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Triggering Receptor Expressed on Myeloid Cells and 5′Adenosine Monophosphate-activated Protein kinase in the Inflammatory Response: A Potential Therapeutic Target

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Abstract

Introduction—The events in the cellular and molecular signaling triggered during inflammation mitigate tissue healing. The metabolic check-point control mediated by 5′-adenosine monophosphate-activated protein kinase (AMPK) is crucial for switching the cells into an activated state capable of mediating inflammatory events. The cell metabolism involved in the inflammatory response represents a potential therapeutic target for the pharmacologic management of inflammation.

Areas covered—In this article, a critical review is presented on triggering receptor expressed on myeloid cell (TREM) receptors and their role in the inflammatory responses, as well as homeostasis between different TREM molecules and their regulation. Additionally, we discussed the relationship between TREM and AMPK to identify novel targets to limit the inflammatory response. Literature search was carried out from the National Library of Medicine's Medline database (using PubMed as the search engine) and Google Scholar and identified relevant studies up to March 30, 2016 using inflammation, TREM, AMPK, as the key words.

Expert commentary—The prevention of phenotype switching of immune cells during inflammation by targeting AMPK and TREM-1 could be beneficial for developing novel management strategies for inflammation and associated complications.

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Declaration of Interests

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Keywords

Triggering Receptor Expressed on Myeloid Cells; Immune cells; Inflammation; 5′-adenosine monophosphate-activated protein kinase; Cell metabolism

1 Introduction

Inflammation is a vital response elicited by the immune system against infections, injury, and pathogenesis meant to restore tissue structure and physiological function. Inflammation is orchestrated by a cascade of molecular events mediated through the biomolecular signals between immune cells and target tissues. The key cellular events in inflammation are initiated by the influx of leukocytes into the affected area. The first mediator to enter the site is granulocytes such as neutrophils, which are quickly followed by monocytes. Monocyte migration from the circulation to the target tissue, and subsequent differentiation and proliferation allow for maturation into macrophages, inevitably progressing into the inflammatory response. These events cause the principal symptoms of inflammation; erythema, hyperemia, and edema. Organ dysfunction is frequently considered the fifth feature of inflammation [1]. Once the initiating stimulus subsides after a vigorous phagocytic phase, the inflammatory events are resolved with the aid of molecules like resolvins [2]. During the resolving phase, neutrophil withdrawal is prominent and granulocytes revert back to their pre-inflammatory phenotype, allowing for the restoration of physiological function. Any dysfunction in these events allow for scar tissue formation, organ dysfunction, and disease progression [3].

Inflammation can be either acute or chronic and is highly regulated. The alterations of the regulatory signals associated with inflammation are linked to the development and progression of chronic diseases like coronary artery disease, diabetes, obesity, and oncologic processes [4]. The extent of inflammation depends on the severity of injury [5]. Acute inflammation can lead to chronic inflammation depending on affected tissue, genetic makeup of the subject, and severity of the injury [5]. The interplay between the inflammatory cells, host cells, and biomolecules/signaling molecules is key in the regulation of inflammation and specific inflammatory pathways [6]. The delicate balance between these cells and their mediators is essential for the regulation of inflammatory responses. The major cells associated with inflammation and their functions are shown in Figure 1.

Inflammatory responses begin when the stimuli signals bind to surface receptors on immune cells. These receptors include G-protein coupled transmembrane receptors, Fc receptors, cytokine receptors, cell adhesion molecules and pattern recognition receptors like TLRs and C-type lectins [7],. Activation of these receptors results in inflammatory events like phagocytosis, degranulation, reactive oxygen species production, chemotaxis and cytokine release [8, 9]. Triggering Receptor Expressed on Myeloid cells (TREM) are a recently discovered cell surface receptor of immunoglobulin superfamily which has implications on inflammation associated with pathologies. Among characterized TREMs, TREM-1 and TREM-2 are of greater importance owing to their antagonistic effects. TREM-1 amplifies proinflammatory mediators where TREM-2 is an anti-inflammatory modulator [10, 11]. The

following sections deals with current understanding about TREM biology with respect to metabolic aspects of inflammation.

2 Triggering Receptor Expressed on Myeloid cells (TREM)

The inflammatory cells present a wide array of receptors that constantly evaluate the immune status (either innate or adaptive) of the body [12]. For example, G-protein coupled transmembrane receptors provoke inflammatory responses upon encountering a specific signal (pathogens, FMLP [N-formyl methionyl leucyl phenylalanine], lipid mediators, complement factors proinflammatory chemokines, endogenous molecules, among others) [13]. Toll-like receptors (TLRs) located on macrophages and dendritic cells are able to perceive general molecular patterns of microbes, like the structure of lipopolysaccharide (LPS) [14]. Similarly, mannose and scavenger receptors bind through mannose or mannose binding lectin and sets up the cell for phagocytosis [15]. In short, inflammatory reactions begin with interactions between receptors collectively called pattern recognition receptors (PRRs). Triggering receptor expressed on myeloid cells (TREM) are another class of cell-surface receptors that can magnify or lessen the inflammatory status depending on the type of PRR signal [16]. The relationship between these two receptors is still a topic of debate.

As the name implies, TREM has been expressed predominantly in myeloid cells, especially neutrophils and monocytes [17]. Granulocytes, dendritic cells and natural killer cells (NK) cells have also been found to have higher TREM expression. T cells and most B cell subsets express TREM molecules in low levels [18]. Apart from cells of the immune system, recent research indicates that TREM expression is not limited to immune cells, but in fact are found on non-immune cells also: fibroblasts, epithelial cells, lymph nodes, spinal cord, lungs, heart, placenta, kidney, and bones all have been found to express TREM [19]. Unfortunately, the exact signaling mechanism and function of these molecules in non-immune cells is still unknown.

Human and mouse are both extensively studied systems for TREM biology. The individual genes of TREM (TREM-1 to TREM-4) belong to the immunoglobulin variable (IgV) domain receptor family. TREM, a cell surface activating transmembrane receptor, is comprised of a positive charged trans membrane domain (due to a Lys residue) and a cytoplasmic tail [20]. The genes for human TREM molecules (TREM-1 and TREM-2) are located on 6p21 (Figure 2). The DNA sequences encoding the TREM are contained within a gene cluster of structurally related receptors that trigger immune responses. TREM-like transcripts (TLT1 to TLT5) and NKp44 are homologous to TREM and they coexist within the structurally similar cluster. TLT genes code for IgV and NKp44 proteins that comprise a NK cell receptor [21, 22]. TLT-l is expressed in megakaryocytes α-granules and neonate thrombocytes, which offers protection against inflammation associated with hemorrhage.

TLT-2 is found in B cells and peripheral lymphoid tissues. Upregulation of TLT-2 is seen in macrophages and neutrophils that are responding to inflammation but expression is minimal in naïve monocytes. Red pulp and marginal metallophilic macrophages in the spleen are the major sites for TLT-4 expression. Dendritic cells also express TLT-4 and are resistant to cavitation by TLR ligands [23]. The first discovery of the sequence homology of TREM-1

open reading frame (ORF) threw light to the elucidation of TREM-2 in murine macrophage cell line and then in humans [16]. Unlike TREMs, TLTs possess a tyrosine receptor inhibitory domain at the cytoplasmic tail domain [21]. Murine gene clusters for TREM has been mapped on chromosome 17C3 (Figure 2) [24]. TREM-3 [25] and TREM-4 [26] are exclusively found in mouse. TREM-3 shares around 40% sequence similarities with TREM-1 and is functionally similar [25, 27]. Plasmacytoid dendritic cells (pDCs) of mouse express TREM-4 (also called pDCTREM) which has around 20% amino acid homology with TREM-1 and TREM-2 [26].

TREM molecules require DAP12 (DNAX activation protein 12) for activation. DAP12 is an immunoreceptor tyrosine-based adaptor that transmits signals generated through surface receptors like TREM [28]. Human DAP12 gene is located on chromosome 19q13.1 and is translated into a 113 amino acid residue, homodimeric protein. Two Cys residues at positions 33 and 35 cross link to form a disulfide bond which constitutes the DAP12 homodimer.

Immunoreceptor tyrosine-based activation motif (ITAM) regulates cellular responses like adhesion, proliferation, migration, differentiation, gene expression, and is necessary for the action of DAP12. ITAMs (first identified in immune system) regulate cellular responses like adhesion, proliferation, migration, differentiation and gene expression. The ITAM motif on the cytoplasm is subjected to phosphorylation by casein kinase II and protein kinase C, an action that is necessary for the regulation of DAP12 [29]. On the other hand, TLTs have an intra-cellular immunoreceptor tyrosine-based inhibitory motif (ITIM) in their cytoplasmic tail to regulate downstream signaling [30]. ITAM bearing DAP12 adaptors bears an acidic amino acid (especially Asp) in transmembrane domain which interacts non-covalently to the transmembrane Lys residue of the receptors including TREMs [31, 32].

More than 20 DAP12 associated receptors have been characterized in humans and mice that act as either activators or inhibitors of the immune responses [33, 34]. These receptors belong to two families: the former to C-type lectin family, which includes MDL-1 (myeloid DAP12-associating lectin-1) and mouse NKG2D, and the latter to the Ig domain superfamily (Ig-SF), which includes TREM, NKp44, SIRP-β (signal-regulatory protein beta), and MAIR-II (myeloid-associated immunoglobulin-like receptor) [35, 36]. The binding between DAP12 and corresponding receptors cannot initiate the intra cellular signaling on their own [35]. Also, the phosphorylated ITAM activates Syk (Spleen tyrosine kinase) and NTAL/LAB (Non-T cell activation linker /linker for activation of B cells), which activates specific downstream signaling pathways including Akt, Ca^{2+}, and MAPK (mitogen-activated protein kinase) [37, 38]. ITAMs are responsible for signal transduction of TREM pathways [39].

2.1 TREM-1

TREM-1 modulates inflammation through cytokine, chemokine and receptor upregulation [40]. TREM-1 is also reported to have the potential to magnify inflammatory responses initiated by TLRs and LPS [41]. The ligands of TREM-1 have been identified in the surface of platelets [42]. The existence of soluble TREM-1 ligands has also been discovered [43]. It has also been found that some damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) are also ligands for TREM-1. These

molecules can act as PRR and function with a similar mechanism to TLRs [44]. Among the DAMPs, high-mobility group box 1 protein (HMGB1) and heat shock protein 70 (HSP70) are thought to be ligands for TREM1 [45]. All this data suggests that TREM1 functions by accepting a diverse array of ligands. The nature and binding kinetics, the mechanism and energetics of their interactions are still unknown.

TREM-1 can elicit diverse responses through a multitude of mediators [46]. TREM-1 signaling mediated inflammatory responses are observed in both infectious and non-infectious models [47]. Upon encountering a ligand, TREM1 phosphorylates ITAM along with DAP12 and the downstream pathway is triggered. Src kinases phosphorylate specific proteins that recruit non-receptor tyrosine kinase Syk, which activates downstream signaling molecules, which, in turn, regulate inflammatory genes as well as NF-κB. These signaling molecules include PI3K, PLCγ, ERK1/2, and MAP kinases. Likewise, TREM-1 signaling modulates Ca^{2+} influx via Syk phosphorylation in an unknown mechanism [48]. In addition to cytokine upregulation, TREM-1 mediated degranulation and production of reactive oxygen species (ROS) aggravate inflammatory responses [42]. Attenuation of inflammation in TREM-1 deficient animal models confirms the proinflammatory signaling of TREM-1 [49].

Even though the exact interaction between TREM-1 and TLRs is unknown, it is believed that cross talk between them exists. TLR ligands have the capacity to upregulate TREM-1 mRNA expression and magnify TLR induced inflammatory responses. The expression of TREM-1 mRNA in LPS challenged macrophages was proven to be mediated by TLR-4/NF-κ B pathway [50]. TLR signaling does not elicit the expected similar result, [48]. Activation studies of TREM-1 by TLR ligands on monocytes also revealed the cumulative amplification of inflammatory cytokines [20]. Ornatowska *et al.* reported that silencing of TREM-1 genes had no direct effect on TLR-4 expression but down regulated Myd88 (myeloid differentiation primary-response gene 88) (adaptor protein) and IL-1b and IL-10, as seen in Figure 3, which suggests a possible mechanism of TREM-1/TLR cross talk [51, 52].

The adaptor protein non-T cell activation linker (NTAL) is phosphorylated following TREM-1 activation [53]. NTAL has been found to be expressed in B cells, NK cells, monocytes, and mast cells. NTAL occupies a downstream position after DAP12 and Syk and binds with growth factor receptor-bound protein-22 (Grb-2), casitas B-lineage lymphoma-1 (c-Cbl) (ubiquitin ligase), and son of sevenless-1(Sos-1) (guanine nucleotide exchange factor) [54, 55], [46]. A study using siRNA knockout NTAL in myelomonocytic cell line revealed negative regulation of TREM-1 responses by way of ERK phosphorylation, TNF-α and IL-8 production, and Ca^{2+} flux alteration. Thus NTAL acts as a checkpoint for regulating the DAP12 mediated activation signals [46].

Caspase-recruitment domain-9 (CARD9) is another mediator of TREM-1 induced NF-κβ activation and production of cytokines. CARD9 joins with Bcl-10 after TREM-1 activation, allowing for IL-2 production. Similarly, CARD11 joins with mucosa associated lymphoid tissue translocation protein 1 (MALT1) and Bcl-10 for NF-κβ activation in lymphocytes [56,

57]. TREM-1 was reported to work with several other PRRs like NAIP, CIITA, HET-E and TP-1-leucine-rich repeat and activates inflammation [58].

2.2 TREM-2

TREM-2 (first identified in human monocyte derived dendritic cells) is an immune regulator that is expressed mainly in myeloid cells and acts by ITAM mediated DAP12 adaptor. Apart from the immunological function TREM-2 is also involved in osteoclastogenesis, brain homeostasis and phagocytosis of bacteria [59]. TREM-2 elicits a protective role from autoimmune diseases [60]. The non-myeloid epithelial cells of the genitourinary tract and fallopian tubes constitutively express TREM-2. TREM-2 signaling also activates downstream effector kinases like ZAP70, SYK and PI3K and PLC-γ. TREM-2 deficient macrophages exhibit an increased susceptibility to inflammation, a finding that illustrates the role of TREM-2 as an anti-inflammatory agent [61].

Like TREM-1, the TREM-2 receptor possesses several ligands on myeloid and non-myeloid cells [37] but many ligands are still unknown. TREM-2 activation results in the upregulation of receptors like CD86, CD40 and MHC class II in dendritic cells. Stimulation of TREM-2 protects the dendritic cells from apoptosis that allows for cytoprotective actions [62]. TREM-2 binds to its corresponding ligands along with the downstream mediators like DAP12, plexin-A1, and semaphorin 6D to form a multimeric complex, the functions of which remain unknown [28].

TREM-2 signaling can also proceed through DAP12, an action that shuts down inflammatory pathways. The TREM-2 pathway runs without NF-κβ but proceeds with Ca^{2+} influx following ERK and PI3K activation. The down-regulation of inflammatory cytokines, especially TNF-α, reveals the antagonistic effects of TREM-2 over TREM-1 [19]. TREM-2 is secreted in Golgi complex and is transported to cell membrane upon stimulation [63]. TREM-2 pathway is mainly involved in cell survival, cell activation, cell differentiation and cytoskeleton orientation [64]. Upon ligand binding with the TREM-2, ITAM associates with the DAP12 and are phosphorylated by SRC kinase, which in turn recruits Syk and ZAP70 kinases. In mouse Syk alone is prominent while in human both Syk and ZAP70 couple to the ITAMs via the SH2 domain. These kinases phosphorylate PI3K, activating it. Then, PI3K phosphorylates membrane phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3) and recruits PLC-γ, TEC-family kinases, and Vav to cell surface. The complex formation of these mediator proteins activates the Akt pathway. Akt/PI3K regulates the translocation of NF-κβ and the expression of inflammatory genes and inhibits the TLR by inhibiting the MAPK signaling at RAF [65].

ZAP70 has also been found to be a target for LAT (T cells), LAB (B cells), and SLP-76 (SH-2 domain-containing leukocyte protein of 76 kDa). Activation of these cells can trigger multiple signaling cascades [66]. LAT/LAB phosphorylation results in the recruitment of mediators like PLC-γ, IL-2-induced tyrosine kinase (Itk), growth factor-receptor-bound protein 2 (GRB2), son of sevenless homologue (SOS), and GRB2-related adaptor downstream of She protein (Gads). Unlike LAT, LAB lacks the PLC-γ binding domain and acts mainly in coordination with GRB2 [67, 68]. LAT recruits SLP-76 and the N-terminal domain of SLP-76 binds Vav, NCK (adaptor protein), and Itk. Gads and PLC-γ interacts

with the PRP domain while HPK1 (hematopoietic progenitor kinase 1) and ADAP (degranulation-promoting adapter protein) bind to the C-terminal domain of SLP-76 [66, 69]. In short, both LAT and SLP-76 are major factors in assembly and stabilization of the signaling complex for TREM-2.

Itk (IL-2 inducible Tcell kinase) presents Vav to the antigen presenting cell (APC) surface in a kinase-independent fashion. Active Itk stimulates PLC-γ by phosphorylating and hydrolyzing PIP2 into diacylglycerol (DAG) and inositol (1,4,5)-triphosphate (IP_3) within the membrane. DAG and IP_3 are second messengers for T-cell differentiation, proliferation and response [24]. DAG activation opens NF-κβ signaling through protein kinase Ch (PKCh) and MAPK pathway via Ras guanyl nucleotide-releasing proteins (RasGRPs) [70, 71]. IP_3 acts as a ligand for the Ca^{2+} channel in the endoplasmic reticulum (ER) membrane [66, 72]. IP_3 activation initiates Ca^{2+} influx which activates the phosphatase activity of calcineurin. Calcineurin is responsible for the activation of kinases, including Ca^{2+}/calmodulin-dependent protein kinase (CaMK) and protein tyrosine kinase 2 (Pyk2), as well as calcineurin-mediated dephosphorylation of nuclear factor activated T-cell (NFAT) results its nuclear translocation. In addition calcineurin mediates dephosphorylation of NFAT results its nuclear translocation. Inside the nucleus, NFAT regulates a wide range of transcriptional factor for various biological responses [73].

As in TREM-1, ITIM controls ITAM activation. The binding of SH2 domain-containing inositol phosphatase-1 (SHIP1) to DAP12 inhibits Syk recruitment, thereby inhibiting PI3K. The regulation of TREM-2 pathway is crucial to preventing uncontrolled cell activation and proliferation [64].

TREM-2 can act in coordination with RANK and its ligands. Both can activate DAP12 by recruiting Syk to activate downstream signaling and, ultimately, result in nuclear translocation of NFATc1 [73]. Sema6D (a family of secreted and membrane associated proteins) was also reported to activate TREM-2/DAP12 signaling by phosphorylating DAP12 which demonstrates a link between TREM-2, cell adhesion, and motility functions [74]. Similarly, the TREM-2/DAP12 complex cross talk with cytokine pathways, integrin signaling and TLRs, which are mediated through Ca^{2+} signaling and Syk activation. At the same time, TLR signaling complex formation is inhibited by DAP12 through PLC-γ activation. PLC-γ acts by limiting the PIP2 availability, which is necessary for the recruitment of the TIRAP/Mal (toll-interleukin 1 receptor domain-containing adaptor protein/MyD88 adapter-like) and MyD88. TIRAP/Mal and MyD88 plays a crucial role in initiating TLR signaling [74, 75]. The key events of TREM-2 signaling are summarized in Figure 4.

2.3 sTREM

Certain clinical conditions, like infections, induce shedding of a soluble form of TREM receptors from the membrane surface into the body fluids. Soluble TREM (sTREM) can be a diagnostic tool for clinically [76]. The plasma level of sTREM-1 is found to be increased after sepsis, systemic inflammatory response syndrome, cardiac arrest, cancer, arthritis, and lung disorders [77]. sTREM-1 is a glycoprotein of 27kDa which may be cleaved from its extra cellular domain by matrix metalloproteinases (MMPs). This discovery was

substantiated by the finding that TREM-1 from CD14+ monocyte cells was decreased after six hours of LPS challenge [78]. TREM-1 mRNA can undergo alternate splicing that may results in sTREM1, the inciting factors of which are not known [79]. sTREM-1 has also been found in cerebral spinal fluid (CSF), in addition to the plasma, of bacterial meningitis patients and can be a marker to distinguish bacterial meningitis from non-bacterial forms [80]. Compared to soluble receptors like ICAM-1 and VCAM-1, it is believed that sTREM-1 and sTREM-2 negatively regulate the TREM receptors by eliciting a neutralizing effect [19].

A myriad of reports are being published in TREM signaling every year. Still the actual mechanism of action of these molecules and its implication to cell metabolism, apoptosis, and cell differentiation as well as a correlation of these biological responses with inflammatory status is limited. To the best of our knowledge the literature correlating the metabolism of immune cells and the target cells with inflammation is lacking.

3 Inflammation *versus* Metabolism – a gap to be filled

Recent findings suggest that cells that upregulate inflammation, such as Th17 lymphocytes and M1 macrophages, rely mostly on aerobic glycolysis for energy production when challenged with LPS. While the cells that mitigate inflammation, Treg cells, M2 macrophages, and memory T cells, prefer oxidative metabolism with limited glycolysis [81]. The energy demand of pro-inflammatory cells is higher than that of unchallenged cells. For instance, upon inflammation, macrophages switch to an activated form that promotes secretion and release of host response signals, facilitating phagocytosis and presenting antigens. [81, 82].

The increase in glycolysis allows for a rapid increase of intercellular ATP that is sufficient to maintain mitochondrial integrity after LPS challenge [83]. This increase in ATP maintains the viability and function of macrophages and other cells associated with inflammation until they perform their designated functions [84]. Similarly the activation of the pentose phosphate pathway provides intermediates for nucleotide biosynthesis and metabolic energy [85]. TH17 cells shift to Treg upon inhibition of glycolysis with 2-deoxyglucose. This shift shows that the plasticity of these cells is a function of their metabolic status [86, 87]. Also, TH1 cells sequester glyceraldehyde phosphate dehydrogenase (GAPDH) from IFN-γ mRNA and this prevents the IFN-γ mRNA from the inhibition by GAPDH to increase the glycolysis [88]. Similarly, the oxidative metabolism of the memory T cells switches to glycolysis upon shifting to effector T cells [89]. This cellular physiology demonstrates a link between inflammation and metabolism [81].

During the resting state, dendritic cells rely on oxidative metabolism and activation with PAMPs, like TLRs, that switch to glycolysis as a main route of metabolism. The activated dendritic cells are characterized by increased surface expression of the glucose transporter GLUT1, enhanced lactate accumulation, limited mitochondrial oxygen consumption and increased flux of PI3K and Akt signaling [83]. The anti-inflammatory cytokine IL-10 blocks TLR activation, prevents the switch to glycolysis, and favors oxidative metabolism in dendritic cells. TLR4 impedes the mitochondrial metabolism by upregulating the iNOS enzyme [90]. NO (nitric oxide) competes with oxygen and inhibits the cytochrome *c* oxidase

reaction of the electron transport chain. In this way, NO alters the mitochondrial integrity, causing the release of cytochrome *c* into the cytosol, leading to the activation of BAX and thereby apoptosis [85]. These facts are the evidences of anti-inflammatory status of the mitochondrial metabolism [83].

M1 macrophages express glycolytic regulator enzyme 6-phosphofructo-2-kinase isoform PFKFB3. This enzyme increases the glycolytic flux by accumulating the intermediate fructose-2,6-bisphosphate [91]. However, on M2 macrophages where the oxidative metabolism is predominant, PFKFB1 is expressed [91]. In M2 macrophages, outstanding oxidative lipid metabolism is evident and mediated through STAT6 induction of peroxisome-proliferator-activated receptor-γ co-activator-1β (PGC-1β) [92]. These changes depend on the activation of M2 macrophages by IL-4. *In vivo* studies showed that the PGC-1β prefers M2 phenotype to reduce macrophage mediated inflammation. This was confirmed by the limited oxidative metabolism in PGC-1β knockdown cells [93].

The expression of pro-inflammatory receptors like TREM-1 on immune cells during the process of inflammation alters the metabolic status of these cells. The demand for high energy biomolecules and the overall energy status of cells increase during the inflammatory phase. Hence, the control of energy yielding metabolic pathways in such cells limits them from conversion to an activated state which, in turn, minimize inflammation.

4 Inflammation *versus* metabolic checkpoint – a new target to be explored

Cellular energy homeostasis is regulated at the metabolic check point (5′adenosine monophosphate activated protein kinase) based on intercellular nutrient/ATP levels. This process is mediated by 5′adenosine monophosphate activated protein kinase (AMPK). AMPK is a protein complex that senses the cellular energy status of the cell with respect to the AMP:ATP ratio. AMPK is especially active during hypoxia, starvation and other physiological stress [94]. The phosphorylation by AMPK inhibits several key regulatory proteins of lipid and carbohydrate biosynthesis and metabolism. At the same time, AMPK activates energy yielding pathways like fatty acid oxidation, glucose and caloric influx, and mitochondrial biogenesis and activation. AMPK regulates the homeostasis between anabolic and catabolic pathways of energy metabolism [95].

Recent research on energetics of inflammation has focused on alterations and regulation of metabolic pathways in inflammatory cells and the target tissues. AMPK is a Ser/Thr protein kinase allosterically activated by AMP (and also by ADP) [96]. A heterotrimeric protein, AMPK possesses a catalytic α-subunit and two regulatory β and γ subunits. The highly conserved Thr 172 of the α-subunit is the site of phosphorylation for the activation of the enzyme by the protein kinase LKB1 (Liver kinase B1). LKB1 is a constitutively expressed protein, thereby, activating the AMPK continuously [97]. Binding of ATP to the γ-subunit reduces Thr 172 phosphorylation while ADP/AMP enhances AMPK activation [98]. If the ratio of AMP:ATP remains unaltered, AMPK can be activated by intracellular Ca^{2+}. Under such conditions, the Ca^{2+}/calmodulin-dependent protein kinase kinase b (CaMKKb) phosphorylates Thr172 for AMPK activation [99]. H_2O_2 has also been reported to activate

AMPK by oxidative modification of Cysteine residues in the α-subunit [100]. Being a key regulator of metabolism AMPK can be a central target for inflammatory diseases.

The activation of AMPK has been found to inhibit the severity of inflammation. The aggravation of inflammatory reactions in AMPK inhibited cells has provided some proof as to its anti-inflammatory effects [101]. AMPK suppresses iNOS in the presence of AICAR (5′-aminoimidazole-4-carboxamide ribonucleoside, an AMPK activator) activated in L6 myocytes and microglial cells which shows its anti-inflammatory role [102, 103]. In palmitate-challenged HUVECs (human umbilical cord endothelial cells), the NF-κβ reporter gene expression was effectively down regulated by AMPK [104]. AMPK mediated NF-κβ inhibition has also been reported in astrocytes, hepatic stellate cells, chondrocytes, neutrophils, and macrophages [101]. The decreased deterioration of IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) and subsequent binding of p65 to IL-6 promoter in LPS challenged macrophages by AMPK is another evidence for anti-inflammatory effects [105]. There are two possible mechanisms by which AMPK inhibits NF-κβ signaling. The first involves the phosphorylation of a transcriptional co-activator, p300, and masking of acetylation at Lys22 of p65 by constitutively expressed AMPK (endothelial cells). This expression in turn blocks the TNF-α binding of NF-κβ to the inflammatory genes [106]. The second involves AMPK phosphorylating IKKb at Ser 177 and Ser 181 to inhibit subsequent phosphorylation of IκBα and p65 (COS-7 cells). This inhibition also blocks the NF-κβ via TNF-α [107].

As with the AMP:ATP ratio, the NAD+ levels in the cells also represents the metabolic status. NAD+ regulates inflammation by a link with the NLRP3 inflammasome via sirtuin deacetylases. This enzyme mediates the proinflammatory IL-1β function and also activates AMPK [108]. The link between alterations in metabolism and NLRP3 expression has been well established in macrophages. The depletion of NAD+ in activated macrophages due to mitochondrial dysfunction reduces the activity of NAD+-dependent deacetylase SIRT. SIRT hypofunction causes the cellular building up of acetylated tubulin, the SIRT substrate, and leads to SIRT polymerization. Mitochondrial ROS activates NLRP3 and NLRP3 cause the localization of tubulin in mitochondria [109, 110]. SIRT1 and SIRT6 switches glycolysis to fatty acid oxidation by way of nicotinamide phosphoribosyl transferase (NAMPT) enzyme [111]. Deacetylation of p65 by SIRT1 inactivates NF-κβ pathway [112] and deacetylation of PGC-1β (also by SIRT1) promotes fatty acid oxidation [113, 114]. Inhibition of PPARγ (a transcription factor that modulate genes for lipid storage) by SRIT1 shifts energy production from glycolysis to fatty acid oxidation [115].

A positive feedback relationship between AMPK and SIRT1 exists [116]. SIRT1 mediated deacetylation of LKB1facilitates its cytosolic translocation and AMPK activation The anti-inflammatory effects of SIRT1 is further confirmed by the enhanced proinflammatory cytokine response in SIRT1 knockdown macrophages [117].

Molecular signaling pathways like JNK, p38, ERK1/2, and MAPK aggravate inflammatory responses [118]. AMPK suppresses the proinflammatory cytokine mediated activation of MAPK and JNK [119]. AMPK suppresses JAK-STAT (Janus kinase-signal transducer and activates transcription) signaling by induction of the orphan nuclear receptor protein SHP

(small heterodimer partner). This prevents STAT3 from accessing DNA and prevents the recruitment of downstream mediator SOCS3 (suppressor of cytokine signaling 3) to its promoter following the IL-6 challenge [120, 121]. AMPK can also decrease leukocyte mobility to the inflammatory site by down-regulating the adhesion molecules like VCAM-1 (vascular cell adhesion protein 1), ICAM-1 (Intercellular Adhesion Molecule 1), selectins, and MCP-1 [122]. AMPKs can also decrease inflammation through the regulation of lipid metabolism. The infiltration of M1 macrophages in adipose tissue and accumulation of lipids in their cytoplasm is considered one of the hallmarks of inflammation [123]. AMPK regulates lipid metabolism by balancing lipid synthesis and oxidation. AMPK mediates phosphorylation of the lipid biosynthetic enzyme acetyl-CoA carboxylase (ACC), leading to its inactivation and subsequent lipogenesis. On the other hand, AMPK enhances lipid oxidation via mitochondrial activation through PGC-1α (peroxisome proliferator-activated receptor gamma coactivator) [124, 125], a very crucial step since fatty acids like palmitate can activate NF-κβ and JNK pathways. Inhibition of AMPK triggers the both NF-κβ and JNK pathways [126]. The anti-inflammatory role of AMPK is given in Figure 5.

AMPK has been considered as a cellular metabolic check point as it regulates all the energy metabolism of the body. Activation of AMPK suppresses the pathways triggering NF-κβ activation and subsequent expression of pro-inflammatory genes. AMPK also inhibit lipid accumulation in the inflammatory and target cells that alleviate inflammation. Strategies that enhance the activity of AMPK in the cells associated with inflammation could result in newer opportunities in the better management of inflammation.

5 Future perspectives

Inflammation is an essential immunological response of the body. It is a delicate balance between leukocyte subsets, secreted biomolecule signals from these cells, and signals from target cells. Chronic inflammation slows the inherent repair process of the body and can become pathologic. The balance between cellular and molecular components is necessary for the regulation of inflammation. PMNLs, macrophages/monocytes, mast cells and T cells are necessary for the initiation and execution of inflammatory responses. The secreted chemokines and cytokines, especially interleukins TNFα and TGFβ, are also significant for inflammation. Targeting inflammation therapeutically is a common approach for disease management.

TREMs play and important role in the inflammatory process. Among the characterized TREM molecules, TREM-1 is considered pro-inflammatory while TREM-2 mitigates the inflammatory response. Even though certain mechanisms have been proposed for the TREM action, the actual mechanism is still unknown. DAP12 mediated signaling for TERM is widely accepted model that involves other mediators such as ERK, MAPK, JNK, PI3K, and calcium. The actual ligands for both TREM-1 and TREM-2 have to yet be defined. The existence of a link between TLR pathway and TREM is also a mystery. Variants of TREM other than TREM-1 and TREM-2 and their soluble forms are yet to be unveiled. Targeting TREM-1 for alleviating the inflammation may be an effective target for developing future anti-inflammatory therapies.

The metabolism and energetics of inflammatory leukocytes and their switching to active forms is the key to study life and longevity of these cells. The energy to deal with the harsh environments like ischemia, ROS and hypoxia during acute inflammation allows these cells to execute their desired function promptly. It is known that activated cells prefer glycolysis rather than oxidative metabolism. Such a shift in metabolism in inflammatory cells is mediated by metabolic checkpoint executed by AMPK. Apart from these, AMPK plays a central role in the inflammatory response by regulating several pro-inflammatory pathways. AMPK limits the availability of lipid metabolites for the synthesis of inflammatory mediators like leukotrienes by channeling them to mitochondria for oxidation. The anti-inflammatory role of AMPK provides a link between metabolism and inflammation.

AMPK may have implications in TREM physiology and their interplay may regulate inflammation. There is no reported literature addressing this concept. Since AMPK may mitigate the inflammatory response, it is thought to exhibit an inhibitory effect on TREM-1 and promote TREM-2 activation. These pathways both share NF-κβ signaling. The accumulation of lipids in inflamed and inflammatory cells after chronic inflammation signifies the down regulation of AMPK. In such cells the TREM-1 expression is greater than TREM-2 expression, which conveys the severity of inflammation. The possibility of alleviating inflammation by AMPK activation, and subsequent TREM-1 inhibition, may provide an opportunity for new regimes for inflammation management.

6 Expert commentary

Mechanism of activation of immune cells to trigger an inflammatory response is the central focus of research aiming to ameliorate the ill effects of inflammation. The prevention of phenotype switching of various immune cell types prior and post inflammation can open new opportunities for the management of inflammation and associated complications. Metabolism and energetics of activated immune cells and the correlation between AMPK and TREM-1 are yet to be unveiled. Antagonistic effects of TREM-1 and TREM-2 in regarding to inflammation is interesting but the underlying mechanism is largely unknown. Simultaneous targeting of AMPK and TREM-1 will be beneficial for the therapeutic management of inflammation.

7 Five-Year view

Even though TREM-1 and TREM-2 takes part in inflammation, their underlying mechanism of activation and action, the potential signals involved, functional ligands, detailed studies on the thermodynamics of ligand binding are warranted. Role of TREM-1 and TREM-2 in non-immune cells in regulating inflammation needs to be explored. The metabolism and energetics of activated inflammatory cells is also gaining significance in the current scenario. The potential role of AMPK in regulating inflammation by altering metabolic pathways has to be fully elucidated. The link between AMPK and TREM expression and signaling is poorly known. Novel approaches to specifically target the activated immune cells can also contribute for developing promising strategies for the treatment of inflammation.

References

Reference annotations

* Of interest

** Of considerable interest

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8 Key issues

- Inflammation is associated with cellular and molecular components.
- Persistence of inflammation causes delay in tissue healing responses after injury/pathology.
- PMNLs, mast cells, monocytes/macrophages, and T cell population are key cellular players of inflammation.
- Present understanding about the mechanism of regulation of inflammation by TREMs is reviewed.
- Signaling pathways and triggers of TREM-1 and TREM-2 can form excellent targets for management of inflammation.
- Metabolism of activated immune cells varies significantly from their pre-activated state.
- Role of AMPK in metabolism of inflammatory cells' and their subsequent activation is well known.
- The possibilities of AMPK mediated TREM activation or vice versa are still a dogma.
- Strategies for targeting AMPK and TREMs simultaneously are beneficial for the management of inflammation

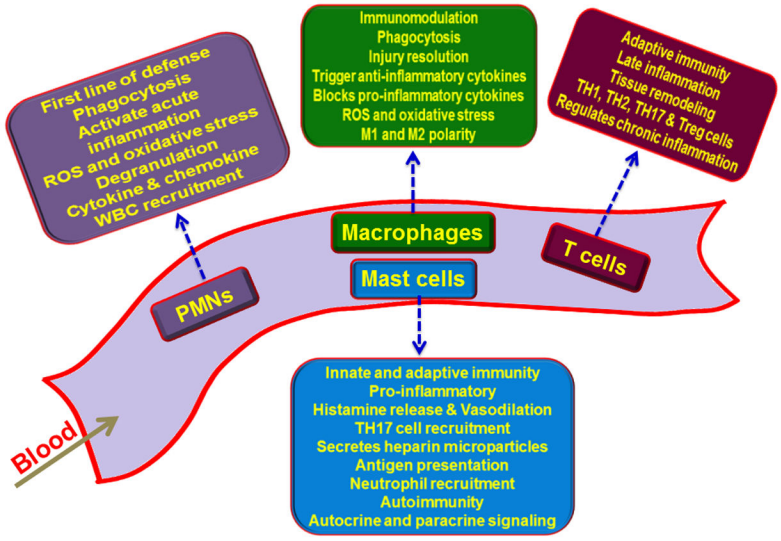

Figure 1. Specific role of immune cells in the progression and regulation of inflammatory responses

Polymorphonuclear leukocytes (PMNs) are phagocytic cells associated with acute inflammation; macrophages have immunomodulatory effect owing to their phagocytic activity, cytokine release and repair responses; mast cells enhance inflammation due to histamine release and induction of vasodilation, and the T cells play role in tissue remodeling after injury.

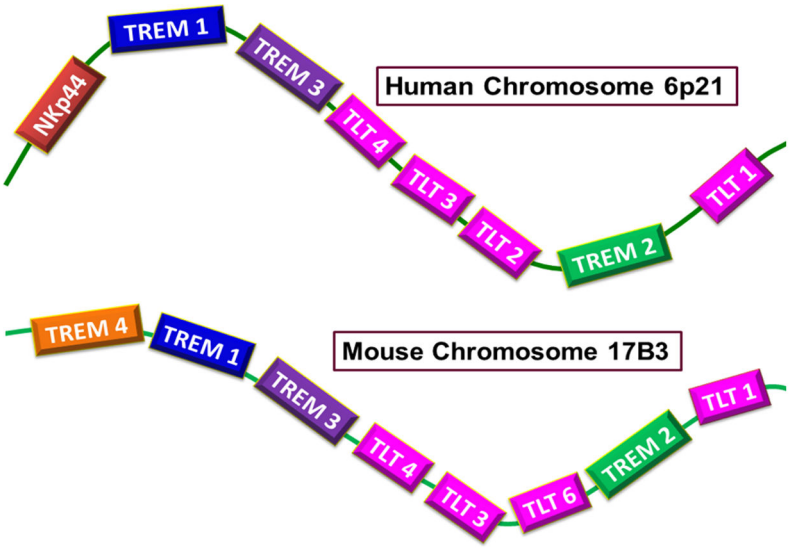

Figure 2. Loci and arrangement of human and mouse TREM gene clusters

Human TREM (triggering receptor expressed on myeloid cells) gene cluster is located on chromosome 6p21 carrying sequences for TREMs and TLTs. Mouse counterpart is located at chromosome 17B3 which bears an additional TREM gene (TREM-4) on comparing with that of human.

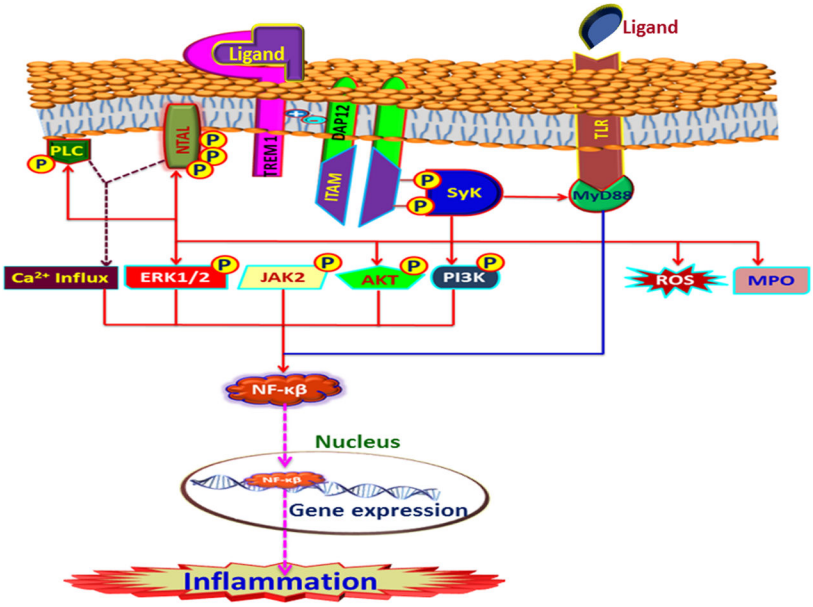

Figure 3. TREM-1 signaling mediated through DAP12 and downstream kinases leading to the expression of pro-inflammatory genes

Upon ligand binding the phosphorylation of ITAM (immunoreceptor tyrosine-based activation motif) associated with the adaptor protein DAP12 (DNAX activation protein of 12 kDa) occurs resulting in the recruitment and activation of Syk (spleen tyrosine kinase). Syk phosphorylates a battery of downstream kinases that activates NF-κβ and facilitates its nuclear translocation where it functions as a transcription factor for a panel of pro-inflammatory genes. TLR (toll-like receptor) signaling also integrates with TREM-1 pathway via NF-κβ signaling. All these events result in inflammation.

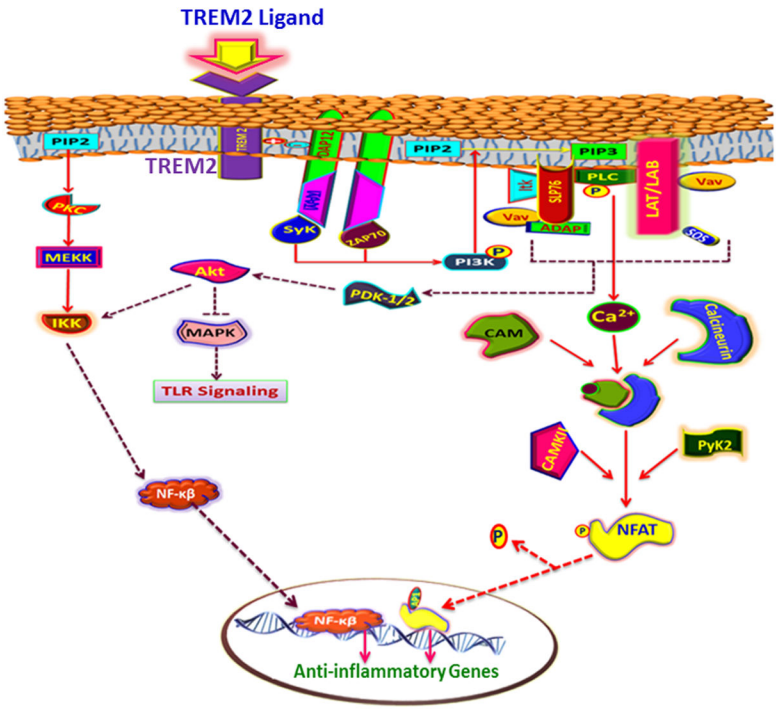

Figure 4. TREM-2 signaling mediated through DAP12 and downstream kinases leading to the expression of anti- inflammatory genes

TREM-2 ligand binding activates DAP12 and downstream Syk and ZAP-70 (Zeta-chain-associated protein kinase 70) which in turn activate PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase) pathway resulting in Ca^{2+} influx. Ca^{2+} activates NFAT (nuclear factor of activated T cells) by phosphorylation through calmodulin kinase. NFAT translocates to nucleus and triggers the expression of anti-inflammatory genes. PI3K inhibits TLR (toll-like receptor) signaling via Akt pathway which in turn inhibits inflammation.

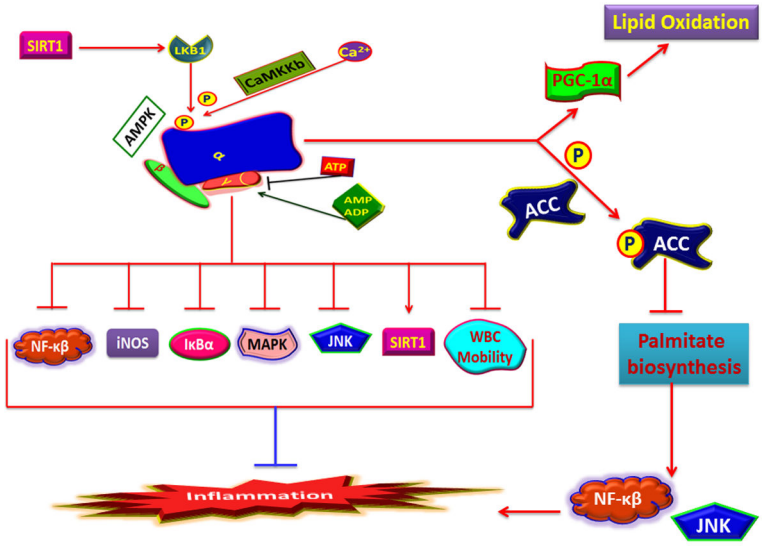

Figure 5. Integration of various cellular signaling pathways of metabolism by AMPK leading to inhibition of inflammatory responses

AMPK (5′ AMP-activated protein kinase) is activated by LKB1 (liver kinase B1) through SITR1 (sirtuin 1 - silent mating type information regulation 2 homolog 1) and Ca^{2+} through CAMKKb (calmodulin-dependent protein kinase kinase 2). On activation, AMPK inhibits a battery of enzymes and pathways to enhance inflammation. At the same time, AMPK activates lipid oxidation through PGC-1α (Peroxisome proliferator-activated receptor-γ coactivator-1α) and inhibits fatty acid synthesis which limits the availability of lipid moieties for the synthesis of pro-inflammatory mediators like prostaglandins.