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Metabolic Shifts in Immunity and Inflammation

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Abstract

Sites of ongoing inflammation and triggered immune responses are characterized by significant changes in metabolic activity. Recent studies have indicated that such shifts in tissue metabolism result from a combination of profound recruitment of inflammatory cells (neutrophils and monocytes) and high proliferation rates among lymphocyte populations. The resultant shifts in energy supply and demand can result in metabolic acidosis and diminished delivery and/or availability of oxygen, leading to hypoxia extensive enough to trigger transcriptional and translation changes in tissue phenotype. Such phenotypic shifts can imprint fundamental changes to tissue metabolism. Here, we review recent work addressing metabolic changes and metabolic control of inflammation and immunity.

Introduction

Ongoing inflammatory and immune responses are associated with dramatic shifts in tissue metabolism. These changes include local depletion of nutrients, increased oxygen consumption and the generation of large quantities of reactive nitrogen and oxygen intermediates (1). Such shifts in tissue metabolism result, at least in part, from profound recruitment of inflammatory cell types, particularly myeloid cells such as neutrophils (PMN) and monocytes. The vast majority of inflammatory cells are recruited to, as opposed resident at, inflammatory lesions (2). By stark contrast, adaptive immune responses are characterized by high rates of local T and B cell proliferation and have significantly different metabolic demands (3, 4). Herein, it is important to understand the interactions between microenvironmental metabolic changes (e.g. glucose, oxygen, ATP) as they relate to metabolic triggers and molecular mechanisms immune cell recruitment / activation into these areas (summarized in Table 1). Importantly, it is imperative to define whether mechanisms initiated by such metabolic shifts might serve as important therapeutic targets.

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Energy Metabolism in Inflammation and Immune Responses

One of the fundamental differences between the inflammatory response and the immune response is the means by which leukocytes obtain energy. Cells of myeloid lineages derive their energy almost exclusively from glycolysis while lymphocytes utilize predominantly oxidative phosphorylation (3, 5). In part, these differences shape the appropriateness of the immune response. For example, evidence in recent years indicates that the abilities of lymphocytes to proliferate and quiesce are strictly controlled by essential metabolites that support anabolic growth (3).

As opposed to lymphocytes which proliferate within tissues, myeloid cells such as polymorphonuclear leukocytes (PMN, neutrophils), macrophages and dendritic cells are recruited to sites of inflammation during immune responses. In transit, these cells expend tremendous amounts of energy. Cell migration, for example, requires large amounts of actin turnover, and by its nature, is particularly ATP demanding (6). Once at sites of inflammation, nutrient, energy and oxygen demands increase to accomplish processes of phagocytosis and microbial killing. It has long been known that PMN are primarily glycolytic cells, have few mitochondria and produce little energy from respiration (7). It is thought predominantly glycolytic metabolism ensures that PMN can function at low oxygen concentrations (even anoxia) associated with deep inflammatory lesions. In this regard, recent studies have revealed that PMN have unique mitochondrial properties, namely that the mitochondria maintain a transmembrane potential via the glycerol-3-phosphate shuttle which functions to regulate aerobic glycolysis as opposed to producing energy (5). This unique mitochondrial phenotype appears to develop along the differentiation pathway from myeloid precursor cells.

T and B cells, by contrast, utilize amino acids, glucose and lipids as energy sources during oxidative phosphorylation. As one might imagine, mitogenic stimulation of thymocytes or naïve T cells is a highly energy demanding process. As lymphocytes proliferate, they become more and more dependent on glucose uptake. Stimulated proliferation of thymocytes can result in nearly twenty-fold increases in glucose uptake, which is accomplished by plasma membrane high expression of glucose transporter-1 (8), which is tightly controlled by hypoxia-inducible factor (HIF, see later). Nutrient uptake in naïve T cells is strictly instructed through IL-7 and IL-4-dependent pathways (9). During periods of high proliferation, even in the presence of adequate oxygen concentration, lymphocytes become progressively more dependent on aerobic glycolysis for ATP synthesis. Lactate production from glycolysis can increase by as much as 40-fold in mitogen-stimulated T cells. When glucose becomes limiting, as it often does at sites of high immune activity, T cells can utilize alternative energy sources, such as glutamine, within the TCA cycle (3).

Transcriptional Control of Immune Metabolism by HIF

Sites of ongoing inflammation and high immune activity can become rapidly depleted of both nutrients and oxygen. Activated PMN, for example, can increase their oxygen demand by as 50-fold in the generation of reactive oxygen intermediates (the so called respiratory burst mediated by NADPH oxidase) necessary to kill bacteria following phagocytosis (10).

Somewhat surprisingly, proliferating T cells only moderately increase oxygen consumption (3). As a global regulator of oxygen homeostasis, the αβ-heterodimeric transcription factor hypoxia-inducible factor (HIF) is a central part of all cellular metabolism (11, 12). HIF-1 and HIF-2 (also called EPAS) are members of the Per-ARNT-Sim (PAS) family of basic helix-loop-helix (bHLH) transcription factors. HIF activation is dependent upon stabilization of an O_2-dependent degradation domain of the α-subunit and subsequent nuclear translocation to form a functional complex with HIF-1β and cofactors such as CBP and its ortholog p300 (13). Under conditions of adequate oxygen supply, iron and oxygen dependent hydoxylation of two prolines (Pro564 and Pro 402) within the oxygen-dependent degradation domain (ODD) of HIF-1α or HIF-2α initiates the association with the von Hippel-Lindau tumor suppressor protein (pVHL) and rapid degradation via ubiquitin-E3 ligase proteasomal targeting (14, 15). A second hypoxic switch operates in the carboxy terminal transactivation domain of HIF-1 or HIF-2α. Here, hypoxia blocks the hydroxylation of asparagine-803 consequently facilitating the recruitment of CBP/p300 (16).

HIF-1α was the original isoform purified by oligonucleotide binding to the 3′ region of the EPO gene (17). HIF-2α was subsequently identified by homology searches and as a binding partner for the heterodimeric partner HIF-1β (18). It was originally thought that the HIF-2α isoform was expressed only in endothelial cells (hence the name endothelial PAS protein or EPAS) (19). HIF-3α is a more distantly related isoform and when spliced appropriately, can encode a protein that antagonizes HRE-dependent gene induction (20). For a number of years, it remained poorly understood how hypoxia might stabilize the expression of HIF. In the past several years, the molecular mechanisms of HIF activation have become clarified. These studies have defined two HIF selective iron and oxygen dependent hydroxylation enzymes (on HIF prolines 564 and 402) within the oxygen-dependent degradation domain (ODD) of the HIF-α subunit (21–24). Since other mammalian prolyl-hydroxylases (e.g. pro-collagen PHD's) were 2-oxoglutarate-dependent (2-OG) (25), it was predicted that the HIF prolyl hydroxylases would also belong to this family of enzymes. Based on conserved structural features (25), a candidate molecular approach was used to define HIF-modifying enzymes. This approach identified the HIF prolyl hydroxylases as the products of genes related to *C.elegans* egl-9, a gene that was first described in the context of an egg-laying abnormal (EGL) phenotype (21). In mammalian cells, three PHD isoforms were identified (PHD 1–3), and shown to hydroxylate HIF-α in vitro (22, 24).

The discovery of HIF-selective PHD's as central regulators of HIF expression has now provided the basis for potential development of PHD-based molecular tools and therapies (26, 27). Pharmacological inactivation of the PHDs by 2-OG analogues is sufficient to stabilize HIF-α (26), but this action is nonspecific with respect to individual PHD isoforms. *In vitro* studies do suggest significant differences in substrate specificity. For example, PHD3 does not hydroxylate proline 564 on HIF-α, and comparison of enzyme activity *in vitro* showed that the ODD sequence is hydroxylated most efficiently by PHD2 (25, 28). These observations have generated an interest in identifying enzyme-modifying therapeutics. Indeed, a number of PHD inhibitors have been described, including direct inhibitors of the prolyl-hydroxylase (29), analogs of naturally occurring cyclic hydroxymates (30), as well as antagonists of alpha-keto-glutarate (26).

Activated T cells show increased expression of HIF-1α. In particular, HIF-1α has been shown to provide an important survival signal for T cells, preventing them from undergoing activation-induced cell death in hypoxic settings. T cell survival in hypoxia is, at least in part, mediated by the vasoactive peptide adrenomedullin (31). Other studies using chimeric mice bearing HIF-1α-deficient T and B cells have revealed lineage-specific defects that result in increased autoimmunity, including autoantibodies, increased rheumatoid factor and kidney damage (4).

HIF function has been studied in some detail in myeloid cells. Cre-*LoxP*-based elimination of HIF-1α in cells of the myeloid lineage (lysozyme M promoter) have revealed multiple features which importantly implicate metabolic control of myeloid function (32). In particular, these studies have shown that PMN and macrophage bacterial killing capacities are severely limited in the absence of HIF-1α, as HIF-1α is central to production of antimicrobial peptides and granule proteases. These findings are explained, at least in part, by the inability of myeloid cells to mount appropriate metabolic responses to diminished O_2 characteristic of infectious sites (32). Finally, compelling evidence have revealed that HIF-1α transcriptionally controls the critical integrin important in all myeloid cell adhesion and transmigration, namely the β2 integrin (CD18) (33, 34).

A growing body of evidence indicates that HIF-mediated signaling pathways in parenchymal cells (e.g. epithelial cells) coordinate inflammatory responses. For instance, intestinal epithelial cells form a critical barrier to the flux of antigenic material across the gut. During episodes of inflammation, barrier function is compromised and can lead to accelerated inflammatory responses. In response to multiple metabolic insults initiated within inflammatory lesions (e.g. decreased O2 supply, increased glucose demand, decreased ATP generation, vasculitis), intestinal epithelial HIF-1α is activated (Figure 1). Studies in mice lacking intestinal epithelial HIF-1α have revealed that HIF-based signaling is central to the protection of barrier function through the induction of multiple genes are important in the restitution of barrier function following injury (35). These findings may be somewhat model-dependent, where epithelial HIF-based signaling has also been shown to promote inflammation in some models (36). Nonetheless, ongoing studies targeting the induction of HIF (through inhibition of PHD's) are promising in animal models of intestinal inflammation (37, 38).

mTOR and Innate Immunity

The mammalian target of rapamycin (mTOR) is an evolutionary conserved serine-threonine kinase that is central to cellular sensing of environmental stress (39). As a integral part of overall metabolism, mTOR monitors cellular ATP:AMP ratios, insulin and amino acid levels (39). mTOR functions as part of two major protein complexes (mTORC1 and mTORC2) that coordinate signaling for anabolic and catabolic metabolism. An important function of the mTORC1 complex is integration of phosphoinositide 3-kinase (PI3K)- and Akt-mediated signaling and in complex and is sensitive to rapamycin inhibition (when complexed to FK506-binding protein 12). mTORC2 on the other hand, phosphorylates Akt Ser 473 but is insensitive to rapamycin inhibition.

In lymphocytes, mTOR controls cell cycle progression from G1 to S phase and can therefore control proliferative responses. It is through these mechanisms that inhibitors of rapamycin (sirolimus) has been used as a potent immunosuppressive agent (40). mTOR is activated by growth factor, extracellular signaling molecules (e.g. Toll-like receptor ligands) and through antigen-induced T cell-receptor signaling. Activation of mTOR through these various stimuli provides increased capacity for aerobic glycolysis and ATP generation during episodes of high T cell proliferation (3). As such, rapamycin has been shown to enrich CD4+CD25+ regulatory T cells (Treg) and recent studies have indicated that mTOR intrinsically regulates T cell memory function (41).

In myeloid cells such as macrophages and DC, mTOR1-based metabolism is particularly important in the integration of PI3K and Akt signaling. This nexus between mTOR and Akt forms a critical linkage to multiple cytokine signaling cascades (39). Emerging evidence suggests that this may be one of the most important regulatory pathways for integrating multiple TLR signaling pathways, and include the production of type I IFN, IL-10, and IL-12/23 (39, 40).

Nucleotide Metabolism in Inflammation and Immunity

In addition to its role in intracellular energy transfer, the nucleotide ATP plays a critical role in extracellular signaling reactions in inflammation and immune responses. Extracellular ATP (or ADP) can directly bind to cell surface purinergic receptors (termed P2-type) or can be metabolized to adenosine at the cell surface, where it is made available to bind and activate adenosine receptor(s) (P1-type). Extracellular nucleotides are metabolized primary by cell-surface enzymes called ectonucleotidases, whose enzymatic activity is to hydrolyze phosphate groups from circulating nucleotides with varying degrees of specificity for their substrates.

CD39 is one such ectonucleotidase initially observed as an activation marker in paracortical lymphocytes, macrophages, and dendritic cells resident within lymphoid tissue (42). Cloning of CD39 revealed the presence of apyrase conserved regions (ACR) and striking sequence homology with yeast guanosine diphosphatase, an enzyme involved in catalyzing the removal of a phosphate from GDP after sugar transfer within the Golgi apparatus (42). Further identification of a number of CD39-like nucleoside triphosphate diphosphohydrolases (NTPDases) have since revealed a family of 8 related proteins, denoted NTPdase1-8 (NTPDase1 representing CD39 under this nomenclature). NTPDase1,2,3 and 8 are transmembrane proteins with 5 ACRs situated on the extracellular region, conferring nucleotidase activity to the enzyme and allowing for hydrolysis of extracellular nucleotides (43). Together, these NTPDases act in a concerted manner to regulate the production of extracellular adenosine monophosphate (AMP).

The second step in metabolism of extracellular adenosine is conferred by the glycosyl phosphatidylinositol (GPI)-anchored membrane protein, ecto-5′nucleotidase (CD73). CD73 is the predominant source for accumulation of extracellular adenosine from released adenine nucleotides (44). CD73 metabolizes AMP to adenosine, which is then either free to act on

adenosine receptors or is transported into the cell by dipyridamole-sensetive channels and degraded by the purine salvage pathway.

Extracellular adenosine binds to one (or more) of four adenosine receptors (AR; A1AR, A2AAR, A2BAR, and A3AR) (45). A number of studies have addressed the contribution of individual ARs in murine mucosal inflammation. While less is known about the role of the A1 or A3AR, both A2A and A2BAR have been shown to attenuate mucosal inflammation and to provide tissue protection (46). From this perspective, A2AAR and A2BAR agonists represent a potential group of therapeutics for the treatment of mucosal inflammation. One study found a critical role for the A2AAR signaling in T cell-mediated regulation of colitis and treatment with a specific A2AAR agonist attenuated the production of pro-inflammatory cytokines and attenuation of colitis (47). Activation of adenosine A2AAR seems to limit reperfusion injury by inhibiting inflammatory processes in neutrophils, platelets, macrophages and T cells (47). The contribution of A2BAR to mucosal inflammation has been somewhat discrepant, where in two separate studies, mice lacking A2BAR have shown either increased and decreased susceptibility to DSS-induced intestinal inflammation (48, 49). Additional studies will be necessary to rectify these differences.

Methylation-dependent Control of Metabolism

Immune responses and cellular differentiation are tightly mediated by epigenetic modifications, which constitute another level of control of gene expression. Regulation of gene expression works primarily through modification of chromatin structure, allowing regions of DNA to be more or less accessible to transcription. Epigenetic modifications include ubiquitylation, acetylation, and methylation of histones, proteins that interact with DNA to form the secondary and tertiary structures of chromatin, and DNA methylation of cytosine residues at CpG dinucleotides. All cell types possess a unique epigenetic profile determined early in differentiation and carried through to fully differentiated cells and tissue (50). It is becoming increasingly appreciated, however, that this epigenetic profile can be perturbed by environmental stress (51). It has been know for many years that changes in epigenetic modifications contribute to a number of cancer types (52) and is now becoming clear that these changes play roles in other disease states as well.

Epigenetic modifications are a crucial part of normal immune system function. The differentiation of T cells from progenitor to the Th1 or Th2 lineage requires silencing of the genes associated with other lineages, which is accomplished via epigenetic mechanisms (53, 54). Similarly, development of two other important T cells lineages, Th17 and regulatory T cells (T regs) is controlled through epigenetic modifications (55, 56). Recent studies also suggest that epigenetic changes are important for cells of the innate immune system such as macrophages (57). Several lines of evidence suggest that aberrant epigenetic regulation plays a role in chronic inflammation. While no DNA demethylase has been identified, there are types of modifications that occur during chronic inflammation that influence DNA methylation states and render genes more or less accessible to transcription (58). Additionally, methotrexate (MTX), a drug commonly used to treat arthritis, actively inhibits DNA methylation by inhibiting DNA methyltransferases (59) and may ameliorate symptoms by up-regulation of silenced anti-inflammatory genes. While histone methylases and

demethylases were only identified recently (60, 61), studies have also found that changes in histone methylation play an important role in inflammatory responses as well (62). Also of interest here are the recent findings demonstrating the role of hypoxia in epigenetic modification through the significant increase in global DNA methylation (63).

While histone methylases and demethylases were only identified recently (60, 61), the identification of site-specific histone demethylases demonstrates that histone methylation is a dynamic process, providing a mechanism for alteration of chromatin conformation in response to cellular stresses such as inflammation. Of particular interest here are the findings that at least two of these histone demethylase enzymes belonging to the Jumonji gene family, JMJD1A and JMJD2B, are induced by hypoxia in a HIFα-dependent manner (64–67). These studies provide insight into new mechanisms for regulation of the cellular response to limiting O_2 supply. Additionally, studies have also demonstrated important links between changes in histone methylation and cellular inflammatory responses as well (62).

Cellular methylation reactions include modification of DNA, RNA, proteins and lipids. These reactions all require a methyl donor for the modification of the target. The methyl donor for the majority of these reactions is S-adenosylmethionine (SAM) (68). SAM is distributed throughout the cell to act as donor for the various methylases. The donation of its methyl group produces S-adenosylhomocysteine (SAH) from SAM. SAH is a potent inhibitor of methyltransferase enzymes because these enzymes have a higher affinity for SAH (69) and SAH is rapidly converted to homocysteine and adenosine by SAH hydrolase. Therefore, inhibition of SAH hydrolase represents a powerful means of inhibiting cellular methylation reactions (70). It has been known for several years that inhibition of methylation had immunosuppressive (71). This led to the development of more specific, reversible, and less toxic SAH inhibitors for use in animal models of inflammation. Utilizing these compounds, it was demonstrated that SAH hydrolase inhibition particularly down-regulates T cell activation and adaptive immune responses. One of these SAH hydrolase inhibitors, DZ2002 [methyl 4-(adenin-9-yl)-2-hydroxybutanoate], has been found to have potent immunosuppressive effects and ameliorates disease in a number of animal models including delayed type hypersensitivity (72), arthritis (72), and EAE (73). Additionally, inhibition of SAH hydrolase has also been shown to influence cells of the innate immune system, particularly macrophages (74). These studies demonstrate that inhibition of antigen-induced immune responses.

Lipid Metabolism and Innate Immunity

A significant metabolic sink during inflammation and within the immune response involves the generation of lipid mediators. The majority of these short-live signaling molecules are generated by either cyclooxygenases or lipoxygenases. As their names might apply, these enzymatic responses require large amounts of oxygen, and as such can function to change intracellular metabolism in fundamental ways.

Polyunsaturated Fatty Acids (PUFAs) are essential to tissue homeostasis but cannot be synthesized in mammals, thus must be obtained from the diet. PUFAs have received much attention in recent years as the metabolism of omega-6 (ω-6) fatty acids appear to have

opposing physiological consequences to omega-3 (ω-3) (75). Dietary ω-6 and ω-3 fatty acids are converted by various desaturases and elongases to arachidonic acid (AA) and eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), respectively, and incorporated into membrane phospholipids. Unsaturated fatty acids are liberated from membranes by phospholipase A_2 (PLA_2) and are further metabolized to generate what are considered pro-inflammatory mediators (e.g. eicosanoids, prostaglandins, thromboxanes, leukotrienes) and anti-inflammatory molecules (e.g. lipoxins, resolvins and protectins). As a general rule, ω-6 PUFAs give rise to pro-inflammatory lipids, whereas ω-3 PUFAs are metabolized to anti-inflammatory lipid mediators.

Oxygenases such as cyclooxygenases (COXs) and lipoxygenases are crucial oxygen-dependent, rate-limiting enzymes in the metabolism of PUFAs. COX catalyzes the conversion of arachidonic acid to prostaglandin G_2 (PGG_2) and subsequently converts PGG_2 to PGH_2 (76). PGH_2 serves as the substrate for numerous enzymes, each resulting in a different PG end product. There are two known isoforms of cyclooxygenase – the COX-1 isoform is constitutively expressed, whereas COX-2 is thought to be inducible (77). As the name suggests, cyclooxygenase requires two molecules of oxygen to catalyzes the oxidation of arachidonic acid to PGG_2 (78), thus it may seem intuitive that in an oxygen depleted environment, such as an inflammatory lesion, that eicosanoid production would be attenuated. Contradictory reports exist in the literature. Some groups observe that hypoxia increases COX-2 but not PGE_2 (79, 80) or prostacyclin (81) levels. Others reports indicate that hypoxia paradoxically stimulates production of prostaglandins (82), likely via induction of COX-2 expression (83). Furthermore hypoxia has been demonstrated to increase cytosolic PLA_2 activity, liberating more unsaturated fatty acids from lipid membranes to act as substrates for COX or lipoxygenases (84). This disparity between hypoxia-induced changes in PGE_2 production may be due to tissue specificity, extenuating metabolic influences or even time-dependent sampling. A recent report examined the difference in PGE_2 levels and COX-2 activity in acute and chronic periodontitis. Their findings indicated that PGE_2 and COX-2 activity increase in acute disease but are suppressed in chronic disease states, which was mechanistically attributed to COX-2 promoter hypermethylation (85). Conversely, the contribution of diminished molecular oxygen in inflamed-hypoxic tissue to eicosanoid production has been poorly characterized. The affinities of various oxygenases for molecular O_2 has been investigated, but the results appear to inconclusive (86).

Much recent attention has been paid to understanding lipid metabolism involved in the resolution of inflammation and in productive immune responses at mucosal sites. Of particular interest are series of cyclooxygenase-derived lipid mediators termed the resolvins and the maresins (87). Resolvins are the best understood of these molecules and are ω-3 PUFA-derived lipid mediators central to activation of the inflammatory resolution program (88). Among them, RvE1 was the first isolated and has been studied in the greatest detail. RvE1 displays potent stereoselective actions in vivo and in isolated cell systems. At nanomolar levels in vitro, RvE1 potently reduces human PMN transendothelial migration, dendritic cell (DC) migration and interleukin (IL)-12 production (87). In several animal models of inflammatory disease, RvE1 and more recently RvE2 (89) displays potent counter-regulatory actions that protect against leukocyte-mediated tissue injury, excessive

pro-inflammatory gene expression. The discovery of a novel family of DHA-derived lipid mediators termed maresins (macrophage mediator in resolving inflammation: MaR) (90). MaR were identified from murine peritonitis exudates and human macrophages that biosynthesized a new class of lipoxygenase-derived lipids derived from endogenous DHA. MaR1 were demonstrated to promote inflammatory resolution with the potency of resolvins, reflected as decreased neutrophil accumulation and increased macrophage phagocytosis during murine peritonitis.

Ischemia/reperfusion injury is a major cause of tissue damage following stroke or transplantation, whereby reactive oxygen species production and lipid peroxidation generated during hypoxia cause significant tissue damage upon reoxygenation. However, brief intermittent exposure to hypoxia (ischemic preconditioning, IPC) has been demonstrated to be protective. Adenosine, mentioned earlier, is generated during IPC and capable of eliciting anti-inflammatory effects (91). COX-2 is protective against ischemia/reperfusion injury, mediates late phase of preconditioning (92), possibly via PGE_2 or prostacyclin (PGI_2). Sphingosine 1-phosphate (S1P) is a sphingolipid signaling molecule that mediates cardioprotection during IPC (93). Sphingosine kinases catalyze the conversion of sphingosine to S1P, which binds to S1P G-protein coupled receptors to mediate cell survival signals. Both the SK1 (94) and SK2 (95) isoform of sphingosine kinase are upregulated in hypoxia, resulting in increased S1P. Concomitantly, conversion of sphingosine to S1P prevents its conversion to ceramide, a pro-apoptotic signaling lipid mediator (96).

Conclusion

The dynamic interplay of leukocytes and parenchymal cells during disease defines an elegant lesson in biology. In particular, studies of model disease systems have allowed for the identification of metabolomic changes now well accepted in the scientific literature. The discovery of differences and similarities between innate and adaptive immune responses will continue to teach us important lessons about the complexity of biological systems. Such information will provide previously unappreciated insight into the pathogenesis disease and importantly, will provide new targets as templates for the development of novel therapies for human disease.

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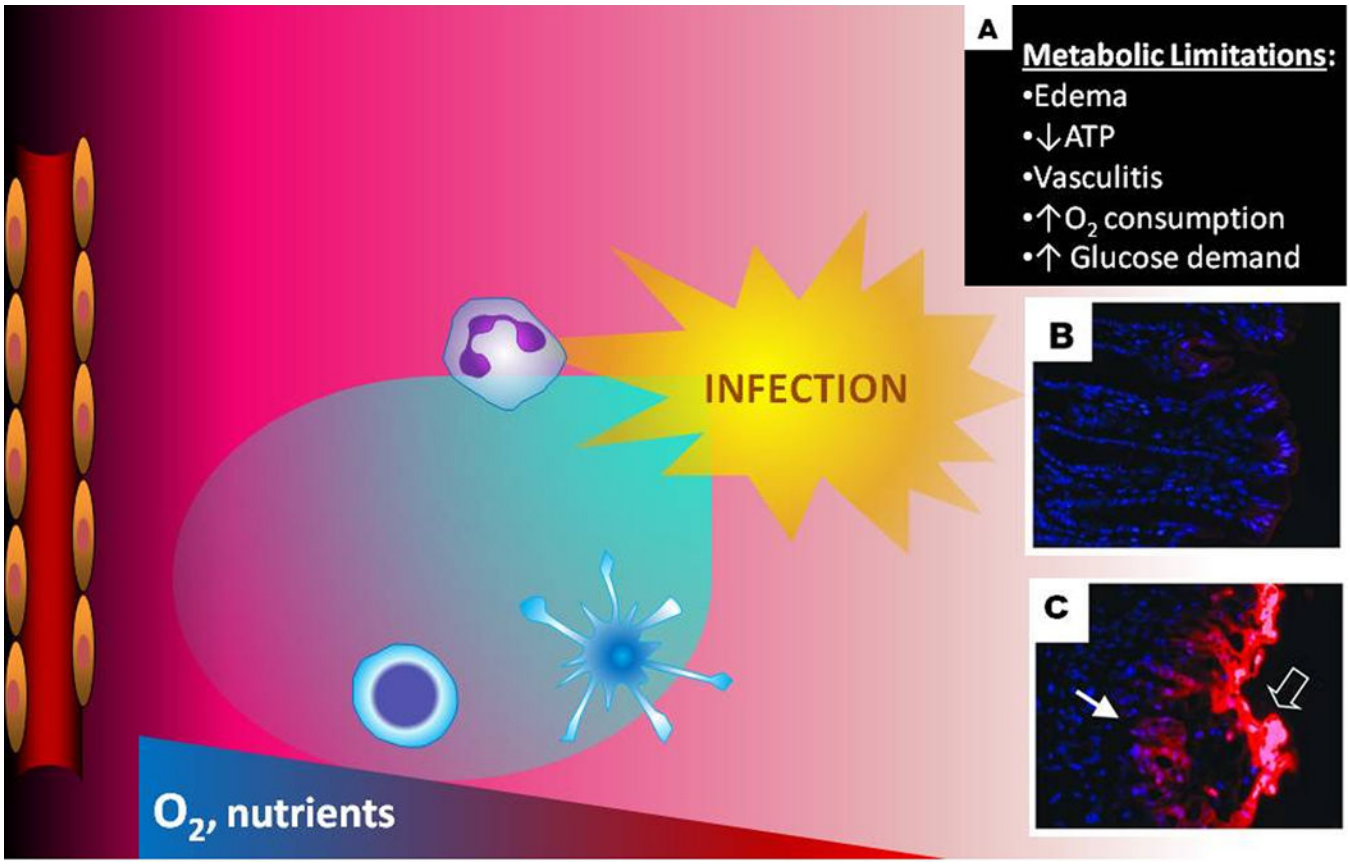

Figure 1. Metabolic stress points in inflammation and immunity

Migration of inflammatory cells to sites of infection changes local tissue metabolism in fundamental ways. A number of metabolic limitations contribute to substantial a shift in tissue metabolism (A). In vivo evidence for inflammation-associated hypoxia (so called "inflammatory hypoxia") using nitroimidazole-based dye retention in vehicle treated mouse colon revealing a degree of "physiological hypoxia" (B) compared to TNBS-induced colitis resulting in intense and deep tissue hypoxia (C). (Adapted from reference 35, DC=dendritic cell; T=T-cell; PMN=neutrophil).

Table 1

Metabolic Comparisons between Innate and Adaptive Immunity

Type of Immunity	Innate	Adaptive
Cells Involved	PMN, eosinophil Macrophage Dendritic Cell	T cell, B cell, NK cell
Metabolic Trigger(s)	Recruitment Differentiation	Local Proliferation Recruitment
Activation Stressor(s)	Migration Phagocytosis Respiratory Burst	Ag-induced Differentiation
Metabolic Adaptor (s)	HIF, mTOR, Akt	HIF, mTOR, Akt
Mitochondria	Few	Many
Primary Energy Source	Glycolysis	Respiration
Methylation Dependence	Unknown	Proliferation Ag-induced Differentiation