria of cancer cells[70].

There are many methods to detect mtDNA methylation but few are crucial.

- *Bisulfite Sequencing*

Bisulfite sequencing is one of the most prominent methods for detecting the DNA methylation. The methylated and unmethylated cytosines cannot be distinguished using existing sequencing and microarray methods since PCR (polymerase chain reaction) amplification erases DNA methylation patterns [71]. DNA methylation involves a chemical change that frequently happens to CpG dinucleotides. This process entails the addition of a methyl group to the cytosine base in DNA. When DNA is exposed to sodium bisulfite, methylated cytosines remain unaltered while unmethylated cytosines are deaminated and become uracil [71]. Once the bisulfite treatment is initiated the DNA, is sequenced. By comparing the sequenced DNA to the original, untreated DNA, the methylation status of each cytosine is ascertained. Hence in bisulfide sequencing the unmethylated sequences has the presence of cytosines which upon the post translation gets converted to uracil while the methylated cytosine residues as it is which acts a point of differentiator in their expression levels [72] as shown in figure-1. Additionally, bisulphite modification does not distinguish between 5-mC and 5-hydroxymethylcytosine (5-hmC). However, a limitation of bisulphite sequencing is its inability to quantify the percentage of methylation at specific sites [73].

- *Pyrosequencing*

Pyrosequencing is another important method of detecting the DNA methylation. Through bisulfite modification, single-nucleotide polymorphisms, or SNPs, can be intentionally produced at CpG sites. This is what the pyrosequencing platform is intended to identify. When sodium bisulfite is applied to genomic DNA, cytosine is predominantly converted to uracil; yet, 5-methylcytosine is shielded from deamination and the CG sequence is maintained in subsequent processes [74].

However, the incorporation of dNTPs and the presence of pyrophosphate (PPi) is detected by an enzyme cascade

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reaction that results in the emission of light. When dNTP is added to the DNA sequence then pyrophosphate is released. This pyrophosphate can be converted to ATP-by-ATP sulfurylase. The ATP so generated is utilized by Luciferase to form luciferin and oxyluciferin that would result in the production of light. Pyrosequencing requires two substrates, adenosine 5′phosphosulfate (APS) and luciferin, along with four enzymes: DNA polymerase, ATP sulfurylase, luciferase, and apyrase [74]. A single-stranded PCR amplicon is used as the DNA template in pyrosequencing. First, a single-stranded DNA (ssDNA) template is annealed to a sequencing primer. The DNA polymerase integrates the dNTP into the developing strand upon the addition of a single nucleotide, releasing pyrophosphate (PPi). After ATP is generated by ATP sulfurylase from PPi and the substrate APS, luciferase is triggered to convert luciferin into the light-emitting compound oxyluciferin [75]. The amount of nucleotide supplied to the elongating strand determines how much light is released. Apyrase degrades leftover nucleotides, enabling the next nucleotide to be added. The methylation level at a specific site in the sample can be accurately measured by comparing the intensity of light emitted during the incorporation of either C or T at a CpG site within the amplified DNA fragment [75]. The mechanism of pyrosequencing is illustrated in Figure2, highlighting the enzyme cascade reaction and real-time light-based detection following nucleotide incorporation.

➢ *Microrna Gene Silencing:*

In mammals, microRNAs (miRNAs) are known to modulate approximately 60% of the transcriptional processes associated with protein-coding genes. MiRNA can also change mitochondrial genes and related epigenetic mechanisms. This approach may identify specific microRNAs that are potentially linked to mitochondrial epigenetics in cancer cells. Investigating individual microRNAs along with their downstream targets could provide valuable insights into the significance of particular microRNAs for research initiatives [76]. Following this, quantitative PCR methods would be advantageous for evaluating the role of specific microRNAs in the progression of various cancers Additionally, the application of microRNA mimics and antimicroRNA agents (such as antagomiRs or miR inhibitors) tailored for specific microRNAs would further validate the regulatory functions of microRNAs in relation to mitochondrial-associated cancers [77].Certain miRNAs also experience silencing through methylation mechanisms in cancerous cells. Notably, Let-7 and miR15/16 are crucial in the down-regulation of the RAS and BCL2 oncogenes, with their expression being diminished in cancerous tissues[78]. A reduction in the levels of miR-125b1, which acts as a tumor suppressor, has been documented in various cancers, including prostate, ovarian, breast, and glial cell malignancies. Experimental studies conducted *in vitro* have demonstrated that miR-125b1 targets the HER2/neu and ESR1 genes, both of which are associated with breast cancer. The epigenetic silencing of miR-125b1 is primarily attributed to DNA hypermethylation. In breast cancer patients, CpG islands located close to the transcription start site have been found to be hypermethylated [79]. Loss of CTCF binding, combined with increased repressive histone marks like H3K9me3 and H3K27me3, has been associated with DNA methylation and the subsequent silencing of miR-125b1. The study proposes that CTCF acts as a boundary element, preventing the spread of DNA methylation. Their findings suggest that methylation negatively affects the expression and function of miR-125b1, leading to its silencing. Moreover, the early epigenetic silencing of certain miRNAs in breast cancer indicates their potential use as tumor biomarkers [80]. Aberrant DNA methylation frequently causes epigenetic silencing of miRNA genes in cancer cells. Nearly one-third of miRNA promoters that are active in normal mammary cells become hypermethylated in breast cancer cells, a much higher rate than that seen for protein-coding genes [81].

- *MiRNA Profiling:*

The analysis of microRNA profiles in test samples can be conducted using array-based techniques and subsequently compared to control samples.

➢ *Biochemical Epigenetic Assays:*

Based in Farmingdale, NY, USA, Epigentek has released multiple kits aimed at evaluating DNA and RNA methylation. These include assays for DNA methyltransferase and demethylase, as well as techniques for methylated DNA immunoprecipitation and quantification, such as the 5-hydroxymethylation assay and 5methylcytosine estimation [82]. Furthermore, the company provides kits for analyzing methyl-DNA binding proteins. Additional kits for quantifying histone modifications are also available. Researchers may consider these kits for their applicability in projects related to cancer cells mitochondrial epigenetics, tailored to their specific needs [82].

XI. METABOLIC REPROGRAMMING IN CANCER CELLS

Cellular metabolism is essential for sustaining normal physiological functions within the body, as it supplies the energy and growth substrates necessary for life processes while also regulating the balance of cellular redox. During tumorigenesis and the progression of tumors, there is a modification in cellular metabolism that satisfies the energy and biosynthetic requirements necessary for the unregulated growth of cancer cells [83]. The initial observations regarding the alteration of cancer cell metabolism were made by Otto Warburg in 1920. This research culminated in the identification of the event known as the 'Warburg Effect,' which is evident in various cancer types. This effect describes the ability of cancer cells to shift their metabolic processes towards anaerobic glycolysis, despite the availability of oxygen, resulting in an increased rate of glycolysis in tumors [84]. In response to the increasing demands of cancer cell proliferation, these cells develop a wide array of mechanisms to adjust their metabolism, a topic that has been the focus of extensive research over the years. These mechanisms may involve the upregulation of Glycolytic Enzymes, enhanced Glucose uptake, increased hexose monophosphate shunt, activation of Serine Synthesis Pathway, and alleviated amino acid and lipid metabolism in

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cancer cells, which delivers vital substrates and energy that support the growth of tumors. Such alterations culminate in what is known as a 'Metabolic Switch, which favors anaerobic glycolysis instead of oxidative phosphorylation as the primary metabolic route in cancer cells [85]. As a result, the idea of 'metabolic reprogramming' has emerged as a key concept in cancer research, emphasizing the ability of malignant cells to derive vital nutrients from an environment that is deficient in nutrition, thus ensuring their persistent growth and proliferation [86]. Enhanced glycolysis in neoplastic cells may result from the increased expression of glucose transporters, such as GLUT1, which is present on the cell membrane, and GLUT4, which must be translocated from the cytoplasm to facilitate greater glucose uptake. This phenomenon is often accompanied by a rise in critical glycolytic enzymes, notably the rate-limiting Hexokinase 2 (HK2) and Pyruvate Kinase [85].Thus, glycolysis takes over as the primary energy route for these cells, even in the presence of oxygen, causing an excessive amount of lactate to be produced. It is important to highlight, that glycolysis is not the exclusive metabolic pathway that malignant cells utilize.

Mitochondria play a crucial role that cancer cells exploit to support their growth and survival by generating oncometabolites, shifting metabolic pathways, disrupting the balance between reactive oxygen species (ROS) and antioxidants, and evading cell death or life control mechanisms[85]. Tumor cells depend on mitochondria to carry out various vital functions, acting as dynamic regulators of malignant processes primarily via metabolic reprogramming. Throughout different stages of cancer development, including neoplastic transformation, tumor progression, metastasis, and therapy response, tumor cells utilize mitochondrial adaptability to meet their changing demands[87]. In particular, proliferating cancer cells use mitochondria as a metabolic engine to satisfy increased energy requirements through ATP production and to supply anabolic precursors necessary for the synthesis of macromolecules like proteins, lipids, and nucleotides [88].

Reactive oxygen species (ROS) are identified as by products resulting from oxygen consumption and cellular metabolic activities. The primary sources of endogenous ROS in tumor cells are mitochondria and NADPH oxidases (NOX) [89]. ROS is essential for understanding both the physiological processes and the pathophysiological aspects of aerobic life. An excess or mislocalized presence of ROS can lead to detrimental effects on cell growth. Increased ROS levels are associated with tumor progression through both genetic alterations and epigenetic modifications [90]. Furthermore, ROS serves as signaling molecules that contribute to DNA damage, which in turn enhances genetic instability and tumor formation. The oxidative stress caused by ROS is closely associated with the hypermethylation of promoters of tumor suppressor genes and a widespread hypomethylation [89].By promoting transfer of methyl groups to cytosine, ROS promotes DNA methylation. This process can occur either through the production of huge complexes involving DNTM1 and DNMT3b or by increasing the expression of DNMTs, which ultimately results in gene hypermethylation. [89]. Superoxide anion, a variant of ROS, increase the expression of DNMTs. An increase in superoxide anion levels results in the upregulation of DNMT1 and DNMT3B, while concurrently inhibiting superoxide anion, which causes a significant drop in DNA methylation and DNMT upregulation. It is also well established that hydrogen peroxide (H_2O_2) elevates the expression of DNMT1 and HDAC1, leading to gene silencing through promoter methylation and histone deacetylation [91]. Research investigating brain function found increased levels of 5-methylcytosine (5mC) alongside decreased 5hydroxymethylcytosine (5hmC) in the adult cerebellum, accompanied by elevated reactive oxygen species (ROS), indicating that ROS may facilitate DNA methylation.

DNA methylation (5mC), demethylation, and hydroxymethylation (5hmC) are key epigenetic modifications found in the mammalian nuclear genome. Hydroxymethylation of DNA is influenced by oxidative stress as well as the enzymatic activity of TET1 [89]. It has been suggested that oxidative stress activates TET enzymes by increasing α-ketoglutarate (α-KG) production, which in turn raises 5hmC levels. This oxidative stress-driven activation of TET enzymes promotes the conversion of 5mC to 5hmC, potentially leading to gene demethylation [89]. By increasing cellular 5hmC levels with ascorbate (vitamin C), one may see how redox modifications affect TET activity. As an antioxidant, vitamin C effectively scavenges primary reactive oxygen species (ROS), and its application results in elevated 5hmC levels, thereby promoting demethylation. In addition to ROS, the availability of oxygen also affects the enzymatic activities of DNMTs and TETs, with hypoxia inducing hypermethylation by diminishing TET activity. Both hypermethylation and hypoxia are well-recognized hallmarks of cancer. TET enzymes belong to the 2-oxoglutarate (2OG) oxygenase family, which act as oxygen sensors. Tumor hypoxia directly suppresses TET activity, resulting in decreased levels of 5-hydroxymethylcytosine (5hmC). This diminished TET function causes an accumulation of 5-methylcytosine (5mC), leading to reduced gene expression. Under hypoxic conditions, 5hmC levels decrease in a dose-dependent manner, paralleling reductions in purified TET1 and TET2 enzyme concentrations [89]. Figure-3 illustrates how oxidative stress, hypoxia, and vitamin C influence TET enzyme activity and thereby modulate epigenetic modifications such as DNA demethylation or gene silencing through the balance between 5mC and 5hmC levels in cancer cells.

- *Glucose Metabolism*

Glucose serves as the primary fuel for cell proliferation. Its metabolism encompasses several pathways, including glycolysis, the hexose monophosphate pathway, and the serine synthesis pathway (SSP) in the cytoplasm, as well as oxidative phosphorylation involving the tricarboxylic acid (TCA) cycle within the mitochondria. Glycolysis is the central pathway for glucose breakdown. The end product of glycolysis, pyruvate, can either be converted into lactate by lactate dehydrogenase and expelled from the cell or transported into mitochondria to fuel the TCA cycle [92].

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➢ *The Warburg Effect*

Tumor cells have a characteristic feature of rapidly growing in a variety of different tissues and thereby taking up the nutrients that would have been essential for a healthy normal cell to thrive. There comes in role of the Warburg effect which forms the basis of all the cancerous cells. The prerequisite for growth of any type of cells is the energy in form of ATP molecules [93]. ATP can be generated through two processes namely Substrate level phosphorylation inclusive of glycolysis thereby generating 2 ATP molecules while the other way of energy production is oxidative phosphorylation involving the electron transport carrier and generating a total of about 34 ATP molecules overall [94]. Glycolysis cannot always be used as an upstream pathway for Kreb's cycle & OXPHOS generation but also is another primitive castle for production of lactic acid in anaerobic respiration occurring in the absence of oxygen as well. Contrary to this, the cancer cells undergo several mechanistic and cellular changes for the Warburg effect to effectively function in them [95]. Essentially the cells stop ATP production via OXPHOS and substitute it with an increased rate of glycolysis. However, the OXPHOS is responsible for generation of more energy in the cancer cells due to the fact that lactic acid so produced benefits the cancer cells. This happens so because when secreted from cells the lactic acid can damage adjacent cells such as cytotoxic T cells & natural killer cells, which would otherwise be capable enough to kill the cancer cells from roots. Hence the aerobic glycolysis prevents the killing of cancer cells by inhibiting and suppressing the immune system to a much larger level [96]. Another very prominent process is that increased uptake of glucose and the formulation of Glucose-6- Phosphate via glycolysis provides the substrates for Pentose phosphate pathway thereby generating NADPH which acts as key player in overcoming the oxidative status experiences by cancer cells and is widely utilized for the synthesis of fatty acid and steroids [97].

Cancer cells grow more rapidly than the blood vessels that nourish them. As a result, when the tumor grows, the oxygen supply to these cancer cells reduces resulting in creation of a hypoxic environment and making the cancer cells prepare themselves to thrive in such hypoxic condition arising around them. However, a shift to aerobic glycolysis could enable the cancer cells to use the substrates from glycolysis and Kreb's cycle to produce other molecules [98].

➢ *Glycolytic Enzymes Involved in Cancer*

- *Hexokinase:*

Hexokinase is the enzyme responsible for converting glucose to glucose-6phosphate (G6P) and serves as the first rate-limiting enzyme of glycolysis. There are four major hexokinase isoforms: Hexokinase 1 (HK1), Hexokinase 2 (HK2), Hexokinase 3 (HK3), and Hexokinase 4 (HK4). HK1, HK2, and HK3 have a high affinity for glucose and are inhibited by excess G6P. In contrast, HK4—also known as glucokinase—has a low affinity for glucose and is not inhibited by G6P [99]. Compared to normal cells, neoplastic (cancer) cells exhibit elevated expression of HK2, which contributes to increased glucose flux. The mutant form of p53 commonly found in malignant cells can bind to the HK2 promoter, modulating its transcription [100]. Additionally, the hypoxia-inducible factor HIF1-α enhances HK2 promoter activity by binding to hypoxia-responsive elements (HREs) within the promoter region. The methylation status of the HK2 promoter also influences its regulation and expression. Telomerase has been shown to regulate autophagy by activating HK2 expression via the telomerase-HK2-mTOR signaling pathway[99]. Recent studies indicate that dysregulation of miR-148a and HK2 signaling contributes to cisplatin resistance in cervical cancer cells, highlighting this pathway as a potential therapeutic target. The proto-oncogene MYC transcriptionally upregulates HK2 expression. Furthermore, the long noncoding RNA (lncRNA) HOTAIR regulates HK2 by interacting with miR-125 and miR143 [101]. For example, miR-143 binds directly to the 3′ untranslated region (3′UTR) of HK2 mRNA, promoting its degradation and reducing mRNA stability. Conversely, the lncRNA UCA1 promotes HK2 transcription by suppressing miR-203, contributing to the aggressive phenotype seen in cancers such as esophageal carcinoma. The specific roles of HK3 and HK4 in cancer cell glucose metabolism remain unclear [101].

- *Phosphofructokinase (PFK-1):*

Phosphofructokinase 1 (PFK1), recognized as the second rate-limiting enzyme in the glycolytic pathway, catalyzes the reaction converting fructose-6phosphate (F6P) into fructose 1,6-bisphosphate (F1,6-BP) [102].The enzyme 6-phosphofructo-2kinase/fructose-2,6-bisphosphatase 3 (PFKFB or PFK2) creates fructose 2,6-bisphosphate, a potent activator of PFK1, at higher ATP concentrations, which causes allosteric inhibition. PFKFB contains two domains that possess both kinase and phosphatase functions. The domain exhibiting kinase activity catalyzes the phosphorylation of F6P to F2,6-BP, whereas the domain with phosphatase activity facilitates the dephosphorylation of F2,6-BP back to F6P [102]. The isoenzyme produced by the PFKB3 gene demonstrates the most significant kinase activity and is found to be overexpressed in various cancer cell types. KLF-4 and ZEB1 are transcription factors that interact with the promoters of PFKP, enhancing its expression and facilitating the proliferation and metastasis of tumor cells. The phosphorylation of PFKP at tyrosine 64 by EGFR is vital for AKT activation and the following β-catenin transactivation, which enhances the expression of oncogenes like MYC and cyclin D1 that contribute to tumor development [103].Meanwhile, in hypoxic environments, PFK1 is modified by O-GlcNAc at serine 529, leading to a decrease in its activity and a rerouting of glucose metabolism to the pentose phosphate pathway, generating NADPH that aids in cellular protection against oxidative damage and supports tumor expansion 104.

- *Pyruvate Kinase:*

In malignant cells, PKM2 expression is elevated compared to PKM1, which functions as a constitutively active tetramer. Research indicates that PKM2 provides a competitive growth advantage for neoplastic cells. Serine and F1,6-BP are identified as two activators of PKM2. This enzyme can exist in either a low-activity dimer form or a

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highly active tetramer form, and the equilibrium between these forms is essential for tumorigenesis. PKM2 has also been implicated in leukemogenesis [104]. PKM2 is tetrameric in leukemia cells, but its SUMOylation causes it to become unstable. PKM2 is tetrameric in leukemia cells, but its SUMOylation causes it to become unstable. A different metabolic route, in which PEP is transformed into pyruvate via PGAM1 phosphorylation by PEP, with PEP serving as a phosphate donor, is indicated by cancer cells having reduced PKM2 activity. In addition, severe clinical signs of liver cancer are strongly associated with PKM2. Increased reactive oxygen species (ROS) can induce redox equilibrium, oxidize the Cys (358) residue, and redirect glucose into the hexose monophosphate pathway, all of which can inhibit PKM2 activity. This promotes the survival of cancer cells under oxidative stress while maintaining antioxidant defenses. [101].

- *Lactate Dehydrogenase-*

The reversible conversion of pyruvate to lactate is catalyzed by lactate dehydrogenase (LDH). LDHs are tetrameric enzymes encoded by four distinct genes: LDHA, LDHB, LDHC, and LDHD. The isozymes LDHA and LDHB are predominantly expressed and can form both heterotetramers and homotetramers. Notably, LDHA—which is encoded by a c-Myc-responsive gene, is highly expressed in many cancers and is essential for maintaining elevated glycolytic flux in tumor cells. [105, 106]. High levels of LDH-A, a cytoplasmic enzyme central to both aerobic and anaerobic glycolysis, are strongly associated with poorer prognosis in cancer patients. Elevated lactate concentrations correlate with tumor malignancy, recurrence, reduced survival, and increased metastasis. Studies have demonstrated that reduced LDH-A expression inhibits glycolysis, tumor growth, and lung metastasis in thyroid cancer models both in vitro and in vivo. In triple-negative breast cancer (TNBC) cell lines, LDH-A knockdown disrupts aerobic glycolysis, significantly reducing cell proliferation, migration, and invasion [105].

- *Enzymes in the Oxidative Pentose Phosphate Pathway*

Many types of malignancies are frequently associated with increased activity or expression of glucose-6-phosphate dehydrogenase (G6PD). The histone methyltransferase NSD2 methylates histone H3 at lysine 36 (H3K36me2) at the G6PD promoter, enhancing its transcription. Several signaling pathways have been identified that elevate G6PD activity or expression in cancer cells[107]. The TP53-induced glycolysis and apoptosis regulator (TIGAR) promotes tumor progression by upregulating G6PD, thereby increasing pentose phosphate pathway (PPP) flux and biosynthesis. Additionally, TAp73, a p53 family member commonly overexpressed in tumors, supports this effect. Conversely, the Bcl-2-associated athanogene 3 (BAG3) protein inhibits G6PD dimerization and enzymatic activity. Mutant p53 loses the ability to suppress G6PD, whereas wild-type p53 binds directly to G6PD, preventing the formation of its active dimer[106].

Elevated levels of 6-phosphogluconate dehydrogenase (6PGD) and its product ribulose-5phosphate (Ru5P) inhibit AMPK activation by interacting with the active LKB1 complex, thereby promoting fatty acid synthesis through the dephosphorylation and activation of acetyl-CoA carboxylase 1 (ACC1). The glycolytic intermediate 3-phosphoglycerate (3-PG) inhibits 6PGD activity, and phosphoglycerate mutase 1 (PGAM1) maintains low 3-PG levels to favor the pentose phosphate pathway in cancer cells. Beyond its metabolic role, 6PGD enhances c-Met phosphorylation, facilitating metastasis, and drives epigenetic reprogramming that supports distant metastatic subclones in pancreatic ductal adenocarcinoma (PDAC). The 6PGD inhibitor 6aminonicotinamide (6AN) reverses these epigenetic changes and suppresses tumor metastasis. Post-translational modifications, particularly acetylation and phosphorylation of 6PGD, regulate lipogenesis, glycolysis, and redox balance. In glioma, EGFR-mediated phosphorylation of 6PGD at Y481 enhances its activity, promoting DNA synthesis and radiation resistance; patients with lower Y481 phosphorylation exhibit improved survival. Dysregulated 6PGD expression accelerates tumor growth and therapy resistance.

XII. CHANGES IN MITOCHONDRIA OF THE CANCER CELLS

Cancer cells undergo several distinct processes in order to switch themselves on aerobic glycolysis to strive through the toughest of times effectively and in a full-fledged manner to prevent any hindrance in their growth and survival [108]. They express a special isozyme Hexokinase which binds to mitochondria enabling them to not only have readily access even to minutest amount of ATP produced by OXPHOS but also have an increased glycolysis as well and thereby preventing the enzyme to inhibit its own product i.e. Glucose-6-phosphate which leads to immense acceleration in the rate of glycolysis to occur in cancer cells [108]. An embryonic isozyme is expressed in cancer cells for pyruvate kinase. However, with a lower catalytic rate than the original pyruvate kinase, this isozyme is responsible for creating a bottleneck for glycolysis thereby allowing the accumulation of glycolytic intermediate designated for a biosynthetic function [109].

Not only the change in glycolysis is responsible for the Warburg effect but the larger picture must also be always taken into the point if fact satisfying several theories for the cancer cells to exist undisturbed. In a healthy tissue energy production via anaerobic respiration occurs in tissue having lower oxygen levels (Hypoxia environment) hence as a result the transcription factors involved in cellular changes also play a significantly important role in increasing the rate of glycolysis through the generation of Hypoxia inducible factor 1 or HIF-1 [110]. This HIF-1 results in an increased production of glycolytic enzymes that accelerates a number of phenomena including the uptake of glucose by cells, higher ATP production and most importantly upstreaming the expression of signaling molecules like vascular endothelial growth factor facilitating the blood vessel growth which further enhances the growth and nutrients being provided to the cancer cells. HIF-1 is hydroxylated in normal cells and polyhydroxylated HIF-1 is destroyed by

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the proteasome thereby leading to the degradation of this factor which further prevents any change in the glycolysis for the energy production in the form of ATP molecules [110].

Polyhydroxylase2 requires alpha ketoglutarate and Vitamin C as their primary quintessential components to be formed with a huge dependence on the oxygen activity for their formation. Since the oxygen is utilized for polyhyoxylase generation hence it creates a hypoxic environment which further prevents the degradation of HIF-1 causing an increased glycolysis in cancer cells [111]. In the cancer cells Kreb's cycle enzymes including succinate, fumarate is dysfunctional so they get accumulated in the mitochondria leading to spill themselves in the cytoplasm which acts as an accelerator for the rate of glycolysis to take place. The enzyme, isocitrate dehydrogenase, a mutant form of which results in the production of the oncogenic metabolite 2-hydroxyglutarate instead of alpha keto glutarate in cancer cells alters the DNA methylation pattern which further suppresses the dependence on growth factors for cell proliferation, division etc. Cancer cells also experience a huge modification in the OXPHOS generation [112]. Typically, in healthy cells the electron transport chain utilizes energy from the Kreb's cycle to pump protons into the intermembrane space of mitochondria thereby generating a proton gradient therein which can be used for production of ATP molecules via ATP synthase. But in the case of cancer cells spilling a matter of fact that these protons refuse to enter the intermembrane mitochondrial space the ATP synthase works in a complete reverse manner and it ends up hydrolyzing ATP to generate a proton gradient. However, due to this the cancer cells overexpress inhibitory factor-1 which inactivates the function of ATP synthase preventing its reverse function and thereby leading to a sufficient energy production [112].

XIII. ONCOMETABOLITES FORMATION

The principal oncometabolites driving tumorigenesis include fumarate, succinate, and the enantiomers of 2-hydroxyglutarate (2-HG) [113]. Cancer cells leverage these metabolites to promote progression and malignancy. Loss-of-function mutations in fumarate hydratase (FH) and succinate dehydrogenase (SDH) are recognized as key driver mutations and important mediators of epigenetic reprogramming [85]. In SDH-deficient cells, excessive succinate and succinyl-CoA accumulation causes widespread lysine hypersuccinylation, altering genome-wide transcription, impairing DNA repair, and contributing to drug resistance[114]. This hypermethylation phenotype is also observed in gastrointestinal stromal tumors with SDH mutations. In renal cancer, FH deficiency or SDH inactivation leads to fumarate or succinate buildup, which inhibits hypoxiainducible factor (HIF) prolyl hydroxylases (PH), stabilizing HIF and promoting angiogenesis by modulating α-KG availability. Isocitrate dehydrogenase (IDH) exists in three isoforms—IDH1 (cytosolic), IDH2 (mitochondrial), and IDH3 (mitochondrial and cytosolic)—with gain-offunction mutations in IDH1 and IDH2 linked to various cancers [115].

➢ *Metabolic Enzymes*

- *Gliomas-*

Mutations in the IDH gene, especially IDH1, are commonly found in diffuse gliomas, including low-grade types such as diffuse astrocytomas and oligodendrogliomas, as well as high-grade secondary glioblastomas. Metabolomic analysis of glioblastoma cells harboring the IDH1 R132H mutation shows that the mutant enzyme converts α-ketoglutarate (α-KG) into D-2hydroxyglutarate, contributing to the glioma CpG island methylator phenotype[116].

- *Acute Myeloid Leukemia-*

IDH mutations, particularly in IDH1 and IDH2, occur in approximately 15–20% of cases. These mutations are associated with global and locus-specific hypermethylation patterns in acute myeloid leukemia (AML) by inhibiting demethylases such as KDM4C [116]. The oncometabolite 2-hydroxyglutarate (2-HG) inhibits the H3K9 demethylase KDM4C during adipocyte differentiation. Moreover, ectopic expression of the canonical IDH1 R132H mutant promotes cytokine-independent growth and blocks the differentiation of hematopoietic cells [117].

- *Chondrosarcomas-*

These are malignant bone tumors that synthesize cartilage matrix, andhas been found to possess mutations in IDH, particularly in the IDH1 and IDH2 genes. Mutation in IDH2 (R172K) was linked to an increase in 2-HG levels, leading to DNA hypermethylation, a halt in differentiation, and the development of sarcoma *in vivo* [118].

- *α-KG, succinyl-CoA, Fumarate*

α-Ketoglutarate (α-KG), succinyl-CoA, fumarate, and citrate are key TCA cycle intermediates that influence epigenetic modifications by fluctuating their concentrations within the cellular metabolite pool [119]**.** α-KG is an essential cofactor for jumonji-domain-containing histone demethylases (JHDMs), which drive histone demethylation. The α-KG dehydrogenase complex (α-KGDC) regulates α-KG levels and supports mitochondrial function across several metabolic pathways. Succinyl-CoA serves as a substrate for lysine succinylation, a post-translational modification that converts lysine residues from cationic to anionic, thereby altering protein structure and function. Elevated succinylation, including increased lysine-222 succinylation, has been associated with tumor progression, particularly in gastric cancer [120]**.** The classification of key metabolic enzymes, their associated epigenetic regulation mechanisms, and their relevance in cancer is summarized in Table 1.

➢ *Protein Metabolism*

In addition to increased aerobic glycolysis and fatty acid synthesis, cancer cells demand a higher intake of amino acids to sustain rapid growth. Beyond protein synthesis, amino acids are vital for energy production, nucleotide biosynthesis, and maintaining redox balance [119]. While glycolysis fuels much of cancer metabolism, amino acids like glutamine, serine, and glycine play crucial roles. Serine,

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in particular, provides one-carbon units essential for tumor progression. Rapidly dividing cancer cells rely heavily on extracellular serine availability [121]. Studies show that epidermal stem cells require serine to undergo metabolic reprogramming that blocks differentiation and promotes tumor growth. Limiting serine intake disrupts sphingolipid composition, inhibiting tumor expansion. Moreover, targeting serine biosynthesis pathways and reducing dietary serine and glycine have emerged as promising therapeutic strategies against cancer [121].

- *Glutamine:*

Glutamine is the most abundant amino acid in the intracellular metabolite pool. Upon entering the cell, it is converted into glutamate by mitochondrial glutaminase 1 (GLS1). Glutamate then serves as a precursor for the TCA cycle intermediate α-ketoglutarate. GLS1 is the key enzyme catalyzing glutamine metabolism through deamidation to glutamate [85]. This glutamate is essential for maintaining the citric acid cycle in the mitochondria after undergoing metabolism by various enzymes. In addition, glutamate is utilized in the synthesis of several non-essential amino acids, whereas glutamine plays a significant role in the biosynthesis of purines and pyrimidines. Moreover, glutamine is crucial for modulating the redox balance within the cell by affecting the synthesis rate of glutathione. Cells use glutamine to replenish the TCA cycle through anaplerosis, enabling cancer cells to sustain biosynthetic activities required for proliferation. Glutamine is a crucial nutrient supporting this metabolic demand [122]. Although glutamine is typically classified as a non-essential amino acid, it becomes conditionally essential for certain cancer cells that depend on external glutamine for growth. These cancer cells consume glutamine at a rate exceeding their own synthesis to support mitochondrial oxidative metabolism [123]. By inhibiting critical enzymes related to glutamine metabolism, notably GLS1, the growth of cancer cells is obstructed through a reduction in glutamine levels and a decrease in the synthesis of ATP and NADH [85].

- *Methionine:*

Methionine is classified as a vital amino acid, crucial for methylation processes. Additionally, it significantly contributes to the cellular redox balance and nucleotide synthesis, working in conjunction with the folate cycle to provide metabolites that facilitate the conversion of cysteine. Research shows that many cancer cells display increased methionine uptake, as observed in animal models of leukemia, breast cancer, hepatocellular carcinoma, and neuroblastoma [85]. Methionine plays a critical role in cancer metabolism by supporting nucleic acid and chromatin methylation, maintaining redox balance, and driving polyamine synthesis, all of which facilitate rapid cell proliferation. Cancer cells often upregulate key enzymes involved in methionine metabolism, notably methionine synthase, essential for methionine biosynthesis, and methionine adenosyl transferases, which convert methionine into S-adenosylmethionine (SAM), the primary cellular methyl donor. Many cancers exhibit a dependence on external methionine for growth, a phenomenon known as the "Hoffman effect", highlighting their reliance on this amino acid [85] where tumors are entirely dependent on externally supplied methionine. Evidence suggests that a diet low in methionine, in contrast to a conventional diet, is associated with increased lifespan. Additionally, the total removal of methionine from the diet has been linked to a reduction in cancer growth or even regression, along with an elevated responsiveness to chemotherapy. Thus, alongside the targeting of methylation, which is methionine-dependent, the strategic targeting of methionine metabolism may be pivotal in improving the efficacy of chemotherapy treatments [124].

- *Cysteine:*

Cysteine, a non-essential amino acid synthesized from methionine or protein breakdown, is primarily acquired by cells through dietary cystine. Cancer cells exhibit increased cysteine uptake compared to normal cells; a change associated with poorer prognosis [85]. Cysteine supports tumor adaptation to hypoxia, especially in ovarian cancer cell lines, by serving as a carbon source for biomass and energy production. Additionally, it is crucial for glutathione synthesis, thereby regulating cancer cell redox balance and metabolic reprogramming [125]. The cellular redox state critically influences chemotherapy effectiveness in cancer treatment. Cysteine metabolism is tightly linked to its cellular uptake, primarily mediated by transporters such as excitatory amino acid transporter 3 (EAAT3), which is upregulated in brain, colon, lung, and prostate cancers [85]. Additionally, cysteine is imported via the cysteine/glutamate antiporter, also elevated in various cancer cell lines and regulated by the redox-sensitive transcription factor NRF2. This highlights cysteine's vital role in sustaining tumor redox balance [126]. Table 2 summarizes major oncometabolites implicated in cancer development, their associated cancer types, underlying mechanisms contributing to tumorigenesis, and notable genetic or metabolic alterations that support their accumulation or activity.

➢ *Fatty Acid Oxidation and Cancer*

Tumors that exhibit rapid growth often rely on fatty acid oxidation (FAO) to fulfill their metabolic requirements, with various cancer types employing this mechanism for survival, proliferation, and invasion. This is particularly true for gastrointestinal (GI) cancers, pancreatic, and metastatic breast cancers, where an overall increase in FAO has been documented [85]. Initial studies on gastrointestinal (GI) cancers have demonstrated a link between obesity and cancer, especially in cases driven by high-fat diets. These diets increase oxygen consumption but reduce respiratory rates, indicating a metabolic shift toward fatty acid utilization. In colon cancer, inhibiting fatty acid synthesis by targeting key enzymes, carnitine palmitoyl transferase 1 (CPT1) or 3-ketoacylCoA thiolase (3-KAT), both rate-limiting in fatty acid oxidation (FAO), has been effective in promoting tumor regression [127]. Various cancers enhance mitochondrial FAO through mechanisms like increased fatty acid uptake, lipolysis, de novo lipogenesis, fatty acid activation, and peroxisomal FAO, either independently or in combination [127].

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- *Lipolysis:*

Cancer cells markedly upregulate lipolysis, breaking down triglycerides into glycerol and free fatty acids to supply substrates for fatty acid oxidation (FAO) and bolster their metabolism. A key enzyme in this process is lipoprotein lipase (LPL), which serves as a ratelimiting factor by hydrolyzing triacylglycerols and phospholipids from lipoproteins [128]. Studies reveal that cancers like triple-negative breast cancer and cervical cancer exhibit elevated LPL levels, indicating increased fatty acid availability. Since LPL is an extracellular enzyme mainly expressed in the tumor microenvironment, cancer cells compensate by upregulating CD36 to enhance lipid uptake and utilize fatty acids generated through lipolysis [128]. Furthermore, LPL also promotes lipid uptake in cancer cells through a distinct mechanism involving the upregulation of the very low-density lipoprotein receptor (VLDLR). Recent studies in breast cancer cell lines reveal a synergistic interaction between LPL and VLDLR that facilitates rapid internalization of lipids [129].

- *Denovo Fatty Acid Synthesis:*

An alternative method to enhance fatty acid oxidation (FAO) in cancer cells, aside from increasing lipid uptake, involves the synthesis of additional fatty acids for oxidation. This process enables cancer cells to thrive in environments with limited nutrients. Fatty acid synthase (FASN), a crucial enzyme, is often overexpressed in various cancers, typically as a result of heightened activity in pathways mediated by EGF, HER2, and PI3K/Akt/mTOR [119]**.** This overexpression leads to an increase in fatty acid synthesis and lipid metabolism. Additionally, fatty acid-binding proteins (FABPs) play a significant role in regulating lipid metabolism and facilitating lipid uptake. Recent research has underscored the involvement of these proteins in cancer progression; for instance, FABP5 is discovered to be elevated in prostate, colon, and breast cancers through both epigenetic modifications and direct gene activation [130]. This increase in the expression of essential genes involved in lipid production and metabolism ultimately promotes the advancement and spread of cancer by prioritizing FAO over glucose consumption. Increased fatty acid synthesis and lipolysis are also dependent on FABP7, another member of the FABP family, and its overexpression in breast cancer causes a noticeable change in the direction of fatty acid synthesis and FAO. [119].

- *Peroxisomal Fatty Acid Oxidation:*

Peroxisomal fatty acid oxidation (FAO) is significantly linked to cancer development. Notably, this metabolic process is often downregulated in certain tumors, particularly those exhibiting elevated levels of hypoxia-inducible factor (HIF), such as renal carcinoma [85]. The reduction in peroxisomal FAO is typically associated with compromised peroxisomes, a phenomenon observed in colon, breast, and liver cancers. Conversely, some studies have indicated an upregulation of peroxisomal FAO in prostate, skin cancer, colon and gastric cancers, suggesting a tissue-specific function of this metabolic pathway. Furthermore, peroxisomal FAO has emerged as a potential therapeutic target for prostate cancer, particularly through the inhibition of the α-methyl acyl-CoA racemase (AMACR) enzyme, which plays a crucial role in this process [85].

- *Nucleotide Metabolism:*

Nucleotides serve as essential substrates in various anabolic processes and are critical for the synthesis of DNA and RNA. A deficiency in nucleotide synthesis impedes cell division and compromises DNA repair mechanisms [131]. Tumor cells harboring p53 mutations or deletions exhibit an increased reliance on one-carbon metabolism, rendering them more vulnerable to DNA damage than their wild-type counterparts, an exploitable weakness for targeted therapies [132]. Nucleotide synthesis in cells proceeds via both de novo and salvage pathways for purines and pyrimidines. Notably, different cancer types may preferentially utilize specific pathways. In tumors, nucleotide metabolism is markedly upregulated to meet the heightened demands of unchecked proliferation, therapy resistance, and metastasis [133].

Proliferating cells, particularly cancerous ones, rely heavily on de novo purine synthesis—a pathway that is significantly upregulated in tumors due to genetic alterations and the activation of key metabolic enzymes. Major enzymes involved in this pathway include ribonucleotide reductase (RNR), dihydrofolate reductase (DHFR), thymidylate synthase (TS), and inosine monophosphate dehydrogenase 1 and 2 (IMPDH1/2) [133]. Targeting these enzymes has shown potential in inducing differentiation in cancer cells across various tumor types. An important downstream product of de novo purine synthesis is cyclic guanosine monophosphate (cGMP), derived from guanosine-5'triphosphate (GTP). cGMP activates cGMP-dependent protein kinases (PKGs) and subsequently stimulates the mitogen-activated protein kinase (MAPK) pathway, which enhances metastatic potential and cellular stemness in tumors. Oncogenic drivers such as mutant KRAS, PI3K, and cMyc further amplify the activity of enzymes within the de novo purine synthesis pathway, thereby supporting malignant transformation and progression. In addition to the de novo pathway, the purine salvage pathway is also enhanced in cancer cells. For instance, suppression of the electron transport chain (ETC) in human lung cancer has been shown to upregulate hypoxanthine phosphoribosyl transferase 1 (HPRT1), increasing salvage activity. Other salvage enzymes, including adenine phosphoribosyl transferase (APRT) and hypoxanthine-guanine phosphoribosyl transferase (HGPRT), are similarly overexpressed in various malignancies, further contributing to tumor growth and survival.

Parallel to purine metabolism, pyrimidine biosynthesis also plays a crucial role in tumorigenesis. Inhibition of key enzymes such as dihydroorotate dehydrogenase (DHODH) and carbamoylphosphate synthase 2 (CPS2/CAD)—both essential for de novo pyrimidine production—has demonstrated efficacy in reducing tumor growth and metastasis[134]. Transcription factors like hypoxia-inducible factor 1-alpha (HIF-1α) can further promote pyrimidine biosynthesis in cancers such as pancreatic carcinoma. As expected, a deficiency in nucleotide availability leads to

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profound transcriptomic reprogramming in cancer cells, reflecting their metabolic vulnerabili [135].

XIV. TARGETING MITOCHONDRIA TO COMBAT CANCER

Regulating the nucleo-cytoplasmic pool of acetyl-CoA has emerged as an attractive anticancer strategy. Two enzymes dominate this metabolic bottleneck: first one is ATP-citrate lyase (ACLY), which is overexpressed in numerous malignancies and is associated with aggressive proliferation rates. In cisplatin (CDDP)-resistant ovarian cancer cells, ACLY is markedly upregulated; silencing this enzyme re-sensitizes the cells to platinum therapy, identifying ACLY as a key driver of acquired CDDP resistance and a promising target for chemosensitization [135]. The other is AcetylCoA synthetase 2 (ACSS2). By capturing acetate, often the dominant acetyl-CoA source under hypoxia, ACSS2 sustains lipid synthesis, histone acetylation, and survival signalling. ACSS2 is frequently over-expressed across solid tumours, and genetic or pharmacological inhibition significantly restrains tumour growth in models of liver, breast, ovarian, prostate, pancreatic and skin cancers, as well as glioblastoma [136].

XV. CONCLUSION AND FUTURE PERSPECTIVES

Mitochondrial metabolism, metabolite-driven epigenetic reprogramming and rewired nutrient pathways form an integrated network that underpins tumour initiation, progression and treatment resistance. Oncometabolites such as fumarate, succinate and 2-hydroxyglutarate reshape the epigenome; altered flux through glycolysis, the pentose-phosphate pathway, fatty-acid oxidation, amino-acid (serine, glutamine, methionine, cysteine) and nucleotide biosynthesis fuels unchecked proliferation while buffering oxidative stress. Enzymes sitting at metabolic crossroads, HK2, LDH-A, G6PD, 6PGD, DHODH, IDH mutants, TFAM, ACLY, ACSS2 and many others, have therefore emerged as double agents, simultaneously supporting bioenergetics and modulating chromatin state.

Therapeutically, this convergent biology offers multiple intervention points:

- *Metabolic Chokepoints*

Small-molecule inhibitors of HK2, LDH-A, G6PD/6PGD, DHODH, CPT1, ACLY and ACSS2 limit essential substrate supply and collapse anabolic capacity.

- *Epigenetic–Metabolic Crosstalk*

Agents that restore TET activity, inhibit mutant IDH1/2, or modulate histone- or DNA-modifying enzymes leverage metabolite dependency to reverse tumour-promoting gene-expression programs.

- *Nutrient Restriction & Synthetic Lethality*

Dietary serine/glycine or methionine restriction, combined with inhibitors of one-carbon or folate pathways, selectively cripples p53-mutant and other metabolically addicted tumours.

- *Redox Manipulation*

Targeting cystine/cysteine transporters (EAAT3, xCT) or glutathione synthesis sensitises tumours to chemotherapy and radiotherapy by dismantling ROS defences.

Future research must integrate metabolic flux analysis, single-cell epigenomics and in-vivo metabolite tracing to map context-specific liabilities. Combining metabolic inhibitors with conventional chemo-radiotherapy or emerging immunotherapies is likely to yield durable clinical responses while minimising resistance. Ultimately, the marriage of metabolism and epigenetics transforms our understanding of cancer from a genetic disorder to a bioenergetic and chromatin disease, opening a rich therapeutic landscape that is only beginning to be explored.

- *Figure Legends:*

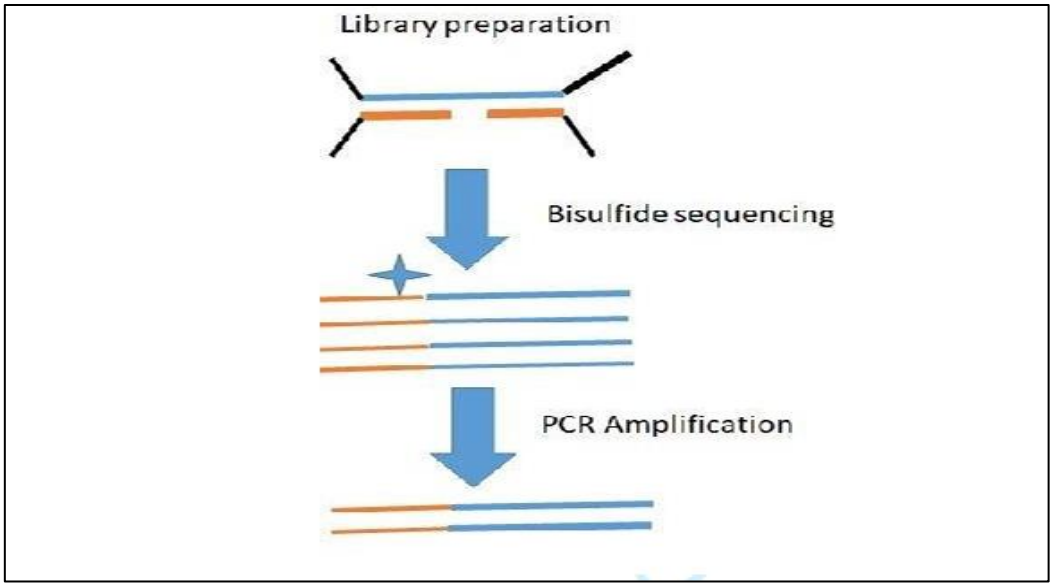

Fig 1 Mechanism of Bisulfite Conversion for DNA Methylation Analysis

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The cytosines in DNA sequences are methylated and are exposed to Bisulfite treatment. The figure shows this treatment protects methylated cytosine from getting converted to uracil. However, unmethylated cytosine gets converted to uracil. During PCR amplification, uracil is read as thymine.

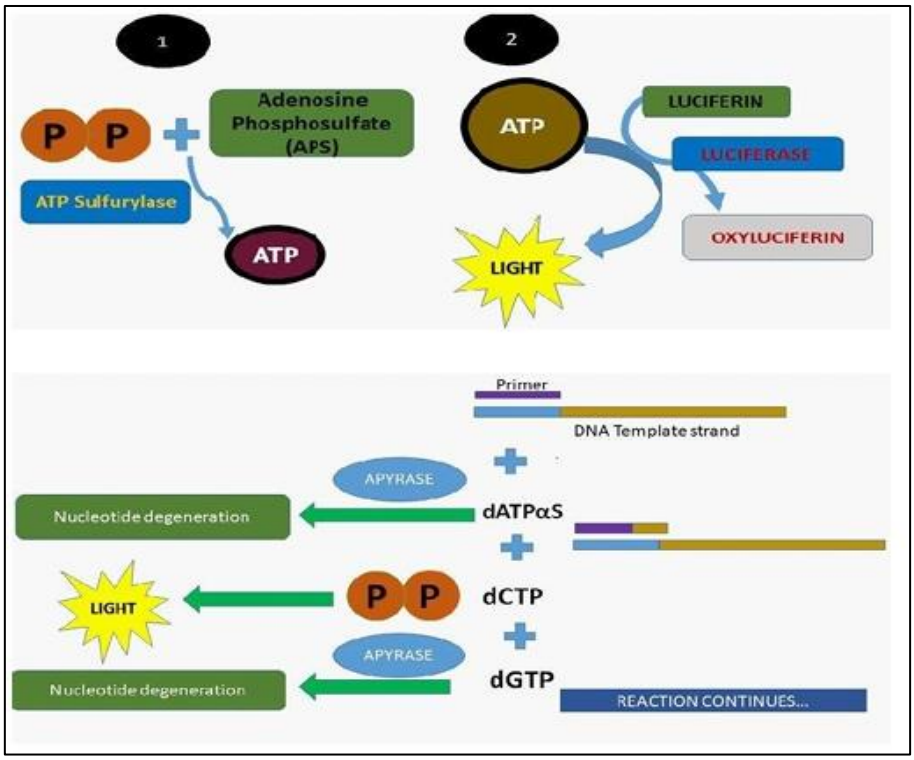

Fig 2 Enzyme Cascade Reaction Mechanism in Pyrosequencing

Prior to mixing with the two substrates (APS and luciferin) and the enzymes, a ssDNA template is hybridised with the sequencing primer. Following a nucleotide's successful insertion by DNA polymerase into a developing DNA strand, PPi is released and interacts with APS in the presence of ATP sulfurylase to produce ATP. When ATP, luciferin, and luciferase are present, oxyluciferin is produced. This produces visible light, which a built-in CCD camera can detect. Before the subsequent nucleotide dispensation, the enzyme apyrase breaks down any unincorporated nucleotides and ATP into its component parts.

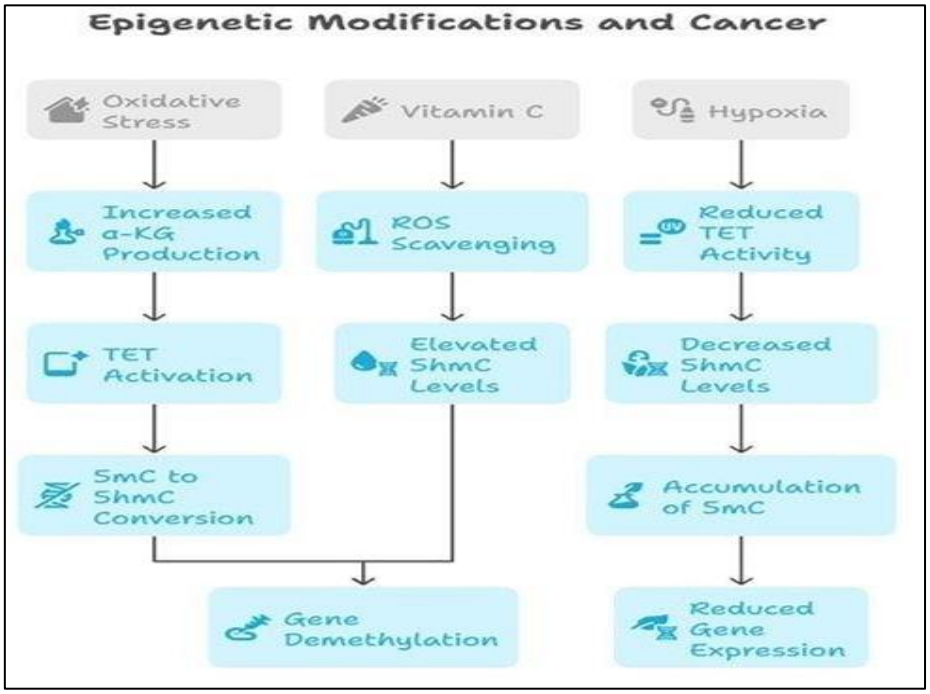

Fig 3 Impact of Oxidative Stress, Vitamin C, and Hypoxia on TET-Mediated Epigenetic Modifications in Cancer.

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Oxidative stress increases α-ketoglutarate (α-KG) production, activating TET enzymes that convert 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), facilitating gene demethylation. Vitamin C enhances 5hmC levels through reactive oxygen species (ROS) scavenging. In contrast, hypoxia suppresses TET activity, leading to decreased 5hmC, accumulation of 5mC, and reduced gene expression, contributing to oncogenic transcriptional silencing.

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Table 1 Classification of Key Metabolic Enzymes, Their Epigenetic Regulation Mechanisms and Relevance of Cancer

Enzyme Class	**Enzyme(s)**	**Epigenetic Regulation Mechanism**	**Cancer Relevance**
Glycolytic Enzymes	HK2, PKM2, PFKFB3, LDHA, GLUT1	DNA methylation, histone modifications (H3K9me2, H3K27ac), and transcription factor binding (HIF-1α)	Supporting the Warburg effect and tumor development, it is upregulated in several cancers.
Gluconeogenic Enzymes	FBP1, FBP2		Promotes glycolysis and is downregulated in malignancies of the stomach, colon, liver, breast, and others.
TCA Cycle Enzymes	IDH1, IDH2	Mutations leading to neomorphic activity producing oncometabolites (2-HG)	Found in gliomas and leukemias, mutations in IDH1/2 linked with epigenetic modifications.
Glutaminolytic Enzymes	GLS1, GLS2	DNA methylation and histone modifications affecting gene expression	Overexpressed in tumors including breast cancer and glioblastoma; promotes anabolic metabolism
Serine Biosynthesis Enzymes	PHGDH, PSAT1, PSPH	Upregulated through MYC and other oncogenic pathways; epigenetic silencing of feedback inhibitors	Overexpression in cancers like melanoma and breast cancer; promotes nucleotide and lipid biosynthesis.
Acetyl-CoA Metabolism Enzymes	ACLY, ACSS2	Histone acetylation and metabolite-driven regulation (acetyl-CoA availability)	Supports histone acetylation and lipid synthesis; overexpression in tumors including liver and prostate.
Pyruvate Metabolism Enzymes	PDH, LDHA	Epigenetic silencing of PDH and activation of LDHA through histone modifications and DNA methylation	Promotes anaerobic glycolysis and lactate synthesis; changed expression in several cancers.

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Table 2 Oncometabolites, Associated Cancer Types, Mechanisms of Action, and Key Genetic or Metabolic Alterations

Oncometabolites	Cancer Type(s) Affected	Mechanism of Action	Key Alterations
2-Hydroxyglutarate (2-HG)	Gliomas, Acute Myeloid Leukemia Chondrosarcoma, Cholangiocarcinoma (AML),	Inhibits α-ketoglutaratedependent enzymes, leading to epigenetic alterations and metabolic reprogramming	Mutations in IDH1/IDH2 (Isocitrate Dehydrogenase)
Lactate	Multiple cancers (e.g., Breast, Glioblastoma, Colon)		Altered glycolytic metabolism due to mutations in various oncogenes like Myc and PTEN
Fumarate	Renal Cell Carcinoma, Paraganglioma	Inhibits prolyl hydroxylases, stabilizing and angiogenesis HIF-1α promoting immune evasion	Mutations in FH (Fumarate Hydratase)
Succinate	Clear Cell Renal Carcinoma, Pheochromocytoma	Stabilizes HIF-1α by inhibiting prolyl hydroxylases, promotes glycolysis and tumor progression	Mutations in SDH (Succinate Dehydrogenase)
Acetyl-CoA	Various cancers (e.g., Lung, Breast, Colon)	Modulates histone acetylation and gene expression to promote cell growth and survival	Enhanced through altered fatty acid metabolism, acetyl-CoA synthetase activation
Methionine	Various cancers (e.g., Breast, Colon)	Affects DNA methylation and cellular proliferation. Drives increased biosynthesis and tumor growth	Dysregulation in methylation pathways (e.g., via mutations in SAM synthetase or altered methionine metabolism)
Citrulline	Various cancers (e.g., Leukemia, Colon)		Elevated in some tumor types due to altered nitric oxide synthase activity
Serine	Glioblastoma, Non-small Cell Lung Cancer (NSCLC)	Promotes biosynthesis of proteins, nucleotides, and lipids required for cell proliferation	Altered serine-glycine metabolism, often driven by MYC or other oncogenes