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Review

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The Role of Energy Metabolism in Driving Disease Progression in Inflammatory, Hypoxic and Angiogenic Microenvironments

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ABSTRACT

Cellular metabolism plays a crucial role in primed inflammatory, hypoxic and angiogenic microenvironments by supporting disease progression in a range of disease entities. To adapt to fluctuating stress-induced microenvironments, pre-neoplastic and neoplastic tissue must utilise a diverse range of molecular mediators to alter their metabolism. Despite being widely documented to play independent roles in disease prevalence, these complex processes exploit a range of key cellular components that act in tandem to restore metabolic equilibrium. Therefore, this review examines the primary molecular mechanisms linking energy metabolism with inflammation, hypoxia and angiogenesis. Furthermore, the review considers a diverse range of conventional and novel mediators that link energy metabolism and hypoxia. Moreover, to investigate their reciprocal relationship and the mechanisms employed to execute their functional effect in greater detail, the roles of glycolysis and oxidative phosphorylation in rheumatoid arthritis and circadian rhythms respectively are reviewed. Lastly, this review explores some current metabolic-based treatments and multi-targeted therapies that could potentially target these fundamental cellular processes.

KEYWORDS: Energy metabolism; Inflammation; Hypoxia; Angiogenesis.

INTRODUCTION

Otto Warburg's initial observation in 1956 demonstrated that tumours exhibit increased levels of aerobic glycolysis.[1] This observation has since resulted in numerous studies investigating the role of mitochondrial energy metabolism in disease progression across many disease entities. As a reflection of its importance in the development of various cancers, the reprogramming of cellular energetics is now beginning to establish itself as one of the new hallmarks of cancer.[2,3] In addition to significant quantities of adenosine triphosphate (ATP), metabolically demanding tumours require glucose for lipid and protein synthesis and *de novo* synthesis of nucleotides for rapid proliferation.[4] More importantly, this altered metabolic phenotype allows tumours to maintain higher proliferative rates and resist apoptosis orchestrated by increased oxidative damage.[5] Moreover, these metabolic phenotypes persist and are sometimes altered in distinct metabolically demanding microenvironments. Therefore, elucidating how diverse metabolic processes converse with distinct functional inflammatory, hypoxic and angiogenic pathways may infer significant insights into how several heterogeneous malignancies arise and subsequently advance beyond therapeutic intervention.

It has been widely documented that inflammation, hypoxia and angiogenesis all play independent roles in disease prevalence and in its subsequent stepwise progression. Some studies, however, have uncovered close associations between energy metabolism and these extensive processes. Therefore, this review focuses on the primary molecular mechanisms that link energy metabolism with inflammation, hypoxia and angiogenesis. In addition to investi-

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gating conventional mediators that link energy metabolism with inflammation and hypoxia, novel mediators that link energy metabolism to inflammation, hypoxia and angiogenesis will also be discussed. This review also explores the mechanisms linking energy metabolism with hypoxia by exploring the roles of glycolysis in rheumatoid arthritis and oxidative phosphorylation (OXPHOS) in circadian rhythms. This review subsequently focuses on the connection between energy metabolism and inflammation in greater detail by examining some of the reciprocal mechanisms linking both processes throughout the gastrointestinal tract. To conclude, this review explores contemporary metabolic-based treatments and multi-targeted therapies that target these key processes.

MOLECULAR MEDIATORS LINKING ENERGY METABOLISM WITH INFLAMMATION, HYPOXIA AND ANGIOGENESIS

Conventional Mediators Linking Energy Metabolism with Inflammation and Hypoxia

HIF1α

Hypoxia Inducible Factor-1α (HIF1α) is an oxygen sensitive transcription factor subunit involved in various cellular processes including hypoxia, angiogenesis, cell survival, inflammation and energy metabolism.[6] Interestingly, cells in hypoxic regions tend to be more resistant to the effects of radiotherapy and other conventional chemotherapeutic agents.[7] As a result, these more resistant cells have been implicated in disease resistance and recurrence, and can lead to more aggressive phenotypes and contribute to subsequent metastasis.[7,8] It is important to note, however, that hypoxia-induced alterations in energy metabolism are physiologically normal, for example, cardiomyocytes upregulate glycolytic ATP production under hypoxic stress.[9] As Figure 1 shows, hypoxia affects metabolism by inducing the overexpression of various glycolytic enzymes, lactate dehydrogenase (LDH) and carbonic anhydrase in addition to inhibiting pyruvate dehydrogenase, a key enzyme that converts pyruvate into acetyl-CoA for subsequent oxidative metabolism.[10] However, it has been shown that hypoxia, specifically HIF1α, plays a key role on T-cell function by modulating T-cell metabolism.

Upon activation, the metabolic demands of T-cells increase dramatically since activated T-cells are highly anabolic and exhibit marked increases in glycolytic metabolism.[11,12] Interestingly, one study hypothesises that one possible mechanism responsible for T-cell anergy is failure to upregulate key meta-

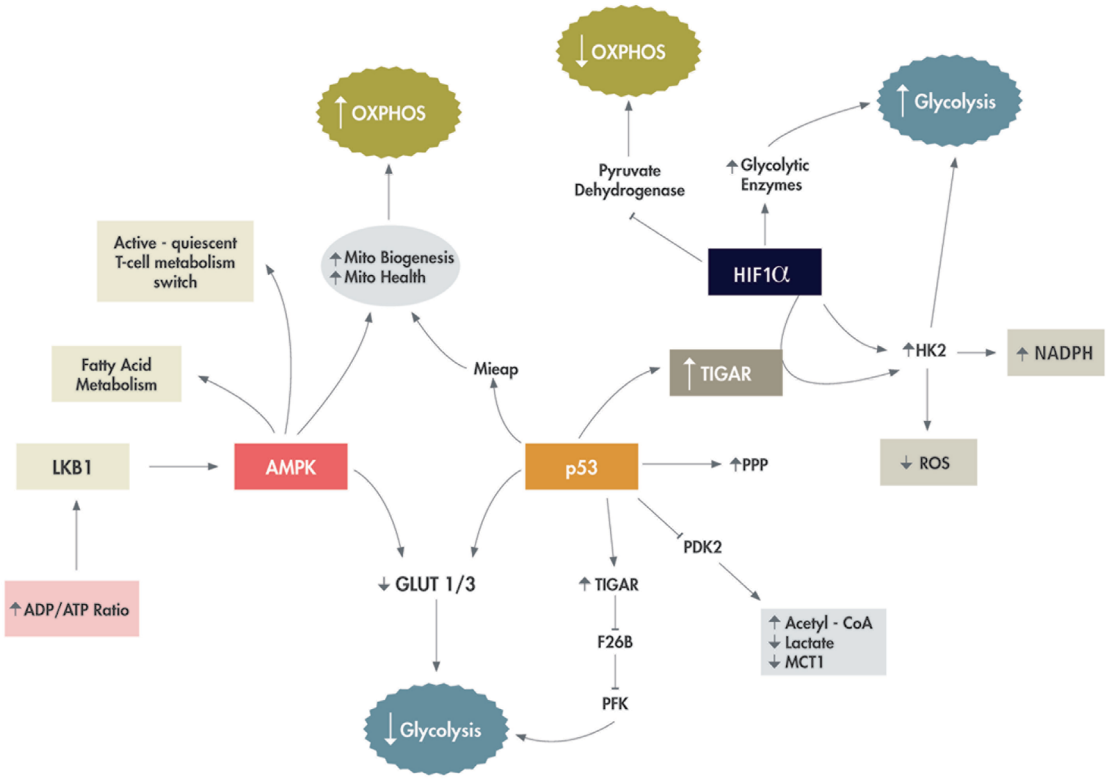

Figure 1: Conventional mediators linking energy metabolism with inflammation and hypoxia. Despite being anti-Warburg, p53, through HIF1α, can also enhance aerobic glycolysis. Hypoxia, through HIF1α, affects metabolism by inducing the overexpression of a host of glycolytic enymes, for example, hexokinase 2. HIF1α also depresses OXPHOS by inhibiting pyruvate dehydrogenase, the enzyme known to convert pyruvate into acetyl-CoA. Through p53 and a HIF1α– dependent mechanism, TIGAR has been shown to form a complex with hexokinase 2 at the mitochondria resulting in an increase in hexokinase 2 activity supporting the production of NADPH and limiting reactive oxygen species. p53, through Mieap, supports OXPHOS by mediating mitochondrial health and biogenesis. p53, *via* TIGAR, primarily reduces glycolysis by degrading F26B, thereby decreasing the activity of PFK, a key glycolytic enzyme and simultaneously diverting glycolytic intermediates into the pentose phosphate pathway. p53 also negatively regulates PDK-2 promoting acetyl-CoA production, decreases lactate production and represses the expression of MCT1. p53, like AMPK, downregulates the expression of GLUT1 and GLUT3 thereby repressing glycolysis further. Moreover, any ADP/ATP ratio imbalance that affects ATP production or its consumption can result in LKB1-induced activation of AMPK. AMPK can subsequently promote OXPHOS by promoting fatty acid oxidation, mitochondrial biogenesis and mitochondrial health. AMPK has also been documented to control the differentiation switch from active glycolytic cytotoxic T lymphocytes to metabolically quiescent CD8+ T cells that preferentially utilise OXPHOS.

bolic machinery, since blocking energy metabolism mitigates T-cell activation and inhibition of these metabolic pathways during activation leads to anergy in Th1 cells.[11] Hypoxia has differential effects on T-cell function, however, as lack of glucose in human $CD4^+$ T lymphocytes results in increased dead cell numbers and increased reactive oxygen species under normoxia but not under hypoxic conditions.[13] Hypoxia also stimulates increased levels of interleukin-1β (IL1β), IL10 and IL8 in these cells, but the lack of glucose reduces secretions of these cytokines, implying that $CD4^+$ T cells are highly metabolically adaptable allowing for proper immune function under highly fluctuating bioenergetic microenvironments.[13] HIF1α also regulates the balance between regulatory T cell and helper T cell differentiation.[14] This differentiation has been shown to be regulated in both regulatory T cells and helper T cells *via* the glycolytic pathway in a HIF1α-dependent manner.[15] In stimulated T_H17 cells, glycolysis and various glycolytic enzymes were actively upregulated, although blocking glycolysis inhibited T_H17 development while promoting T_{REG} differentiation.[15] HIF1α activity is key for mediating glycolytic activity and subsequently contributes to lineage choices between T_H17 and T_{REG} cells, whereas lack of HIF1α results in reduced T_H17 development but enhances T_{REG} differentiation.[15] Some evidence suggests that HIF1α mediates this effect through mammalian target of Rapamycin (mTOR).[15,16] These studies support the view that hypoxia mediates T-cell function and drives chronic inflammation through HIF1α by regulating T-cell metabolism.

AMPK

AMP-activated protein kinase, or AMPK, is a sensor of cellular energy metabolism and exhibits anti-Warburg effects by promoting fatty acid oxidation, mitochondrial biogenesis and the expression of genes necessary for oxidative metabolism (Figure 1).[17-20] As aerobic glycolysis is a common entity in many cancer types, it is exciting to speculate that drugs that activate AMPK might therefore have therapeutic and clinical utility. Any metabolic imbalance that either inhibits the generation of ATP or accelerates ATP consumption results in increases in the ADP/ATP ratio resulting in AMPK activation due to the accumulation of ADP.[17] As a result, activated AMPK acts to switch off ATP-consuming anabolic processes and restores energy imbalances by switching on alternative catabolic pathways that increase cellular ATP.[17,21] One of these mechanisms involves down-regulating protein synthesis. For example, AMPK down-regulates protein synthesis of target of rapamycin complex 1 (TORC1), which is known to promote HIF1α translation, thereby reducing HIF1α expression and decreasing the expression of key glycolytic and glucose transporters required for aerobic glycolysis.[22] Using a mouse model of Peutz-Jeghers syndrome, deficiency of either AMPK or Liver Kinase B1 (LKB1), the protein kinase responsible for induction of AMPK activation, led to the upregulation of HIF1α, hexokinase 2 and glucose transporter member 1 (GLUT1).[23]

Activated immune cells tend to favour aerobic glycolysis whereas quiescent cells preferentially utilise oxidative metabolism.[11,12] Therefore, agents that activate AMPK may have anti-inflammatory effects. LPS-induced activation of dendritic cells results in reduced activation of AMPK, whereas knockdown of AMPK leads to the maturation of dentritic cells that exhibit increased glucose uptake.[24] Interestingly, AMPK downregulation in macrophages results in increased expression of various pro-inflammatory cytokines whereas expression of AMPK had the reverse effect.[25] Therefore, AMPK promotes macrophage polarisation towards an anti-inflammatory M2 phenotype rather than the pro-inflammatory M1 phenotype. In addition, AMPK has been shown to monitor metabolic stress in cytotoxic T lymphocytes and control the differentiation switch from metabolically active cytotoxic T lymphocytes to metabolically quiescent $CD8^+$ T cells, highlighting the important role of AMPK in various metabolic, immune and inflammatory processes.[26]

p53

The transcription factor p53 regulates metabolism by lowering aerobic glycolysis and promoting oxidative phosphorylation through a variety of molecular mechanisms.[27,28] p53 primarily supports oxidative phosphorylation by functioning as a mitochondrial checkpoint protein, regulating mitochondrial DNA copy number and mediating mitochondrial biogenesis.[29,30] p53 promotes mitochondrial health *via* the p53-inducible protein Mieap that controls mitochondrial quality by repairing or eliminating unhealthy mitochondria.[31] In intestinal metaplasia patients with progressive disease, oxidative-induced damage results in telomere shortening and mutations in the p53 gene abrogate p53's role as the checkpoint of proliferation and apoptosis.[32] Other studies have also shown that p53 plays a vital role in the synthesis of key components of the electron transfer chain.[33-35]

p53 mediates its central metabolic role through *TP53*-induced glycolysis and apoptosis regulator, or TIGAR.[27,36] TIGAR acts as a phosphatase and degrades fructose-2,6-Bisphosphate (F26B) thereby decreasing the activity of phosphofructose kinase 1 (PFK1), a key enzyme of the glycolytic pathway.[27] p53, *via* TIGAR, decreases glycolysis by diverting glycolytic intermediates into the pentose phosphate pathway (PPP).[37] p53 also negatively regulates the expression of Pyruvate dehydrogenase kinase 2 (PDK-2) thereby inactivating the pyruvate dehydrogenase complex responsible for converting pyruvate to acetyl-CoA.[38] Thus p53, activating the pyruvate dehydrogenase complex, favours oxidative phosphorylation through the production of acetyl-CoA.[38] Furthermore, p53 directly downregulates the expression of GLUT1 and GLUT4.[39]

The role of p53 is highlighted in hypoxic microenvironments. Through a hypoxia-induced HIF1α dependent mechanism, TIGAR has been shown to form a complex with hexokinase 2 at the mitochondria resulting in an increase in hexokinase 2 activity.[36] This complex reduces glycolytic flux supporting pentose phosphate pathway activity, generates NADPH in the process and promotes antioxidant function thereby limiting reac-

tive oxygen species-associated apoptosis and autophagy.[36] p53 also represses the expression of monocarboxylate transporter 1 (MCT1) preventing the efflux of lactate under hypoxic conditions.[40] It has been speculated that aberrant p53 expression may even promote tumour progression as some evidence suggests that p53 may enhance aerobic glycolysis rather than inhibit it.[27,28,41] In addition, the mechanism by which p53 regulates the glycolytic pathway may be tissue and context specific which is thought to reflect different types of cellular stress, that is, metabolic, oxidative and hypoxic stress.[27,42]

NOVEL MEDIATORS LINKING ENERGY METABOLISM WITH INFLAMMATION, HYPOXIA AND ANGIOGENESIS

NFκB

Despite some early studies linking nuclear factor kappa B (NFκB) with energy metabolism, recent studies have increasingly shown NFκB to possess an equally important central role in various metabolic and pathological diseases.[43] Inflammation is a key factor in the development of metabolic diseases such as atherosclerosis, insulin resistance, type 2 diabetes and obesity.[43-45] The central role of NFκB in immunity, inflammation and carcinogenesis has been well documented.[46-48]

NFκB regulates cellular respiration in a p53-dependent manner (Figure 2).[49] Translocation of the NFκB family member RelA to mitochondria is inhibited by p53, however, in the absence of p53, RelA is transported into mitochondria and recruited to the mitochondrial genome where it represses mitochondrial gene expression, oxygen consumption and cellular ATP levels, thereby contributing to the switch to glycolysis.[49] Indeed, it was reported that the RelA subunit also upregulates transcription of GLUT3 resulting in increases in glucose uptake and glycolytic flux.[50] The elevated glycolytic flux stimulates further IKK/NFκB pathway activity in a positive feedback loop that subsequently promotes H-Ras-induced oncogenic transformation in mouse embryonic fibroblasts.[50] This was the first functional study to show that NFκB promotes cell growth and carcinogenesis by metabolic manipulation, but crucially, p53 was central to this pathway, as introduction of p53 disrupted the link between NFκB and glycolysis.[50]

Intriguingly, the role of NFκB is reversed in normal mouse embryonic fibroblasts upon glucose starvation, whereby NFκB inhibition causes cellular reprogramming to aerobic

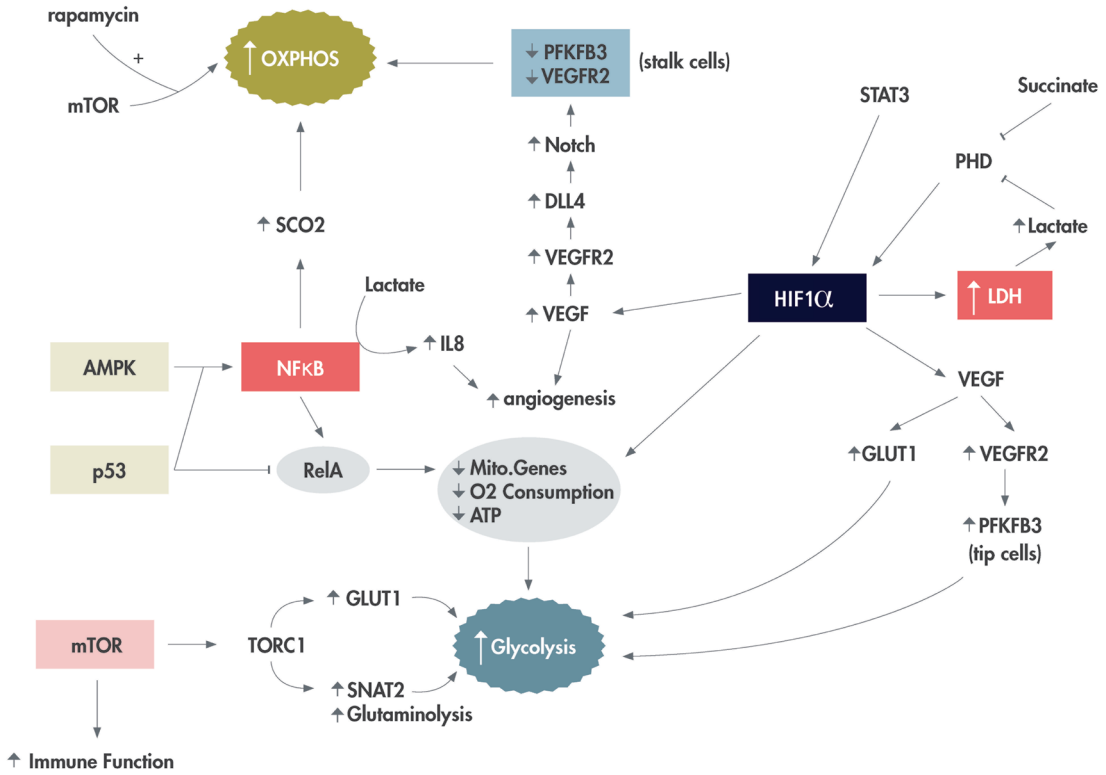

Figure 2. Novel mediators linking energy metabolism with inflammation, hypoxia and angiogenesis. NFκB regulates cellular respiration in a p53-dependent manner. In the absence of p53, the NFκB family member, Rel A, represses mitochondrial gene expression, oxygen consumption and cellular ATP levels thereby promoting glycolysis. NFκB promotes OXPHOS through an AMPK-p53-mediated mechanism by upregulating SCO2, a key electron transfer chain component. Furthermore, endothelial tip cells increase their glycolytic rate and promote angiogenesis by upregulating numerous glycolytic constituents such as LDH and GLUT1, primarily through HIF1α, VEGF, VEGFR2 and PFKFB3 signalling. However, the activation of VEGFR2 in tip cells induces the expression of Notch ligand DLL4 in neighbouring stalk cells activating Notch signalling. As a result, this reduces VEGF2 and PFKFB3 expression thereby lowering glycolytic flux and promoting OXPHOS in stalk cells. VEGF can also control angiogenesis through the glycolytic metabolite lactate, as lactate inhibits PHD resulting in HIF1α activation subsequently promoting OXPHOS and glycolysis. In addition, lactate has been shown to induce the production of the pro-inflammatory cytokine IL8. mTOR, succinate and STAT3 can also mediate metabolism. mTOR plays an important role in the modulation of both adaptive and innate immune function. TORC1, one of mTOR's signalling forms, upregulates glycolysis, glutaminolysis and the expression of SNAT-2. Moreover, mTOR inhibition results in a metabolic bias towards OXPHOS. Succinate can mediate metabolism through the inhibition of PHD and HIF1α. Similarly, STAT3 can regulate tumour cell metabolism through HIF1.

glycolysis.[51] The role of NFκB in upregulating mitochondrial respiration in this circumstance involves the p53-mediated upregulation of mitochondrial synthesis of cytochrome c oxidase 2 (SCO2), a key component of complex IV of the electron transport chain.[51] Hence, NFκB can act as a focal checkpoint of metabolic homeostasis in conjunction with AMPK and p53 to regulate the response to low cellular ATP levels.[51] Therefore, despite its prominent role in the Warburg effect, the metabolic plasticity of NFκB confers adaptivity in cells to adapt to fluctuating oxidative and hypoxic microenvironments.

VEGF and PFKFB3

In response to hypoxia-induced pro-angiogenic stimuli, endothelial cells rapidly switch from a metabolically inactive state of quiescence to an active migratory and proliferative state.[52] Effective vascular sprouting relies on coordinated navigating tips cells and on proliferating stalk cells that elongate the sprout. Until recently, only genetic signals were known to play a role in this angiogenic switch. However, the angiogenic switch also requires a change in endothelial cell metabolism.[52] Interestingly, endothelial cells are thought to be addicted to glycolysis as they rely minimally on oxidative phosphorylation for ATP generation.[52,53] For instance, the glycolytic inhibitor 2-deoxy-D-glucose induces significant endothelial cell death.[54]

Endothelial cells increase their glycolytic rate by upregulating a range of glycolytic constituents including GLUT1, LDH and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3).[52] PFKFB3 has been shown to be critical for angiogenic sprouting, and its inactivation reduces endothelial cell proliferation and migration, and impairs motility and formation of endothelial cell lamellipodia and filopodia.[54] Conversely, PFKFB3 overexpression stimulates the sprouting of mitotically-inactivated endothelial cells and promotes tip cell formation.[54] This entire process of tip and stalk cell differentiation, however, is under tight control of vascular epithelial growth factor (VEGF) and Notch signalling (Figure 2).[53]

VEGF promotes tip cell induction and filopodia formation inducing the expression of the Notch ligand Delta-like 4 (DLL4).[53] One of the main genetic signals of vessel sprouting is orchestrated through Notch.[55] DLL4 subsequently activates Notch signalling in neighbouring cells and suppresses VEGF receptor 2 expression and tip cell behaviour.[53] Therefore, the activation of VEGF receptor 2 in tips cells upregulates PFKFB3 levels and glycolysis but induces the expression of the Notch ligand DLL4 in neighbouring stalk cells activating Notch signalling, lowering VEGF receptor 2 expression resulting in lower PFKFB3 expression and glycolytic flux.[53] Interestingly, overexpression of PFKFB3 overcomes the pro-stalk activity of Notch signalling thereby promoting tip cell behaviour, indicating that highly glycolytic endothelial cells can overcome inhibitory genetic signals.[54]

VEGF also controls angiogenesis through the glycolytic metabolite lactate.[52] Once taken up by endothelial cells through MCT1, lactate competitively inhibits the oxygen-sensing propyl hydroxylase domain protein 2 (PHD2), resulting in activation of HIF1α and an increase in VEGF receptor 2 expression.[56] Lactate signalling also induces VEGF expression.[57] In addition to its angiogenic role, lactate also indirectly releases NFκB inducing IL8 expression, another promoter of angiogenesis.[58] VEGF has also been shown to induce the production of IL8 in endothelial cells.[59] In addition to promoting aerobic glycolysis, VEGF stimulates mitochondrial biogenesis through Akt-dependent signalling, and plays a significant role in fatty acid metabolism.[60-62] These studies demonstrate a close relationship between VEGF-induced metabolism, hypoxia, angiogenesis and inflammation in endothelial cells and highlight how stressed endothelial cells adapt to an altering milieu that could potentially favour tumour progression.

mTOR, Succinate and STAT3

mTOR is a serine/threonine kinase that controls cell proliferation and metabolism in response to a range of extracellular stimuli such as the availability of nutrients, growth factors and stress.[63] mTOR plays an important role in the modulation of both innate and adaptive immune function (Figure 2).[64] As discussed, activated T cells switch to an anabolic metabolism using aerobic glycolysis as a major supply of ATP to fuel the rapid synthesis of proteins , nucleotides and other biosynthetic products.[63] TORC1, one of two currently recognised signalling forms of mTOR, has been shown to be heavily involved in the up-regulation of enzymes involved in glycolysis, glutaminolysis, the pentose phosphate pathway, surface expression of GLUT1 and expression of the glutamine transporter, SNAT-2.[65-67] Similarly, inhibition of mTOR results in a metabolic bias towards oxidative phosphorylation and has been shown to produce a larger CD8 memory T cell pool.[68] Ongoing clinical trials investigating the efficacy of mTOR inhibitors suggest that mTOR-mediated metabolism does play a central role in regulating biological outcomes within immune cells, however, a key question remaining is how mTOR-mediated metabolism is coupled to immune function.[5]

Increasing evidence also proposes that succinate, a citric acid cycle metabolite that accumulates due to succinate dehydrogenase mutations, transmits an oncogenic signal from the mitochondria to the cytosol, directly inhibiting PHD and resulting in HIF1α stabilization under normoxic conditions, with resultant increased expression of genes that facilitate angiogenesis, metastasis and glycolysis (Figure 2).[69] By adding succinate to glioblastoma multiforme-derived cells cultured under hypoxic conditions, HIF1α stabilization is induced which increases stem cell fractions and preserves the tumour stem cell niche thereby promoting tumour survival.[70] Recently, it has been reported that succinate as a metabolite in innate immune function enhances IL-1β production during inflammation through HIF1α thereby promoting disease progression.[71]

The signal transducer and activator of transcription factors (STATs) are a family of transcription factors that regulate cell growth, survival, differentiation and motility.[72] One of the STAT members, STAT3, has long been recognised as a critical regulator of tumour cells.[72] STAT3 has been recently found to act as one of the central mediators of aerobic glycolysis through both HIF1α and independent mechanisms (Figure 2).[72,73] Upon translocation to the mitochondria, serine phosphorylation of STAT3 contributes to tumour cell transformation and tumourigenesis.[74-76]

EXPLORING THE MOLECULAR MECHANISMS THAT LINK ENERGY METABOLISM AND HYPOXIA

Glycolysis, Hypoxia and Rheumatoid Arthritis

It has been 35 years since the link between increased glycolytic activity and rheumatoid arthritis (RA) was first established.[77] In normal synovial tissues, glycolysis is the primary pathway for mitochondrial substrate oxidation of pyruvate.[78] Levels of two major glycolytic enzymes glyceraldehyde 3-phosphate dehydrogenase and LDH were found to be significantly increased in the synovial cells between fresh non-rheumatoid and rheumatoid synovial tissue.[77] More recently, one study detected elevated lactate and reduced glucose levels in the synovial fluid in RA.[79] Moreover, it is plausible that metabolic alterations that favour aerobic glycolysis are a result of hypoxia-induced mitochondrial mutagenesis and dysfunction.[80] Despite studies lacking strong evidence of a direct relationship between inflammation and glycolysis in RA, it is interesting that some glycolytic components are characterised as being autoantigens, for example, glucose-6-phosphate isomerise, aldolase and enolase.[78] However, studies need to be undertaken to examine the role of metabolic autoantigens in cancer initiation and progression.

On the other hand, the link between hypoxia and inflammation has been well documented *in-vivo*.[81-84] Significantly higher levels of synovial fluid tumour necrosis factor-α (TNFα), IL-1β, interferon-γ and macrophage inflammatory protein-3α in combination with low partial oxygen pressures of <20 mm Hg were found in patients with inflammatory arthritis.[84] Interestingly, TNFα blocking therapy reverses joint inflammation and hypoxia.[83] Another study also demonstrated that hypoxia-induced IL-17A expression is localised to neutrophils, mast cells and T cells within inflamed synovial tissue supporting the concept that IL-17A is a key mediator in inflammatory arthritis.[81]

Numerous mechanistic processes within the inflammatory joint may alter energy metabolism profiles. RA is associated with increased levels of HIF1α and HIF2α.[85,86] HIF1 also induces the expression of GLUT1 and GLUT3.[87] Furthermore, HIF has been shown to regulate the levels of hexokinase II, glyceraldehyde *3*-phosphate dehydrogenase, LDH and cytochrome oxidase in the inflammatory synovium.[87-91] RA is also commonly associated with mutations in p53.[92-94] As discussed, p53 can regulate glucose metabolism through NFκB, however, loss of p53 promotes the positive feedback cycle between the IKK-NFκB pathway and glycolysis thereby promoting oncogenic transformation.[50,95] It is also plausible that angiogenic factors, such as VEGF, within the hypoxic inflammatory joint may induce alterations in energy metabolism profiles.[96,97] Therefore, it may be enticing to speculate that metabolic perturbations within the inflammatory joint are a consequence of the combined contribution of many reciprocal mechanisms, for example, aberrantly expressed HIF1α, HIF2α, VEGF, NFκB and mutations in p53.

AMPK, Hypoxia and Circadian Rhythms

Significant time-of-day oscillations in glucose metabolism are observed in both humans and rodent models, at both the whole body and cellular level.[98] It has been speculated that various mitochondrial functions may be regulated by the circadian clock thereby serving as a central coordinator between the clock and cellular energy metabolism.[99] For example, cytochrome c oxidase activity is increased in the brains of 2 month old wistar rats during wakefulness compared to sleep to meet increased energy demands.[100] AMPK is one of the main metabolic sensors responsible for transmitting energy dependent signals to the mammalian clock.[101]

A molecular oscillator exists whereby the transcription factors CLOCK and BMAL1 work together to drive the expression of many genes responsible for the mammalian molecular clock, including those encoding their own inhibitors, the period (PER1, PER2 and PER3) and cryptochrome (CRY 1 and CRY2) proteins.[101] CRY1 and CRY2 are transcriptional repressors that are necessary for circadian clock function.[102] The E3 ligase component F-box/LRR-repeat protein 3 (FBXL3) catalyzes the polyubiquitination of CYR1 and CRY2 and thus stimulates their proteosomal degradation.[103] AMPK-mediated serine phosphorylation of CRY1 and CRY2 initiates the interaction between CRY1, CRY2 and FBXL3 and stimulates the degradation of both cryptochromes.[104] Casein kinases, CKIε and CKIδ, are also important modulators of circadian rhythm in mammals.[101] Genetic disruption or pharmacological inhibition of these casein kinases alters behavioural and cellular circadian rhythms in mice.[105] Casein kinases phosphorylate serines in PER2, however, AMPK was reported to phosphorylate CKIε at serine 389 thereby increasing its enzymatic activity and indirectly leading to destabilisation of PER2 and alterations in circadian rhythm.[106]

AMPK has also been implicated in circadian rhythm entrainment in mice as pharmacological activation of AMPK by intraperitoneal injection of both 5-aminoimidazole-4-carboxyamide ribonucleaoside (AICAR) or metformin casues a phase shift of the liver clock.[104,106] In addition, AICAR stimulation altered clock gene expression in wild type mice but not in mice lacking the AMPKγ3 subunit implying that AMPK activation may play a role in circadian entrainment.[107] Furthermore, AMPK possesses a close relationship with silent mating type information regulation 2 homolog 1 (SIRT1), another fuel-sensing molecule key to nutritional status and circadian regulation. AMPK

not only enhances SIRT1 activity by increasing NAD^+ levels but activation of SIRT1 causes AMPK phosphorylation *via* LBK1 activation.[108,109] AMPK is also associated with regulating other metabolic sensors known to have key roles in circadian regulation such as poly (ADP-ribose) polymerase 1 and nicotinamide phosphoribosyltransderase.[110,111] These studies suggest that the effectiveness of widely prescribed drugs that regulate glucose homeostasis, such as metformin, may be ameliorated by altering the timing of treatment through AMPK-mediated control of circadian function by pharmacological intervention.

RECIPROCAL MECHANISMS LINKING ENERGY METABOLISM TO INFLAMMATION IN GASTROENTEROLOGICAL DISEASES

It is apparent thus far, that the combined effect of various molecular processes, can act in tandem to significantly alter the local microenvironment and attenuate disease progression. Little is known about how energy metabolism profiles cooperate with inflammatory processes to facilitate metaplastic progression in gastroenterological disease entities. However, some recent research has provided some insight on metabolic signatures in Barrett's oesophagus, oesophageal adenocarcinoma, Inflammatory Bowel Disease (IBD), gastritis and gastric cancer.[112-116]

Recent research has demonstrated that both oxidative phosphorylation and glycolysis are reprogrammed early in the inflamed Barrett's disease sequence and may act mutually to promote disease progression in Barrett's oesophagus.[117] Subsequent to screening 84 genes using a PCR microarray, validations utilising *in-vitro* and *in-vivo* models found that 3 genes associated with mitochondrial energy metabolism, *ATP12A*, *COX4I2* and *COX8C*, were differentially expressed across the Barrett's sequence.[117] In addition, tissue microarrays demonstrated significant epithelial and stromal alterations using surrogate protein markers of oxidative phosphorylation, ATP synthase subunit 5 beta and heat shock protein 60, or ATP5B and HSP60 respectively.[117] Moreover, significant alterations across the Barrett's sequence were also demonstrated using surrogate protein markers of glycolysis, pyruvate kinase isozyme M2 and glyceraldehydes 3-phosphate dehydrogenase, or PKM2 and GAPDH respectively.[117] Interestingly, ATP5B in sequential follow up surveillance biopsy material segregated Barrett's non progressors and progressors to high grade dysplasia and adenocarcinoma thereby highlighting the prognostic advantage of metabolic profiles in these pre-neoplastic patients.[117] Finally, utilising the *in-vitro* model, the authors present evidence that Barrett's and adenocarcinoma cells exhibit significantly altered levels of various oxidative parameters, whereby the adenocarcinoma cell line maintains an equilibrium between both metabolic pathways while the Barrett's cell line favours a more detrimental oxidative phenotype that may be selected for during early stages of disease progression .[117]

Other studies, although mostly indirectly, link inflammation to energy metabolism. IL-6, documented as being increased in myofibroblasts of Crohn's disease patients, has also been shown to increase the expression of hexokinase 2 and PFKFB3 in murine embryonic fibroblasts.[118,119] Moreover, increased secreted and immunological levels of IL-6 have been found in Barrett's tissue compared to matched normal adjacent squamous epithelium.[120] Aberrant expression of p53 is also associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus.[121] Therefore, since mutated p53 enhances IL-6 promoter activity in renal cell carcinoma, it may be plausible that p53, known to modulate oxidative phosphorylation and glycolysis, simultaneously alters inflammatory and metabolic profiles in pre-neoplastic and neoplastic microenvironments of the oesophagus.[50,122] Similarly, HIF1α, known to mediate hypoxia-induced alterations in glycolytic metabolism and to possess an intrinsic relationship with p53, has been shown to be differentially expressed across the Barrett's sequence.[6,36]

Interestingly, despite increased oxidative phosphorylation in Barrett's oesophagus, ulcerative colitis is associated with low levels of this metabolic pathway.[114,123] Loss of oxidative phosphorylation precedes the development of dysplasia in ulcerative colitis and thus could potentially be utilised to predict cancer.[114] Furthermore, following preneoplastic progression, cancer cells restore mitochondria indicative of an increase in energy demands for growth and proliferation.[114] In addition, one study showed that increasing mucosal levels of ATP can protect mice from colitis and thus increasing ATP synthesis could be a plausible therapeutic approach for ulcerative colitis.[123] Such reductions in oxidative phosphorylation, thought to be caused by defects in complex I of the electron transport chain, have also been reported in atrophic and active chronic gastritis.[115,124] Gastric cancer is additionally associated with a complex I-induced defective electron transport chain.[125] As well as decreased mitochondrial respiration, gastric cancer exhibits shifts to glycolysis.[113,126] Decreased fructose-1,6-bisphosphatase (FBP), the enzyme which functions to antagonise glycolysis though NFκB, has been shown to be decreased in both gastric cell lines and gastric carcinomas thereby promoting glycolysis.[127,128] PDK-1 and PKM2 are also overexpressed in gastric and colorectal tumour tissue and their expression is associated with poor survival.[129-131] Moreover, knockdown of PKM2 has been shown to repress the proliferative and migratory capabilities of colorectal cancer cells.[130]

IBD patients are known to have high levels of HIF1α and HIF2α.[132] IBD patients also exhibit increased colonic expression of various glycolytic enzymes and these alterations in metabolism are thought to be triggered by hypoxic stress.[133] Such extensive regulation of various glycolytic intermediates could be mediated by central regulators of metabolism known to associate with HIF, for example, PFKFB. One study in gastric cancer cell lines and tissue found that both PFKFB3 and PFKFB4 significantly responded to hypoxia through HIF1α and this subsequently promoted the Warburg effect.[134] Interestingly, alterations in the gut microbiome, as demonstrated by the fucosyltransferase 2 polymorphism in Crohn's disease patients for example, could also affect the host mucosal state and thus increase disease susceptibility.[135] Therefore, further studies directly linking inflam-

mation with energy metabolism profiles through these distinct processes would enhance our understanding on the mechanisms involved in inflammatory-induced neoplastic progression in gastrological diseases.

INNOVATIVE METABOLIC-BASED TREATMENTS AND MULTI-TARGETED THERAPIES

In order to replicate and divide, tumour cells need to possess the ability to acquire large quantities of proteins, lipids and nucleotides.[5] As these processes are highly metabolically demanding, cells additionally require vast quantities of ATP. Consequently, targeting glucose metabolism and nucleotide biosynthesis could have significant advantages on combating metabolic transformation. In addition, altering the metabolism of susceptible or predisposed pre-neoplastic or neoplastic tissue may prevent subsequent disease progression.

Table 1 highlights some of the diverse therapeutic strategies currently being employed to target various aspects of energy metabolism. Significant research has begun to focus on targeting upstream regulators of metabolic pathways such as HIF, phosphoinositide 3-kinase (PI3K), Akt, mTOR and AMPK.[5] For example, PI3K inhibitors such as BEZ235 have been shown to target metabolism leading to cancer regression in Kras-mutant murine lung adenocarcinomas.[136] The AMPK activator metformin, primarily used to treat patients with type 2 diabetes, has been shown to be protective as those treated with metformin were found to be cancer free over 8 years versus those on alternative treatment regimes.[137] Additional AMPK activators are also being investigated for their potential therapeutic use.[138] Interestingly, methotrexate, a chemotherapeutic known to target nucleotide biosynthesis, enhances the antianabolic and antiproliferative effects of AICAR, an alternative AMPK agonist.[139] Moreover, targeting nucleotide biosynthesis may be more favourable as nucleotide building blocks necessary for proliferating tumour cells can be synthesised by endogenous glucose and glutamine due to poor vascularisation.[5] Therefore, blocking ribose-5-phosphate synthesis, with 5-fluorouracil (5-FU) for example, could provide a better therapeutic window. Dichloroacetate, an inhibitor of PDK-1, has also been shown to re-sensitise gastric cancer cells with hypoxia-induced resistance to 5-FU through the alteration of glycolysis.[140]

Therapeutic agents that target the glycolytic pathway such as 2-deoxyglucose, lonidamine, 3-bromopyruvate and TLN-232 have also shown significant promise.[5] Despite not showing substantial effects on tumour growth as monotherapeutic drugs, their use in conjunction with other chemotherapeutic reagents seems to sensitive tumours by reducing ATP levels and perhaps by indirectly limiting the availability of macromolecules synthesised through anapleurotic interactions.[141] In addition to being combined with radiotherapy, some glycolytic inhibitors are currently being used in phase I, II and III clinical trial.[5,142] Inhibitors that target glucose transport across the plasma membrane, such as phloridzin and phloretin, have also shown efficacy in inhibiting *in-vitro*, xenograft and *in-vivo* tumour growth.[143,144] Inhibition of PFKFB3 with 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one, or 3-PO, known to be a selective agent against neoplastic cells, has been shown to reduce cellular lactate, ATP, NAD^+ and other cellular metabolites within several human malignant hematopoietic and adenocarcinoma cell lines.[145]

Additional therapeutic modalities that can be exploited include targeting HIF1α, lactate transporters, amino acid metabolism and lipid metabolism.[5] Altering diet is also a unique

Drug	Target	Mechanism	Reference(s)
2-deoxyglucose	Glycolytic Pathway	Inhibits the production of glucose-6-phosphate	(5,142)
3-bromopyruvate	Glycolytic Pathway	Inhibits GAPDH	(5)
3-PO	Glycolytic Pathway	Inhibits PFKFB3	(145)
5-FU	Nucleotide Biosynthetic Pathway	Inhibits cell proliferation	(5)
BEZ235	PI3K/mTOR Pathways	Inhibits PI3K signalling & mTORC1/ mTORC2	(136)
Dichloroacetate	Glycolytic Pathway	Inhibits PDK-1	(140)
Lonidamine	Glycolytic Pathway	Inhibits hexokinase and mitochondrial respiration	(5)
Metformin	AMPK agonist	Activates AMPK	(137)
Methotrexate	AMPK / Nucleotide Biosynthetic Pathway	Activates AMPK	(5,139)
Phloretin	Glucose Transport	Inhibits sodium-glucose transporters 1 & 2	(143,144)
Phloridzin	Glucose Transport	Inhibits sodium-glucose transporters 1 & 2	(143,144)
PX-478	HIF1α	Inhibits HIF signalling	(5)
Salicylate	AMPK agonist	Activates AMPK	(138)
TLN-232	Glycolytic Pathway	Inhibits PKM2	(5)

Table 1: Metabolic-based compounds.

and beneficial therapeutic approach. For example, a ketogenic diet relies on food that does not increase plasma glucose but produces ketone bodies that can be used as a carbon source thereby bypassing glycolysis.[146] Even though the ketogenic diet has been shown to have mixed results, further studies may reveal that it is a cancer specific therapy.[146] More recently, micro RNAs have shown promise at targeting cancer metabolic pathways. A recent study demonstrated that mir-122 targets PKM2 and affects metabolism in hepatocellular carcinoma.[147] Despite the encouraging evolution of metabolic-based treatments and multi-targeted therapies, more work is required to understand which pathways are activated in distinct tumour types thereby allowing the identification of pharmacological targets that can avert disease progression and alleviate tumour burden.

CONCLUSION

Cellular energy metabolism plays a crucial role in inflammatory, hypoxic and angiogenic microenvironments by supporting malignant progression in a range of disease entities. Pre-neoplastic and neoplastic tissue must use a diverse range of molecular components to alter their metabolism to adapt to fluctuating oxidative, hypoxic and metabolic stresses. This involves exploiting various molecular elements such as HIF1α, AMPK or p53 that have the potential to function rapidly to acute onsets of stress. It is evident from ongoing research, however, that tumour cells can survive these stresses by adjusting their metabolism through a range of alternative pathways and novel mediators such as NFκB, VEGF and mTOR. Substantiating the reciprocal relationship between energy metabolism in inflammatory and hypoxic diseases is evident in RA and circadian rhythms. In addition, it is clear that the inflammatory microenvironment of the gastrointestinal tract presents clear indication of this mutual association. Therefore, understanding the underlying mechanisms that permit premalignant cells to transform, survive, thrive and subsequently adapt in response to a range of metabolic-based therapies will aid considerably in the development of effective and specific multi-targeted therapies.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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