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Nutrient sensing, signal transduction and immune responses

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Abstract

Most cells in the body have a constant supply of nutrients, which are required to sustain cellular metabolism and functions. In contrast, cells of the immune system can encounter conditions with a limited nutrient supply during the course of an immune response. Cells of the immune system frequently operate in complex nutrient restricted microenvironments such as tumour or inflammatory sites. The concentrations of key nutrients such as glucose and certain amino acids, can be low at these sites, and this can have an impact upon immune cell function. Nutrient sufficiency is important to supply the metabolic and biosynthetic pathways of immune cells. In addition nutrients can also act as important cues that influence immunological signalling pathways to affect the function of immune cells. This review will describe the various nutrient sensing signalling pathways and discuss the evidence that nutrients are critical signals that shape immune responses.

Introduction

Nutrient restrictive immune microenvironments: Most tissues are well vascularised and replete with nutrients and oxygen. Therefore, under normal homeostatic conditions circulating immune cells or those within tissue are adequately supplied with the fuels they require to maintain energy homeostasis and cellular processes. However, this is not always the case and certain microenvironments can be significantly less accommodating. At inflamed sites the influx of inflammatory cells such as neutrophils and monocytes increases nutrient consumption and can lead to low glucose availability and tissue hypoxia [1]. Neutrophils have low levels of mitochondrial respiration and few functional mitochondria and as a result have a high demand for glucose to fuel glycolytic energy production as well as to support other cellular processes and effector functions [2-4]. At sites of infection there is additional demand for nutrients caused by the infecting pathogen. Glucose is an important fuel for many pathogenic bacteria, including the common human pathogen *Staphylococcus aureus,* and glucose levels can drop during bacterial infection [5, 6]. Additionally, many virus' have been shown to reprogram the cells they infect towards increased glucose uptake and glycolysis to facilitate viral replication [7-11]. The microenvironment within solid tumours can also be considerably metabolically restrictive for infiltrating immune cells. Tumour cells consume large amounts of glucose, and other nutrients such as glutamine, and as a result the tumour microenvironment can become depleted of nutrients [12-15]. Additionally, tumour cells and tumour promoting immune cells such as myeloid derived

suppressor cells express enzymes such as arginase and indoleamine-2,3-dioxygenase that consume arginine and tryptophan respectively [12, 16]. Solid tumours can also become hypoxic due to insufficient vascularisation [17]. As mentioned above, tissue hypoxia can be a feature of certain immune microenvironments and while this will not be discussed in detail herein, it is the subject of various other review articles [18, 19].

Systemic nutrient alterations: Metabolic syndrome, a health care crisis that is reaching epidemic levels world wide, is a clustering of conditions including central obesity, dyslipidaemia and hypertension that increases the risks of morbidities such as cancer and cardiovascular disease. Another feature of metabolic syndrome is altered immune function [20]. Fatty acids, cholesterol and cholesterol derivatives have all been proposed to have roles in controlling immune function and the dysregulated systemic levels of these molecules in patients with metabolic syndrome is likely to underpin the observed alterations in immune function [21]. The levels of molecules like oxysterols can also be altered in discrete immune microenvironments. For instance, tumour cells release oxysterols into the tumour microenvironment [22] and activated macrophages make large amounts of the oxysterol 25-hydroxycholestrerol (25HC) [23]. It is also clear that dietary and microbiome derived molecules such as short chain fatty acids have a role to play in the control of immune responses.

Therefore, many of the environments in which immune cells operate can have variable levels of important nutrients, including glucose, amino acids, fatty acids and cholesterol/oxysterols. These molecules are all important for cellular metabolism or as structural components of the cell, but importantly, these molecules can also directly impact upon immune signalling pathways to influence immune activation, differentiation and function. Indeed, there is a growing appreciation that nutrients are important cues that can shape immune responses. This review article will discuss the various nutrient sensing signalling pathways and the roles they play in regulating the function of immune cells.

Glucose and Glutamine sensing

Glucose and glutamine are important fuels that feed into different parts of the ATP generating pathways of the cell, glycolysis and oxidative phosphorylation (OxPhos), but can also supply various biosynthetic pathways. The levels of these fuels can impact upon multiple signalling pathways that are integral to the control of immune responses.

AMPK/mTORC1 signalling:. AMPK is a complex multi-subunit kinase that is an acute sensor of cellular energy homeostasis becoming activated in response to an increased AMP:ATP ratio that occurs when energy levels are decreased (Figure 1A). Activated AMPK functions to restore energy homeostasis by turning off anabolic processes that consume ATP (such as fatty acid synthesis) and up-regulating catabolic processes that generate ATP (such as glycolysis). In activated T cells AMPK can be activated within an hour of being placed in limiting concentrations of glucose [24, 25]. AMPK is likely to have analogous glucose sensing roles in other glycolytic immune cells that are reliant upon glucose as a fuel for generating ATP, such cytokine activated NK cells [26]. AMPK is essentially a sensor of the cellular ATP pool, consequently AMPK is likely to be activated in a given immune subset when an important ATP generating metabolic pathway is disrupted; hypoxia or glutamine deprivation will inhibit OxPhos and thereby activate AMPK in immune cells that rely on mitochondrial ATP production. Indeed, glutamine deprivation also results in AMPK activation in antigen stimulated T cells, highlighting the importance of both glucose and glutamine for ATP production in activated T cells [25].
Historically the role of AMPK in the immune system has been slightly controversial with

conflicting reports when comparing *in vitro* versus *in vivo* approaches, and whole body knockout versus tissue specific knockout models [24, 27-30]. Studies using pharmacological AMPK activators and AMPKα1-/- mice suggested that AMPK has anti-inflammatory roles; though it should be noted that some of the anti-inflammatory effects of these AMPK activators may be AMPK-independent and whole body knockout studies can be difficult to interpret [31]. A recent comprehensive and detailed metabolic study in T cells demonstrates that AMPK is a key metabolic regulator that provides T cells with the metabolic plasticity to adapt to nutrient restrictive conditions such as those found in the inflammatory microenvironment. As a result, T cells lacking AMPK have defective primary responses to viral and bacterial infection and also show defects in memory formation [24, 25]. AMPK also controls the function of mammalian Target of Rapamycin complex 1 (mTORC1) as activation of AMPK results in the inhibition of mTORC1 [24, 25]. mTORC1 is also an important metabolic regulator and has widespread roles in controlling immune cell functions [32]. Therefore, glucose or glutamine levels can impact upon an AMPK/mTORC1 signalling axis that is important in the control of immune responses (Figure 1A).

O-linked β-N-acetylglucosamine transferase (OGT): In addition to supplying glycolysis and OxPhos, glucose and glutamine are also used for generation of Uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) through the hexosamine biosynthetic pathway (HBP); approximately 2-5% of total glucose in the cell is used through the HBP [33]. UDP-GlcNAc is utilized by glycosyltransferases for various cellular processes including O-GlyNAcylation, the reversible addition of N-acetylglucosamine (GlcNAc) to proteins on serine or threonine residues. O-linked GlcNAc transferase (OGT) adds GlcNAc to proteins while O-linked GlcNAc hydrolase (OGA) removes the GlcNAc from serine/threonine residues. O-GlcNAcylation has emerged as one of the most abundant post-translational modifications that can control many aspects of protein function including stability, localization and transcriptional activity [34, 35]. O-GlcNAcylation can compete with protein phosphorylation as both types of modification target serine and threonine residues on a protein. As a result, there can be extensive crosstalk between these two protein modification pathways [36-38]. Levels of UDP-GlcNAc and protein O-GlcNAcylation are dependent on the supply of both glucose and glutamine in T cells arguing that OGT and O-GlcNAcylation are important nutrient sensing mechanisms in these cells [39]. OGT is essential for normal T cell development, activation and clonal expansion [39, 40]. A number of signalling molecules that are important for T cell function are found to be O-GlcNAcylated including c-Myc, NFAT and NF-κB (Figure 1B) [39-41]. c-Myc is O-GlcNAcylated on a threonine residue that can also be phosphorylated by the kinase GSK3; phosphorylation on this site promotes c-Myc degradation and O-GlcNAcylation of this residue is predicted to stabilize c-Myc protein [42, 43]. Indeed, OGT and O-GlcNAcylation are essential for sustaining c-Myc protein expression in CD8 cytotoxic T cells [39]. Given the number of proteins that appear to be O-GlcNAcylated in T cells it is likely that other proteins are involved in mediating the important role observed for OGT in CD8 T cells [39]. While this protein modification has not been studied in depth in other immune cell subsets, there is evidence to suggest that glucose/glutamine dependent O-GlcNAcylation has an important role for other aspects of immune function. LPS induces an increase in O-GlcNAcylation of numerous proteins in the RAW 264.7 macrophage cell line and this has been liked to cytokine production [44]. The pattern recognition receptor Nod2 has been shown to be O-GlcNAcylated resulting in altered downstream signalling to NF-κB [45]. Indeed, there are also multiple reports that NF-κB can be directly regulated by O-GlcNAcylation on multiple residues [40, 41,

46, 47]. An increase in protein O-GlcNAcylation is also observed upon activation of neutrophils which has been linked to neutrophil motility [48, 49].

Glycolytic flux links glucose to immune signalling: Glucose is the substrate for glycolysis and so it follows that flux through this metabolic pathway is sensitive to the levels of glucose available. The flux through glycolysis can impact upon immunological signalling pathways and affect immune function in a number of ways. The glycolytic metabolite phosphenolpyruvate (PEP) can affect Ca^{2+} signalling and the activation of the nuclear factor of activated T cells (NFAT) transcription factor in antigen stimulated T cells. PEP represses sarco/ER Ca^{2+}-ATPase (SERCA) activity, which is responsible for Ca^{2+} reuptake into the ER; therefore, PEP enhances cytosolic Ca^{2+} signalling and promotes NFAT nuclear activity. T cells activated in low glucose have reduced PEP levels, reduced cytostolic Ca^{2+} signalling and reduced nuclear NFAT, leading to defective T cell activation (Figure 1C) [14]. The function of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is also sensitive to glycolytic flux in T cells. GAPDH has additional roles outside its function as a glycolytic enzyme including acting an RNA binding protein to inhibit the translation of certain proteins including IFNγ and IL2 in T cells. The rate of glycolytic flux in activated T cells controls the balance of these different GAPDH functions; high rates of glycolysis prevent GAPDH binding to IL2 and IFNγ mRNA and thereby maximize the production of these cytokines (Figure 1D). On the other hand, if glucose is limiting, reduced glycolytic flux allows GAPDH to inhibit IFNγ and IL2 production [50]. In myeloid cells GAPDH is a component of the IFNγ-activated inhibitor of translation (GAIT) complex that binds defined 3' untranslated region (UTR) elements within a family of inflammatory mRNAs and suppresses their translation, though it is not yet clear whether GAPDH's role in the GAIT complex is affected by glucose or glycolytic flux [51].

Amino acid sensing

Amino acids are important for biosynthetic pathways in immune cells, including protein and nucleotide synthesis. Furthermore, they can also be directly metabolised to generate immunomodulatory molecules such as nitric oxide; arginine is a substrate for inducible nitric oxide synthase (iNOS). Thus, it is not surprising that immune cells, in particular lymphocytes, greatly increase amino acid uptake in response to immune stimulation. Amino acids of particular importance to lymphocytes include glutamine, methionine, tryptophan, arginine, and leucine. Depletion of any of these amino acids results in impaired responses to immune activation [16, 52-55]. T lymphocytes increase nutrient uptake in response to antigen stimulation through up-regulating the expression of nutrient transporters. This is critically important in the generation of effector cells, indeed T cells lacking the glucose transporter Glut1, the large neutral amino acid transporter Slc7a5, or the glutamine transporter Asct2 fail to differentiate into effector cells [56-59]. In addition to the role for amino acids as cellular fuels, certain amino acids can also be considered important signalling molecules; a number of signalling pathways important for immune responses are acutely sensitive to changes in the levels of certain amino acids and are discussed below.

Amino acids and mTORC1: In recent years the serine threonine kinase mTORC1 has

emerged as a central regulator of immune cell function. mTORC1 has diverse roles in controlling the function of immune cells in both the adaptive and innate arms of the immune system [32, 60]. For instance, in T cells mTOR signalling is essential for lineage commitment of Th1 and Th17 effector cells, whilst in macrophages Rheb-dependent activation of mTORC1 has been implicated in the monocyte-macrophage differentiation and mature macrophage phagocytosis [61-63]. The regulation of this kinase complex is complicated; mTORC1 activity turned on by growth factor or antigen signalling and switched off by other signalling pathways including AMPK, as described above (Figure 2A). However, mTORC1 activity is also acutely sensitive to the availability of certain amino acids and this arm of mTORC1 regulation overrides other signalling pathways; in the absence of amino acids mTORC1 is turned off even in the presence of strong growth factor signalling (Figure 2). Recent advances have begun to unravel the systems through which mTORC1 activity is controlled by amino acid availability in mammalian cells. Amino acids act through various amino acid sensors that promote the activity of the Rag GTPases to facilitate mTORC1 activation [64]. Cytosolic sensors for leucine and arginine have been identified as Sestrin2 and Castor, respectively [65, 66], and the solute transporter Slc38a9 has been identified as a lysosomal arginine sensor [67, 68]. In activated lymphocytes, mTORC1 activity is exquisitely sensitive to leucine availability [57]. The importance of leucine abundance on the regulation of mTORC1 activity in T lymphocytes is further highlighted by studies in mice lacking the leucine metabolizing enzyme BCATc (cytosolic branched-chain aminotransferase). Activated T cells from these mice have higher intracellular leucine concentrations and show increased mTORC1 activity compared to WT controls [69]. While the data clearly shows that leucine is essential for mTORC1 activity in immune cells, the evidence for a similar sensitivity to arginine is lacking. Activated T cells do not seem to be acutely sensitive to arginine deprivation as is the case for leucine [57, 70]. Interestingly, effector T cells up-regulate Slc7a5 mediated amino acid transport in response to arginine deprivation [71]. Therefore, it is tempting to speculate that this response may be a compensatory mechanisms to sustain mTORC1 activity in the absence of arginine by increasing leucine influx. More work will be required to elucidate the respective roles for arginine and leucine sensing in immune cells but it seems likely that mTORC1 activity may have differential sensitivities to arginine and leucine in distinct immune cell types.

Glutamine availability is also essential for mTORC1 activity in activated lymphocytes; acute glutamine deprivation has an equivalent inhibitory effect on mTORC1 to leucine deprivation [57, 58]. This is because glutamine is required for efficient leucine uptake into these cells through the Slc7a5 amino acid transporter (Figure 2B) [57, 58, 72]. Slc7a5 is an obligate antiporter: one amino acid in, one amino acid out. Slc7a5 has high import affinities for large neutral amino acids including leucine, valine, tryptophan and methionine and a high export affinity for glutamine [73]. Thus, in the context of amino acid sensing and the impact on mTORC1, Slc7a5 will transport glutamine out of the cell whilst importing leucine into the cell (Figure 2B).

Amino acids and c-Myc: The transcription factor c-Myc (myelocytomatosis oncogene) is a key controller of the metabolic reprogramming seen in T cells in response to antigen stimulation [74] as well as macrophages responding to M-CSF [75]. One role for c-Myc is to promote or sustain the expression of a cohort of nutrient transporters, including glucose transporters, amino acid transporters and the transferrin receptor (CD71). The importance of iron transport for lymphocyte function is evident in patients that have a missense mutation in their transferrin receptor. These patients have severe immunodeficiency characterised by impaired T and B cell function [76].

Constitutively active c-Myc mutations are a common occurrence in cancers, thus it is understandable that lymphocytes have mechanisms in place to ensure tight control of c-Myc expression. c-Myc protein has a very short half life in lymphocytes and sustained expression of c-Myc is only possible in cells that have high rates of amino acid uptake and protein synthesis [39, 43, 57]. Also, as mentioned above, c-Myc levels are dependent on glutamine fuelled O-GlcNAcylation in effector T cells [39]. c-Myc protein expression is effectively "fine-tuned" by amino acid availability, which is dependent on amino acid levels in the local microenvironment and levels of amino acid transporter expression. This mechanism for regulating c-Myc expression is important for immune responses. For example, during the first division of antigen activated T cells there is unequal distribution of the amino acid transporter Slc7a5 between the daughter cells. As a result the daughter cell proximal to the antigen presenting cell (APC) has increased amino acid uptake, c-Myc expression and mTORC1 activity compared to the distal daughter cell [77, 78]. This asymmetric distribution of c-Myc and mTORC1 activity leads to distinct metabolic signatures in each daughter cells and is thought to contribute to effector versus memory T cell differentiation [77, 78].

General control non-derepressible 2 kinase (GCN2): The integrated stress response in eukaryotic cells can be induced by various stimuli, including ER stress, presence of dsRNA, oxidative stress and amino acid deprivation. The common response to these cellular stresses is to enforce a general down-regulation of protein synthesis and switching on autophagy, whilst driving increased translation and expression of certain transcription factors, such as ATF4. This is achieved by inactivation of the eukaryotic initiation factor 2a (eIF2a) following phosphorylation by stress sensing kinases. The serine/threonine protein kinase GCN2 senses low cellular amino acid levels through binding to uncharged transfer RNA (tRNA) leading to kinase activation and subsequent phosphorylation of eIF2a (Figure 2C)[79].
In dendritic cells, GCN2 activiation in response to virus (or live virus vaccination) enhances antigen presentation to CD8 cells [80]. Conversely, GCN2 activity in gut APC restrains excessive Th17 responses; mice lacking GCN2 develop stronger Th17 responses and more severe colitis than WT controls, in an induced colitis model [81]. APCs in the GCN2-null mice show defective autophagy and excessive ROS accumulation resulting in enhanced inflammasome activation [81]. Thus, amino acid levels and GCN2 signaling acts to balance the immune response by inducing autophagy and cross-presentation of viral antigens in APCs and limiting excessive ROS accumulation and inflammasome activity during cellular stress. Amino acid sensing by GCN2 is also important for lymphocytes. The enzyme Indoleamine 2,3-dioxygenase (IDO) suppresses T cell responses, at least in part, by depleting tryptophan levels leading to the activation of GCN2 within the T cell (Figure 2C). Activation of GCN2 in CD8 T cells results in proliferative arrest and anergy, while in CD4 T cells GCN2 activation can lead to the generation of regulatory T cells [82, 83]. Studies using murine EAE show that mice with GCN2-null T cells have a lower frequency of regulatory Tregs in the CNS and subsequently develop worse symptoms than WT control mice [84, 85].

Fatty acid sensing and immune function

Free fatty acids (FFA) are aliphatic chains of varying carbon length that can be saturated or unsaturated containing a carboxylic acid [86]. Free fatty acids can be obtained

exogenously through diet, produced by the gut microbiome and can also be produced from breakdown of triacylglycerides in the liver and adipose tissue. While FFA can be used as a cellular fuel for generating ATP, they also act as ligands for several g protein coupled receptors (GPCR) [87]. Many immune cells types have been demonstrated to express GPCR receptors for FFA including macrophages, neutrophils, T cells and dendritic cells [86]. These receptors can be classified based on the carbon number of their fatty acid ligands. GPR40 and GPR120 (also called Fatty acid receptor (FFAR) 1 and FFAR4, respectively) are responsive to long-chain fatty acid (LCFA, >C12), GPR43, GPR41 (also called FFAR2 and FFAR3 respectively) are activated by short-chain fatty acids (SCFA, C2-C6) [88]. GPR109a (also called Hydroxycarboxylic Acid Receptor 2) is ligated specifically by the 4 carbon SCFA butyrate [89]. Medium-chain fatty acids (MCFA C9-14) appear to signal through GPR84 and also GPR40 [90, 91].

SCFA sensing: SCFA, such as acetate, propionate and butyrate, can be produced by a number of tissues, notably the liver, but the major source of SCFA is the gut microbiome. SCFA are metabolic by-products of intestinal microbiota fermentation that can be taken up by the gut and reach the circulation via the portal vein and the liver [92]. SCFA produced in the gut are used as a fuel source for certain cells including colonic epithelial cells; in germ free mice colonic epithelial cells are severely nutrient and energy deprived [93]. Microbiome derived SCFA are also important fuels for B cell responses; SCFA fuel energy producing pathways in B cells and boost antibody responses [94]. Mice with low SCFA production due to microbial insufficiency were defective for pathogen-specific antibody responses, while a SCFA supplemented diet restored normal B cell responses [94]. SCFA can also function as potent signalling molecules that have an anti-inflammatory effect on the function of immune cells. Indeed, SCFA may have therapeutic uses for inflammatory diseases such as colitis; colonic irrigation with SCFA has showed some benefit for patients with colitis and in mice, acetate in the drinking water markedly reduced colitis severity [95-97]. SCFA signalling through the GPCRs GPR43, GPR41 and GPCR109a (Figure 3A); GPR41 is expressed primarily on adipocytes, GPR43 is highly expresses on polymorphonuclear leukocytes (PMNs) and lymphocytes, and GPR190a is expressed on various immune cells including neutrophils and macrophages but not lymphocytes [98-103]. SCFA can impact upon the differentiation of both CD4 and CD8 T subsets, promoting CD4 regulatory T cell (Treg) formation and optimal CD8 memory T cell responses [104, 105]. Tregs are important in maintaining immune homeostasis and Tregs numbers in the colon lamina propria are dependent on the gut microbiome; germ free mice have dramatically reduced Treg numbers in the colon [105, 106]. Microbiome derived SCFA are important in promoting Treg formation in the colon through multiple mechanisms; directly through ligating Treg expressed GPR43 [99]; and indirectly though ligating GPR109a on macrophages and DCs to induce the expression of IL10 [107]. SCFA also suppress the production of pro-inflammatory mediators from neutrophils, such as TNFα and nitric oxide [108]. Additionally, SCFA can have direct actions in the cells independent of GPRs, notably SCFA can impact upon the levels of protein acetylation. Acetate is converted to acetyl-CoA, the substrate for acetylation reactions, while butyrate and propionate are inhibitors of histone deacetylases (HDAC) (Figure 3A). Elevated levels of acetate promotes the acetylation of the glycolytic enzyme GAPDH facilitating elevated glycolytic flux and robust CD8 memory T cell responses [104]. Butyrate and propionate mediated inhibition of HDACs affects histone acetylation in T cells; butyrate/propionate promotes acetylation at the FoxP3 locus in Tregs inducing FoxP3 protein expression [109, 110]. SCFA-mediated inhibition of HDACs also potentiates the ability of DCs to promote Treg differentiation and inhibits pro-inflammatory macrophage and neutrophil function [108, 111]. HDACs can also

deacetylate non-histone targets including NFκB, which may also be important for the anti-inflammatory actions of butyrate and propionate [112].

LCFA sensing: GPR120 is strongly activated by omega 3 fatty acids including the essential fatty acid, α-linoleic acid which is not endogenously synthesised; therefore GPR120 is important in responding to diet obtained fatty acids [113]. GPR120 is highly expressed in CD11c+ macrophages and adipocytes [114]. Exogenously derived omega 3 fatty acids, including docosahexaenoic acid (C22, DHA) and eicosapentaenoic acid (C20, EPA) have clear anti-inflammatory effects on macrophages. Ligation of GPR120 by DHA results in decreased TLR2/3/4 and TNFα mediated signal transduction leading to reduced proinflammatory cytokine production (TNFα, IL6, IL1β) [114, 115]. The anti-inflammatory function of GPR120 involves the sequestration of TAB2 to bind to β-Arrestin-2 rather than TAK1, leading to decreased TAK1 signalling and decreased NFκB and JNK activation (Figure 3B)[114]. There is also evidence that LCFA inhibit the activation of the NLRP3 inflammasome; DHA acting through GPR120, and also GPR40, supresses caspase 1 cleavage and IL1-β secretion in macrophages by increasing β-arrestin-2 binding to NLRP3 (Figure 3B)[115].

MCFA sensing: While the effect of MCFA on the immune response has not been extensively studied, there is evidence that MCFAs such as capric acid, undecanoic acid and lauric acid can impact upon the function of certain immune cells. The MCFA receptor GPR84 is highly expressed on macrophages and neutrophils; LPS stimulated macrophages also show strong induction of GPR84 expression [90]. The data suggests that MCFA, acting through GPR84, can enhance LPS-induced IL-12 and TNFα expression in macrophages [90, 116]. Ligation of GPR84 also induces the production of IL8 and chemotactic responses in human polymorphonuclear leukocytes [116]. Therefore, the data available suggests that, in contrast to SCFA and LCFA, MCFA have proinflammatory effects on immune cell function.

CD36 scavenging receptor. CD36 is a well characterised receptor for triacylglycerol substrates and is highly expressed in scavenging immune cells such as macrophages [117]. CD36 is responsible for receptor mediated endocytosis of triacylglycerol-rich lipoprotein particles, such as low density lipoproteins (LDL) and very low density lipoproteins (VLDL), and also has a high affinity for oxidised LDL (oxLDL) [118-120]. Triglycerides can be used to generate intracellular FFA to fuel OxPhos following fatty acid oxidation in the mitochondria (Figure 3C). Macrophage polarisation to M1 or M2 phenotypes is closely linked to cellular metabolism; M1 macrophages rely on glycolysis while M2 are fuelled by fatty acid oxidation and OxPhos. IL-4 induced CD36 is crucial for generating M2 macrophages; CD36 deficiency disrupts M2 macrophage metabolism and polarisation [121]. Therefore, CD36 expression can affect immune function by supplying cellular metabolic pathways, but additionally CD36-mediated scavenging can also directly impact upon immune signalling pathways (Figure 3C). In macrophages, CD36 mediates the internalisation of various molecules, such as oxLDL, and the subsequent lysosomal conversion of these molecules into crystals, such as cholesterol crystals, that then activate the NLRP3 inflammasome to promote IL1β production [122]. In addition, through an undefined mechanism CD36 augments TLR4-6 signalling to prime the inflammasome, inducing the expression of inflammatory genes including IL1β and NLRP3 (Figure 3C)[122]. In macrophages, ligation of CD36 with oxLDL also leads to the

recruitment of the plasma membrane ion transporter Na^+/K^+ ATPase and the subsequent activation of the Src family kinase Lyn [123]. Therefore, CD36 is important in controlling macrophage function through supporting the oxidative metabolism of fatty acids and also through promoting inflammatory signalling.

Cholesterol and Oxysterol sensing and immune function

Cholesterol is an important component of the plasma membrane that is involved in maintaining membrane integrity and fluidity, but cholesterol also has roles in signal transduction. There are multiple branches off the cholesterol biosynthesis pathway that generate intermediates that are important for steroid hormone production, protein prenylation and also have direct effector and regulatory roles in the immune response [124]. Cholesterol can also be oxidized into various oxysterol molecules, such as 25HC, that are important in the control of various aspects of the immune cell function. Cholesterol, oxysterols or indeed flux through the cholesterol biosynthesis pathway can directly regulate signal transduction pathways including those involved in the type 1 interferon response. While oxysterols have a substantially shorter half-life to cholesterol there is evidence that the levels of these molecules can accumulate in discrete immune microenvironments [22, 23]. In particular, activated macrophages and tumour cells have been shown to produce and secrete oxyterols; activated macrophages upregulate the expression of cholesterol 25-hydroxylase (CH25H) and produce large amounts of 25HC while tumour cell secrete a number of different oxysterol species [22, 23]. Macrophage derived 25HC can have direct immunoregulatory effects, 25HC affects the plasma membranes of host cells to suppress viral fusion, but many of the immunoregulatory effects of 25HC on the immune response are through changes in signalling pathways [125]. Under certain conditions systemic levels of oxysterols can also be elevated. Patients with aspects of metabolic syndrome, hypercholesteremia, type II diabetes or hyperlipidemia, have elevated plasma levels of oxidized cholesterol species [126, 127]. Healthy individuals injected with LPS showed increased plasma levels of 25HC, arguing that inflammatory processes can also promote elevated levels of systemic oxysterols [128]. This section will describe the signal transduction pathways that are sensitive to levels of cholesterol and oxysterols and the role they play in controlling immune responses.

Srebp signalling: The Sterol response element binding proteins (Srebp) are transcription factors that are the master regulators of fatty acid and cholesterol synthesis as they promote the expression of most of the enzymes in these biosynthetic pathways [129]. Srebp transcription factors are activated through a complex mechanism that involves the transport of a precursor Srebp protein from the endoplasmic reticulum (ER) to the Golgi apparatus, multiple protease cleavage events and the subsequent translocation of the cleaved active transcription factor to the nucleus (Figure 4A). One key regulator of this process is Srebp cleavage-activating protein (SCAP) that escorts Srebp from the ER to the Golgi [130]. SCAP contains a sterol-sensing domain and acts as a cholesterol sensor; cholesterol binding induces a conformational change in SCAP that promotes its interaction with the ER anchoring INSulin-Induced Gene (INSIG) proteins, thus retaining SCAP and Srebp in the ER [131, 132]. The oxysterol 25HC interacts with INSIG rather than SCAP but with the same result, the SCAP and INSIG interaction is promoted leading to the retention of SCAP/Srebp in the ER (Figure 4A)[133]. In addition to the role

for Srebp transcription factors in controlling fatty acid and cholesterol biosynthetic pathways, Srebp has been described to have a number of direct immunoregulatory roles. The Srebp1a isoform is required for the inflammatory functions of macrophages, such as IL1β production, through promoting the expression of the inflammasome component Nlrp1a; Srebp1a deficient mice are resistant to LPS induced sepsis [134]. Srebp1c has been linked to the regulation of IL17 expression in Th17 T cells [135]. The SCAP/Srebp signaling axis has also been shown to be an important factor in anti-viral responses in macrophages. Genetically disrupting this Srebp activation through deleting SCAP specifically in macrophages is sufficient to render mice resistant to viral challenge. This is because changes in flux through the cholesterol biosynthetic pathway impact directly upon type 1 interferon signalling; decreased synthesized cholesterol in the ER results in the activation of STING/TBK1 signalling to induce IRF3 activity and the expression of interferon regulated genes (Figure 4B) [136]. Another reason why flux through the cholesterol biosynthetic pathway is likely to be important is because intermediates in this pathway can act as agonists for RORγt transcription factors and so impact upon the differentiation of Th17 CD4 T cells [137, 138].

Inflammasome activation: Cholesterol crystals can potently affect immunological signaling pathways. Free cholesterol has very low solubility in aqueous environments and for this reason cholesterol is complexed to apoproteins for transport in the bloodstream. However, in pathologies such as atherosclerosis, elevated levels of free cholesterol result in the formation of cholesterol crystals within arterial plaques and within the macrophages at these sites. These cholesterol crystals stimulate inflammatory signalling pathways through activation of the NLRP3 inflammasome [139]. As mentioned above, CD36 is important for inflammatory signalling in macrophages due to its function as a lipid transporter but also due to its interaction with inflammatory signalling pathways. Indeed, CD36 seems to be particularly important for the formation of cholesterol crystals in macrophages in the context of atherosclerosis (Figure 4C)[139]. Targeting CD36 in atherosclerotic mice resulted decreased inflammasome activation, lower serum concentrations of IL-1β and decreased concentrations of cholesterol crystals in the atherosclerotic plaques [122].

Oxysterols as ligands for nuclear receptors: A number of different oxysterol species, including 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol and 27-hydroxy-cholesterol, are ligands for Liver X receptors (LXRs) [140]. LXRs forms a permissive heterodimer with retinoid X receptor (RXR) and regulate transcription through binding to LXR response elements [141]. In the absence of ligand LXRs act as transcriptional repressors but switch into transcriptional activators when ligand in bound. LXRs are best characterized as important regulators of systemic sterol homeostasis and control the expression of a panel of genes involved in sterol transport between cells and tissues [140]. Importantly, LXRs are also described to have important immunoregulatory roles. Mice deficient in LXRs spontaneously develop a lupus-like autoimmune condition arguing that LXRs are important for the maintenance of self tolerance [142]. This is explained, at least in part, because in macrophages LXRs facilitate the phagocytosis and clearance of apoptotic cells, LXRs promote cholesterol efflux to prevent lipotoxicity, and LXRs inhibit the expression pro-inflammatory genes by suppressing NF-κB and AP1 activities [142]. LXRs are also important for maintaining neutrophil homeostasis, and in lymphocytes LXR agonists inhibit mitogen driven proliferation [143, 144]. Additionally, LXRs have a role in the differentiation of different CD4 T cells subsets; LXR agonists

inhibit the Th17 differentiation through a mechanism that involves Srebp1c/Aryl hydrocarbon receptor-mediated inhibition IL17 expression [135, 145]. LXR agonists have also been described to inhibit IgE production in human and murine B cells [146]. Oxysterols are also agonists for RORγt, which is required for Th17 T cell differentiation. The oxysterol, 7β,26-dihydroxycholesterol (7β,26-HC), has been identified as a potent RORγt agonist and enhances the differentiation of Th17 CD4 T cells in mice and humans [147]. Mice deficient in CYP27A1, a key enzyme in generating 7β,26-HC, have decreased formation of both CD4 Th17 T cells and IL17 producing γδ T cells [147].

Other signalling effects of oxysterols: 25HC can be further oxidised to 7α,25-Dihydroxycholesterol (7α,25diHC) by CYP7B1 [148], which has been identified as a potent agonist of the G protein-coupled receptor EBI2 (also called GPR183) [149, 150]. 7α,25HC signalling through EBI2 acts as a chemoattractant that directs the migration of multiple immune cell subsets and is important for adaptive immune responses, such as T cell-dependent antibody responses [149, 150]. Another study showed that 25HC amplifies inflammatory signalling in macrophages by recruiting AP1 transcription factors to TLR responsive genes [151]. In this study 25HC was found to be involved in inflammatory-induced pathology of influenza infection.

Final remarks:

The phrase “you are what you eat” has been used for some time to convey the idea that ones diet, healthy or otherwise, has a big influence on ones wellbeing. It is now becoming clear that this phrase also resonates at the cellular level with respect to our immune cells. The identity of an immune cell, the pro and anti-inflammatory characteristics of immune cells, can be significantly influenced by the nutrients that are available to it in the local microenvironment. At the same time there is an increasing appreciation that there is an inflammatory component to the majority of diseases. A detailed understanding of the relationship between nutrients and immune responses is likely to reveal exciting opportunities for developing new approaches to promote health and wellbeing and to treat inflammatory disease.

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Figure Legends:

Figure 1: Glucose and Glutamine sensing pathways. **(A)** Glucose and Glutamine are important fuels for the ATP generating pathways, glycolysis and mitochondrial OxPhos. AMPK is an energy sensing kinase whose activity is sensitive to the ratio of ATP to AMP. Once activated, AMPK turns off the key metabolic regulator mTORC1. **(B)** Glucose and glutamine are both required to supply the hexosamine biosynthesis pathway (HBP). This pathway generates UDP-GlcNAc, the substrate for the enzyme O-GlcNAc transferase (OGT) that is responsible for O-GlcNAcylation, the addition of N-acetyl-glucosamine to proteins. O-GlcNAcylation in immune cells controls the activity of a number of key signalling molecules including c-Myc and NFκB. **(C)** The glycolytic intermediate phosphoenolpyruvate (PEP) can inhibit the activity of the SERCA Ca^{2+} channels that are involved in Ca^{2+} reuptake and the termination of cytosolic Ca^{2+} signalling. Under glucose replete conditions PEP sustains Ca^{2+} mediated activation of NFAT, facilitating T cell activation. When glucose is limiting, Ca^{2+} signaling and NFAT activation is restricted. **(D)** GAPDH has multiple roles in the cell, acting as a glycolytic enzyme and also a RNA binding protein. GAPDH binding to IFNγ and IL2 mRNA inhibits the translation of these cytokines. Under glucose replete conditions GAPDH is engaged in glycolysis and is not available to inhibit the translation of IFNγ and IL2. When glucose is limiting, GAPDH is available to bind to IFNγ and IL2 mRNA and inhibit the expression of these cytokines.

Figure 2: Amino acid sensing pathways. (A) The activation of mTORC1 requires both the localization of mTORC1 to the lysosomal membrane, which is controlled by amino acid availability, and the activation of the the GTPase Rheb, which is controlled by multiple signaling pathways that converge on the GTPase activating protein TSC2. mTORC1 localized to the lysosome is in a complex with multiple members of the Rag GTPase family, Ragulator and v-ATPase. The activity of the Rag GTPases, and so mTORC1 recruitment to the lysosome, is controlled by the cytosolic amino acid sensors; CASTOR, (cytosolic arginine sensor) and Sestrin 2 (cytosolic leucine sensor). Lysosomal arginine can also impact upon mTORC1 localisation to the lysosomal membrane through Slc38a9. TSC2 inactivates Rheb as it promotes the hydrolysis of Rheb bound GTP to GDP. Multiple signalling pathways control Rheb mediated mTORC1 activation through controlling TSC2 activity. These include growth factor stimulated signalling pathways (PI3-kinase/Akt, Erk, p90RSK), which inhibit TSC2 thus activating mTORC1, and stress activated pathways such as AMPK, which promote TSC2 activity thus inhibiting mTORC1. **(B)** While leucine and arginine are directly sensed by the cytosolic sensors Sestrin 2 and CASTOR, glutamine is required for mTORC1 indirectly. Glutamine is important for mTORC1 activity because it facilitates Slc7a5-mediated leucine uptake. Slc7a5 is an obligate anti-porter and must transport a glutamine out of the cell to import leucine. **(C)** GCN2 is a general amino acid sensor that is activated by uncharged tRNA molecules that accumulate when amino acid concentration drop. Tryptophan levels can become limiting in various inflammatory microenvironments due to the action of IDO that is expressed by various cells including tumour cells and myeloid derived suppressor cells; reduced tryptophan levels lead to GCN2 activation.

Figure 3: Free Fatty acid sensing pathways. (A) Short chain fatty acids (SCFA) bind to the G protein linked receptors GPR41 and GPR43; the 4 carbon SCFA butyrate also binds to GPR109a. Acetate can directly impact upon cell signalling as it can be converted to Acetyl-CoA, the substrate for protein acetylation reactions; elevated acetate promotes GAPDH acetylation and elevated glycolysis. Butyrate and proprionate also promote protein acetylation as they are inhibitors of the HDAC deacetylases. HDACs deacetylate histones as well as non-histone substrates including NFκB. Butyrate or propionate mediated inhibition of HDACs promotes FoxP3 expression in T cells. **(B)** Long chain fatty acids (LCFA) have anti-inflammatory effects, signaling through GPR40 and GPR120 receptors to inhibit the proinflammatory NFκB and JNK signalling pathways and to inhibit the NLRP3 inflammasome through a mechanism involving βarrestin2. **(C)** CD36 mediates receptor mediated endocytosis of triglyceride rich lipoproteins. FFA released following lipolysis of triglycerides can be converted to acetyl-CoA by β-oxidation to fuel OxPhos (i). oxLDL binding to CD36 acts together with TLR4-TLR6 to prime the NLRP3 inflammasome inducing the expression of IL1β and NLRP3 mRNA (ii). Binding of oxLDL can induce the interaction of CD36 with the plasma membrane Na^+/K^+ ATPase leading to the initiation of intracellular signalling and the activation of the src family tyrosine kinase Lyn (iii).

Figure 5: Cholesterol and oxysterol sensing pathways. (A) Srebp is synthesized as a integral membrane protein localized to the ER. Generation of activate Srebp transcription factors requires SCAP-mediated translocation of Srebp to the Golgi ① followed by two cleavage events mediated by site-1 protease (S1P) and site-2 protease (S2P). The result is the release of soluble Srebp that can translocate to the nucleus ② and promote the expression of target genes that contain Srebp response elements (SRE). Cholesterol binds to SCAP and promotes the interaction of SCAP with the ER-anchored protein INSIG, preventing Srebp translocation to the Golgi. 25HC binds to INSIG and also promotes the SCAP:INSIG interaction preventing Srebp activation. **(B)** Synthesized cholesterol in the ER negatively impacts upon type 1 interferon signalling. Decreased cholesterol synthesis results in STING/TBK1-mediated activation of IRF3 and the induction of interferon sensitive genes. **(C)** CD36 mediated endocytosis of oxLDL can lead to the formation of cholesterol crystals in the lysosome and lysosomal destabilization leading to the activation of the NLRP3 inflammasone and caspase 1 mediated cleavage of proIL1β to generate mature IL1β. **(D)** LXR are nuclear receptors that form a permissive heterodiamer with RXR and bind to LXR response elements (LXRE). In the absence of ligand LXR/RXR act as transcriptional repressors. Oxysterol ligands bind to LXR and convert the LXR/RXR diamer into a transcriptional activator. The oxysterol 7β,26-dihydroxycholersterol (7β,26-HC) acts as an agonist for the RORγt transcription factor, which is required for Th17 T cell differentiation.

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Figure 1: Glucose and Glutamine sensing pathways

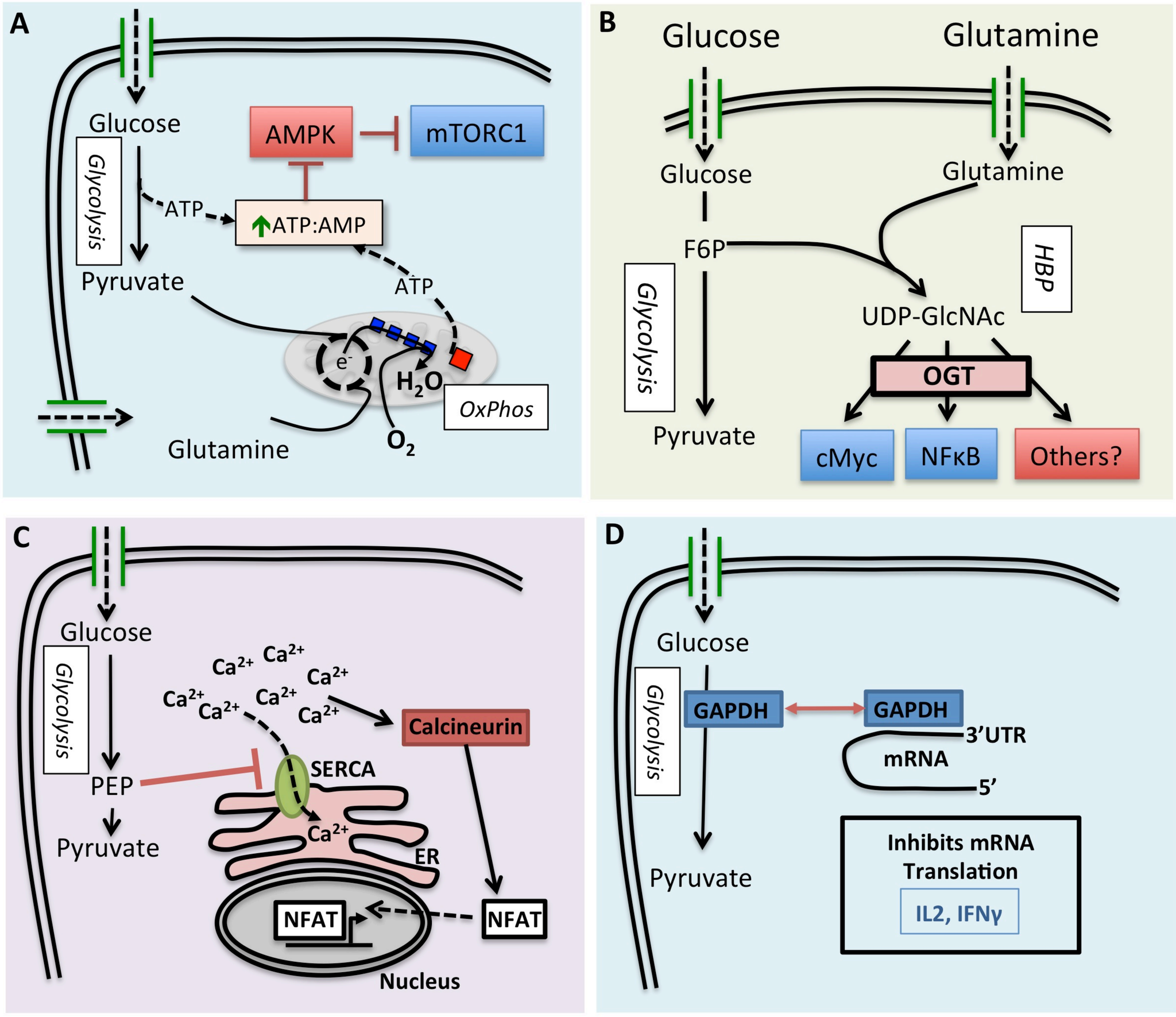


Figure 2: Amino acid sensing pathways

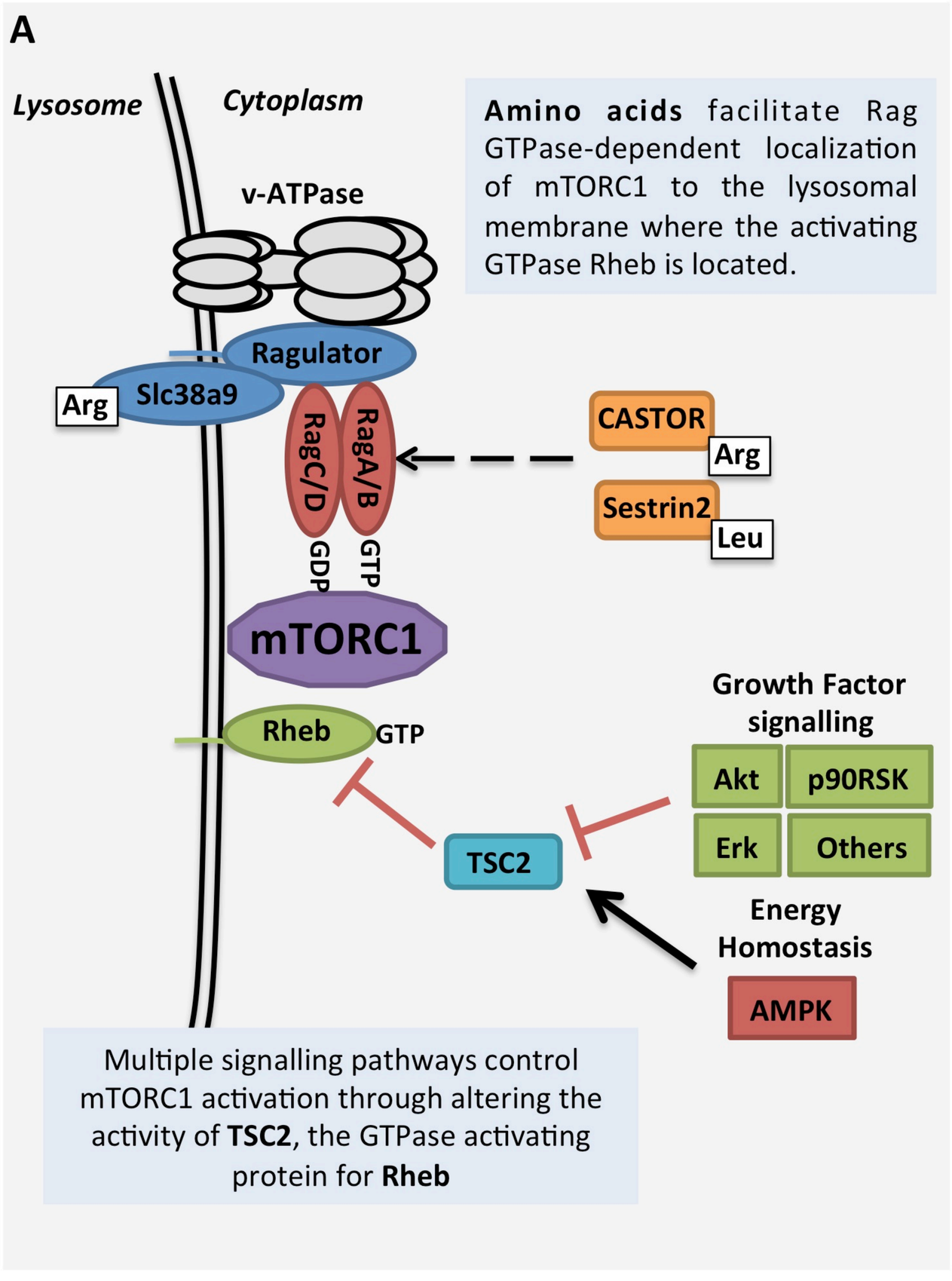
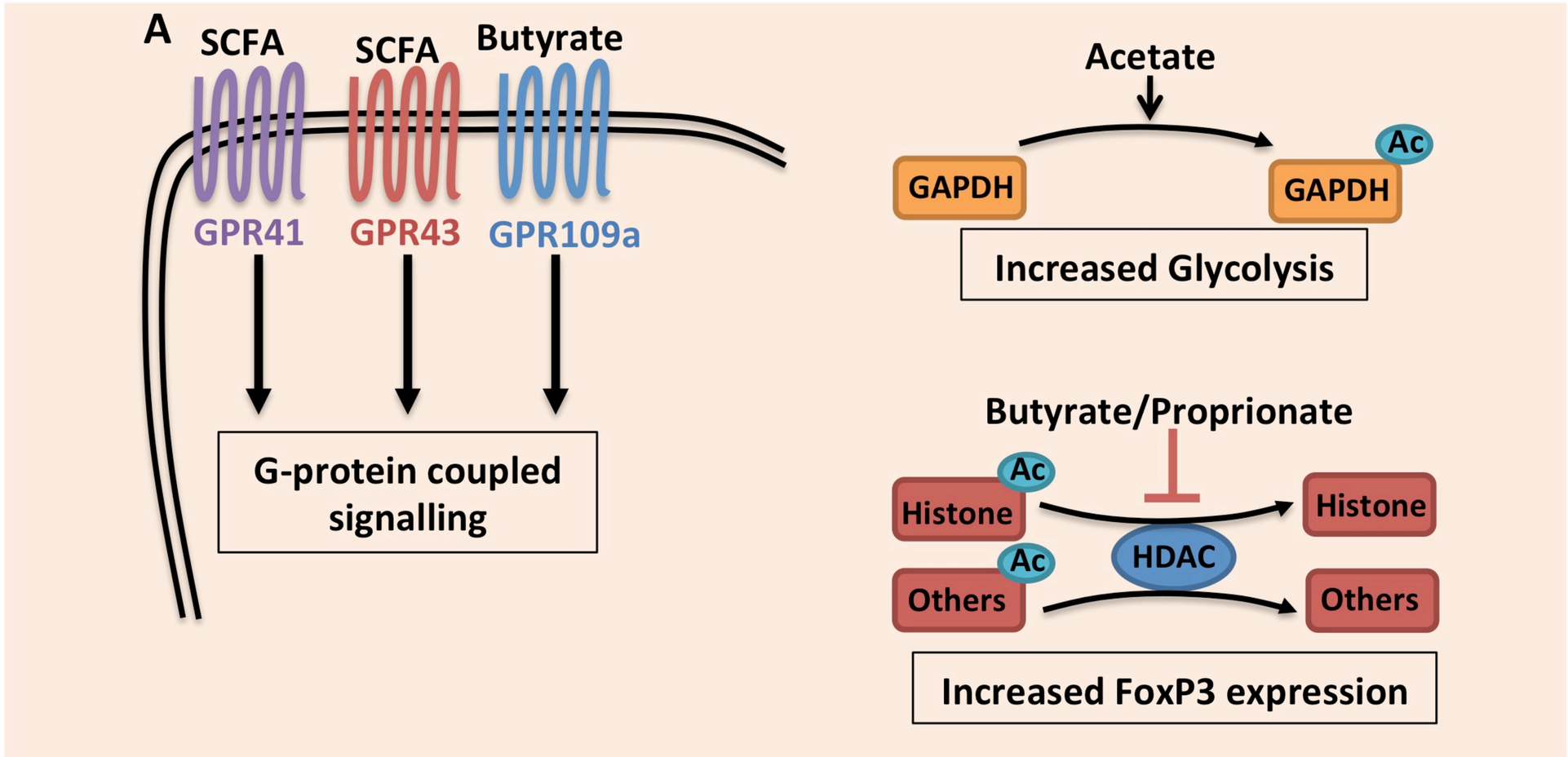
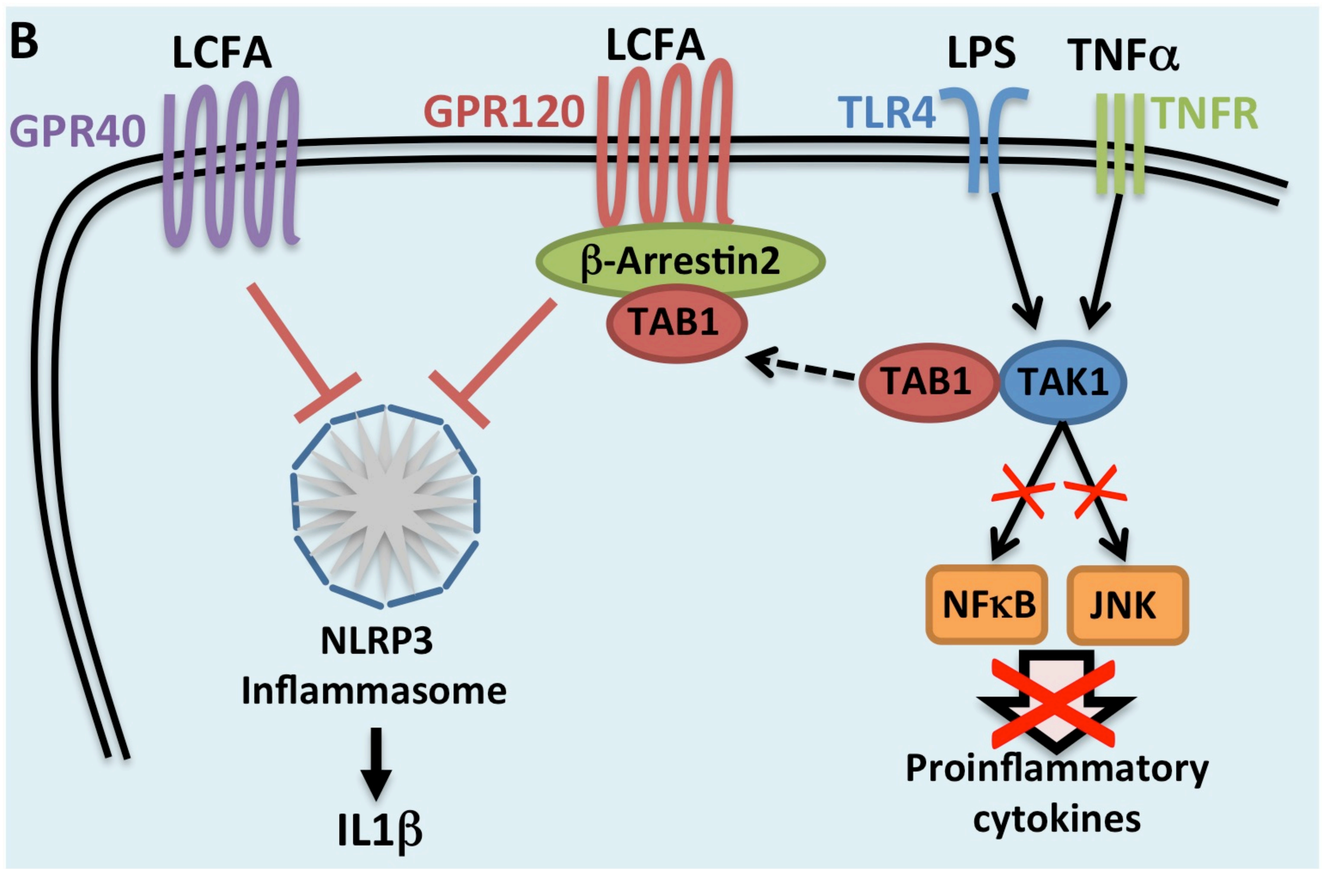


Figure 3: Free fatty acid sensing pathways





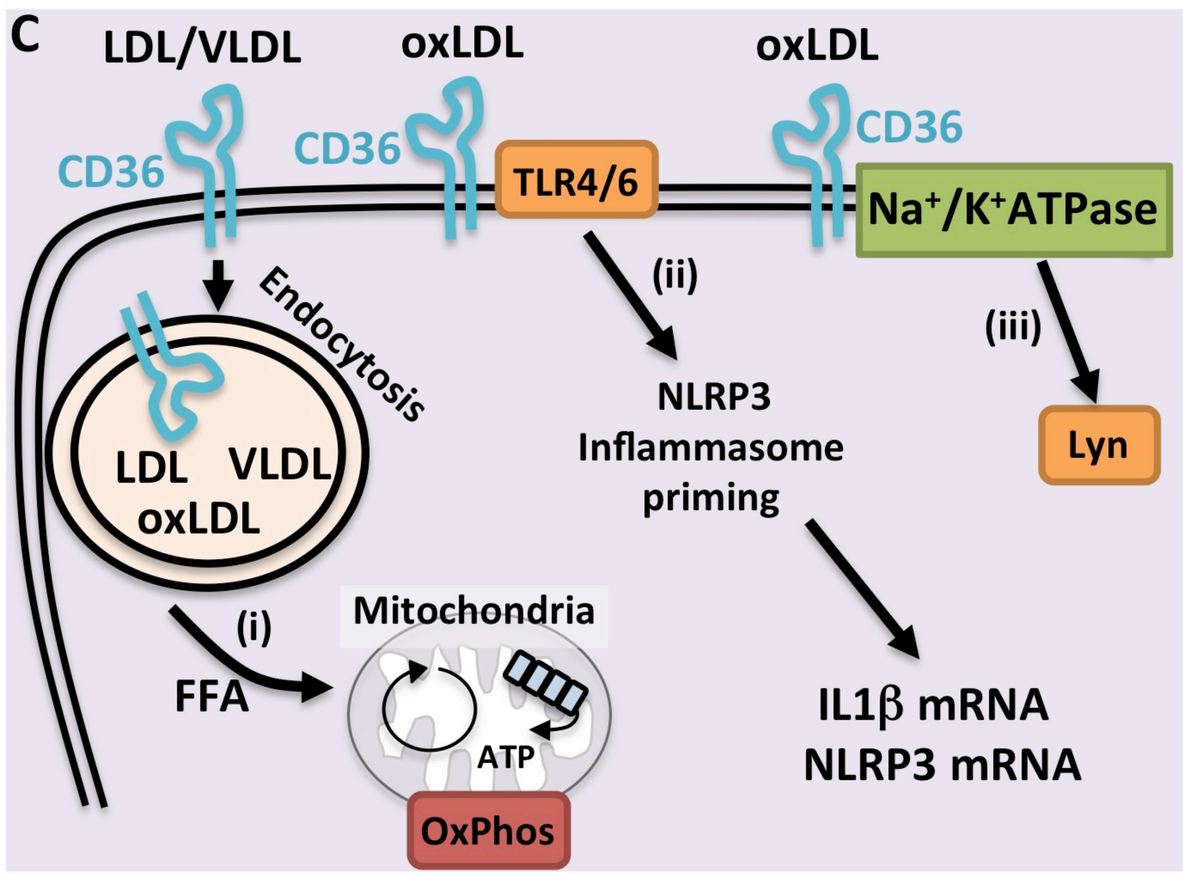


Figure 4: Cholesterol and oxysterol sensing pathways