International Immunopharmacology 73 (2019) 128–145

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Inflammation research sails through the sea of immunology to reach immunometabolism

V. Kumar*

Children's Health Queensland Clinical Unit, School of Clinical Medicine, Faculty of Medicine, Mater Research, University of Queensland, St Lucia, Brisbane, Queensland 4078, Australia
School of Biomedical Sciences, Faculty of Medicine, University of Queensland, St Lucia, Brisbane, Queensland 4078, Australia

ARTICLE INFO

Keywords:
Inflammation
Macrophages
Neutrophils
T cells
PAMPs
Immunometabolism

ABSTRACT

Inflammation occurs as a result of acute trauma, invasion of the host by different pathogens, pathogen-associated molecular patterns (PAMPs) or chronic cellular stress generating damage-associated molecular patterns (DAMPs). Thus inflammation may occur under both sterile inflammatory conditions including certain cancers, autoimmune or autoinflammatory diseases (Rheumatic arthritis (RA)) and infectious diseases including sepsis, pneumonia-associated acute lung inflammation (ALI) or acute respiratory distress syndrome (ARDS). The pathogenesis of inflammation involves dysregulation of an otherwise protective immune response comprising of various innate and adaptive immune cells and humoral (cytokines and chemokines) mediators secreted by these immune cells upon the activation of signaling mechanisms regulated by the activation of different pattern recognition receptors (PRRs). However, the pro-inflammatory and anti-inflammatory action of these immune cells is determined by the metabolic stage of the immune cells. The metabolic process of immune cells is called immunometabolism and its shift determined by inflammatory stimuli is called immunometabolic reprogramming. The article focuses on the involvement of various immune cells generating the inflammation, their interaction, immunometabolic reprogramming, and the therapeutic targeting of the immunometabolism to manage inflammation.

1. Introduction

Inflammation is known to ancient Indian Ayurvedic physicians dating back to 1500 BCE and 600 CE [1]. It is well documented in the *Brihat Trayee*, the *Charaka Samhita*, the *Susruta Samhita*, and the *Astanga Samgraha*. Inflammation and the associated edema have got an attention in Ayurveda as pathological manifestation of the disease [1,2]. It is known to different context called *Shotha, and Shopha* along with other terms used in Ayurveda including *Svayathu, Utsedha* and *Samhata* [1]. In Ayurveda it is characterized by elevation, edema, heaviness and pain. Even Ayurveda has shown an interconnection between chronic inflammation and cancer [3]. Hippocrates (an ancient Greek physician) introduced the term edema for inflammation in the 5th century BCE. Later on Aulus Celsus (30 BCE–38 CE) described inflammation with four cardinal signs including redness (*Rubor*), elevated heat (*Calor*), swelling (*Tumor*), and pain (*Dolor*) as occurring during acute inflammation in response to the localized acute infection or trauma [4]. **These four signs of inflammation are known as "Celsus tetrad of inflammation".** Galen, the physician and surgeon of Roman emperor Marcus Aurelius, is often credited with introducing a fifth sign of inflammation called loss of function in the affected tissue/organ. However, *Virchow* in 1871 more precisely added the description of fifth sign of inflammation described as *function laesa* (loss of function) that viewed inflammation as inherently pathological to host [5,6].

Modern medicine uses the term inflammation that is a derivative of Latin word *inflammare* (to set on fire) [6]. Immunologists consider inflammation as a host generated protective immune response evolved to protect the host in response to acute trauma or pathogens or their PAMPs by containing the damage or removing/killing the pathogen responsible for infection [7]. The process of inflammation involves a complex network of cellular and molecular signaling cascades directed to restore the tissue or organ homeostasis, repair, and regeneration. However, severe and systemic acute inflammation may result in pathology, organ failure and death as seen during sepsis. Furthermore, if inflammation persists for a longer duration of time (for months and years) and becomes chronic, may cause chronic inflammatory diseases including cancer and autoimmunity. The cellular components of immune system playing active role in the process of both acute and

* Children's Health Clinical Unit, Faculty of Medicine, Mater Research, University of Queensland, St Lucia, Brisbane, Queensland 4078, Australia.
E-mail address: vij_tox@yahoo.com.

https://doi.org/10.1016/j.intimp.2019.05.002
Received 2 March 2019; Received in revised form 18 April 2019; Accepted 1 May 2019
Available online 13 May 2019

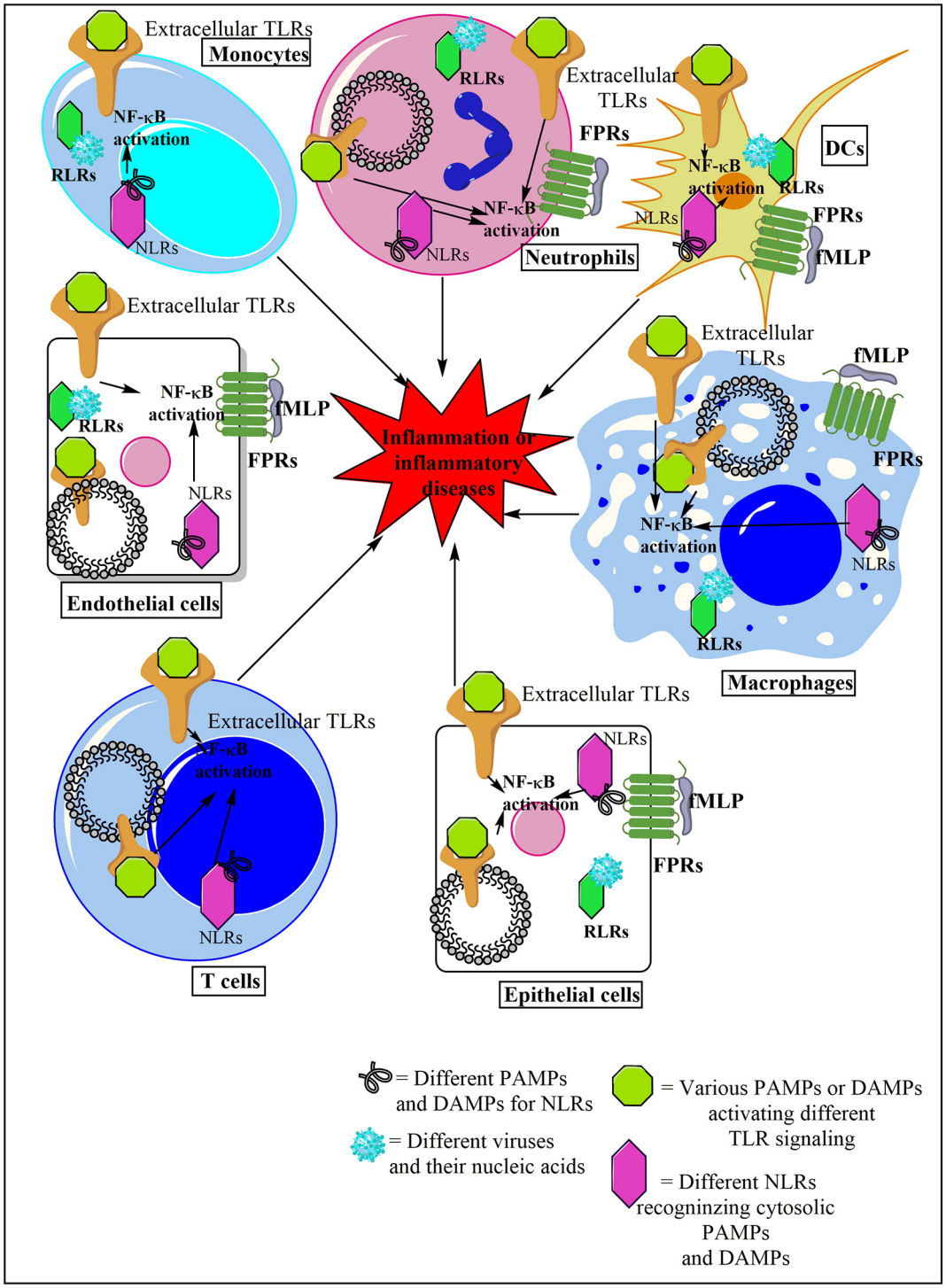

Fig. 1. Schematic representation of different immune cells expressing different PRRs and their role in the generation of pro-inflammatory immune response. The activation of different PRRs (FPRs, TLRs, NLRs, and RLRs) via their corresponding ligands (PAMPs, DAMPs, and pathogens) leads to the activation of NF-κB signaling and other pro-inflammatory signaling event causing the initiation of inflammation or other inflammatory diseases including cancer, allergy, autoimmunity, and the generation of infection associated inflammatory immune response. Detail is mentioned in the text.

chronic inflammation involve endothelial cells (ECs), epithelial cells, monocytes/macrophages, mast cells (MCs), neutrophils, dendritic cells (DCs), innate lymphoid cells (ILCs), mucosal-associated invariant T (MAIT) cells, natural killer (NK) cells, and different subsets of T cells (Fig. 1) [8–11]. These cells maintain immune homeostasis through immunometabolism, and immunometabolic reprogramming observed during the process of inflammation. Thus the present article is designed to highlight the role of major immune cells in the process of inflammation (both acute and chronic inflammation), immunometabolic reprogramming among these immune cells from normal homeostatic stage to the stage of inflammation, and the therapeutic targeting of immunometabolic reprogramming to target inflammation.

2. Immunopathogenesis of inflammation

2.1. PRRs and their role in the initiation of inflammatory cascade or the process of inflammation

Inflammation can develop in any organ exposed directly to the outer environment including mucosal surface of gastrointestinal tract (GIT), reproductive tract, respiratory tract, and skin or to the vital organs including liver (hepatitis), kidneys (nephritis), brain (meningitis), and lungs (pneumonitis) etc. due to the exposure to various infectious agents or pathogens, PAMPs, xenobiotics or DAMPs produced by the host in response to cellular stress and acute trauma. The recognition of both PAMPs and DAMPs by various pattern recognition receptors (PRRs) expressed by innate immune cells including the endothelial cells lining the blood vessels and vital organs, epithelial cells present in the skin and lining the mucosal surfaces or barrier surfaces of GIT (epithelium lining the intestine), respiratory (lungs), and reproductive (Vaginal and urethral epithelial cells) tract, monocytes/macrophages, neutrophils, and mast cells (MCs) etc. plays a crucial role in induction of inflammatory immune response. The innate immune cells express various pattern recognition receptors (PRRs) such as formyl peptide receptors (FPRs), toll-like receptors (TLRs), intracellular PRRs (Nod-like receptors (NLRs; NOD1 and NOD2)), RIG-like helicases (RLH) such as MDA-5, C-type lectin receptors (CLRs) [Dectin 1 or CLEC7A, dectin 2 or CLEC6A, DC-specific ICAM3-grabbing non-integrin (DC-SIGN)], complement receptor 3 (CR3), Triggering receptors expressed on myeloid cells (TREM-1) and myeloid DAP-12 associated lectin (MDL-1) [12–15].

2.2. FPRs in inflammation

FPRs are members of the family of seven-transmembrane G protein-coupled receptors (GPCRs) that are well conserved among mammals [16]. Human FPRs (FPR1, FPR2, and FPR3) are primarily expressed by myeloid cells (neutrophils and monocytes) (Fig. 1) and are considered as myeloid cell receptors with the exception that neutrophils lack FPR3 [17]. Additionally, FPR1 is also expressed by astrocytes, hepatocytes, microglia, and immature DCs, whereas FPR2 is expressed by astrocytoma cells, epithelial cells, hepatocytes, microvascular endothelial cells, and neuroblastoma cells [17]. FPR1 usually recognizes short peptides of approximately 3–5 amino acids starting with N-formylmethionine, which are cleavage products of bacterial (*Escherichia coli*-derived peptide N-formylmethionyl-leucyl-phenylalanine (fMLP)) and mitochondrial proteins including mitochondrial formylated peptides (MFPs) to initiate the inflammatory immune response [18–20]. On the other hand, FPR2 serves as a low-affinity receptor for many of the potent FPR1 agonists including mitochondrial proteins [19]. FPR2 is activated by longer peptides with a-helical, amphipathic properties including the most prominent FPR2 ligand called staphylococcal-derived phenol-soluble modulins (PSMs) and causes neutrophil infiltration, a hallmark of inflammation [21]. PSMs also upregulate the neutrophil complement receptor CD11b via FPR2 activation in an Agr-quorum-sensing response-dependent manner [22]. FPR2 also serves as PRR for various other pathogens (Both bacteria and viruses including *Listeria monocytogenes* (*L. monocytogenes*), *Enterococcus faecium* (*E. faecium*), *Helicobacter pylori* (*H. pylori*), *Streptococcus pneumoniae* (*S. pneumoniae*), and human immunodeficiency virus (HIV)) and cause monocyte activation, neutrophil infiltration, and apoptosis of lymphocytes [21,23–28]. Even the lack of both FPR1 and 2 in mice is associated with their death during pneumococcal meningitis induced by *S. pneumoniae* due to the impaired inflammatory immune response including increased neutrophil infiltration with an impaired level of anti-inflammatory cytokines and antimicrobial peptides (AMPs) [29]. FPR2 also plays a crucial role in the resolution of inflammation by acting as a receptor for lipoxin A_4 (LXA_4) and resolving D1 (RvD1) [30]. The details of FPRs in inflammation and immunity are described elsewhere [12,31,32].

2.3. TLRs in inflammation

TLRs are expressed by almost every type of innate immune cells including epithelial cells and endothelial cells along with both myeloid and lymphoid immune cells [33]. TLRs form a separate family of PRRs comprising of two major domains characterized by leucine-rich repeats (LRRs) and Toll/internuekin-1 receptor (TIR) domain [34]. Till date a total of 10 functional TLRs (TLR1-TLR10) in humans and 13 active TLRs in laboratory mice have been discovered [35]. They are expressed both on the cell surface of immune cells and in the cytosolic organelles including lysosomes, endosomes, endolysosomes, and phagosomes [35]. For example, TLR1, TLR2, TLR4, TLR5, TLR6, and probably TLR11 and TLR12 of laboratory mouse and TLR10 of humans are expressed on the cell surface of innate immune cells normally [35]. However, TLR4 and TLR2 are also found to express intracellularly in endothelial cells, epithelial cells and DCs [35]. TLR3, TLR7, TLR8, and TLR9 recognize intracellular pathogens, their PAMPs, and DAMPs are expressed in intracellular compartment including phagosomes, endosomes, lysosomes and phagolysosomes. The activation of TLR signaling in the presence of pathogens (including bacteria, virus, fungi, and parasites), their PAMPs (Lipopolysaccharide (LPS, a TLR4 ligand), peptidoglycan (PGN, a TLR2 ligand), lipoteichoic acid (LTA, also TLR2 ligand), double stranded RNA (dsRNA, a TLR3 ligand), single stranded RNA (ssRNA, a TLR7 and TLR8 ligand), bacterial flagellin (a TLR5 ligand), and CpG oligodeoxynucleotide (ODN) or CpG DNA, a TLR9 ligand), and several DAMPs activates nuclear factor-kappa B (NF-κB) (Fig. 1) to initiate the pro-inflammatory event by inducing the release of various pro-inflammatory cytokines (IL-1, IL-6, TNF-α etc.) and type 1 interferons (IFNs) along with mediating the generation of free radicals including reactive oxygen and nitrogen specie (ROS and RNS) [34,35]. TLR9 is the first cytosolic PRR discovered in 2000 involved in the detection of the pathogen (Bacteria)-derived cytosolic DNA as a PAMP to initiate the synthesis and secretion of type 1 IFNs via the activation of NF-κB [36]. The observation was made in respect to the inability of *TLR9*$^{-/-}$ mice to elicit the innate immune response against bacterial CpG ODN or CpG DNA. TLR9 is expressed mainly in B cells and plasmacytoid DCs [37]. The detailed TLR signaling event involved in the inflammatory immune response is described somewhere else [38–41].

2.4. NLRs in inflammation

NLRs (Nucleotide-binding domain, leucine-rich repeat containing receptors) comprise of three separate domains found throughout the evolution of animal kingdom [42]. Alternatively NLRs are also known as CATERPILER, NOD, and NOD-LRR [43–45]. The N terminus of NLRs either have a pyrin domain, a caspase recruitment domain (CARD), or a baculovirus inhibitory repeat (BIR) domain [42,43]. However, the N terminus of the NLRX1 protein contains a domain that differs from any of these three domains with a similar three-dimensional fold. The central NBD or NACHT (nucleotide-binding domain or NAIP, CIITA (Class II transactivator), HET-E and TP1) domain exerts a dNTPase activity and oligomerization [42]. The NBD is responsible for the formation of a signal-receptive state in the presence of nucleotides including ATP molecules. The C terminus of NLRs comprises of a series of leucine-rich repeats (LRRs) varying in their number and composition [43]. All these three domains play a crucial role in protein-protein interactions and networks. Along with cytosolic TLRs, NLRs also serve as the prominent intracellular or cytosolic PRRs to sense intracellular pathogens, their PAMPs, and DAMPs responsible for the induction of inflammation via the activation of MAP (Mitogen-activated protein) kinases (MAPKs) and NF-κB (Fig. 1) [46–48]. For example, NOD1 and NOD2 are two NLRs sensing the cytosolic PGN meso-DAP and muramyl dipeptide to activate MAPK and NF-κB to initiate the inflammatory cascade [14]. In addition to their PRR role, NLRs also regulate major-histocompatibility complex (MHC) genes to affect adaptive immunity in response to RIP2 (Receptor interacting Protein 2

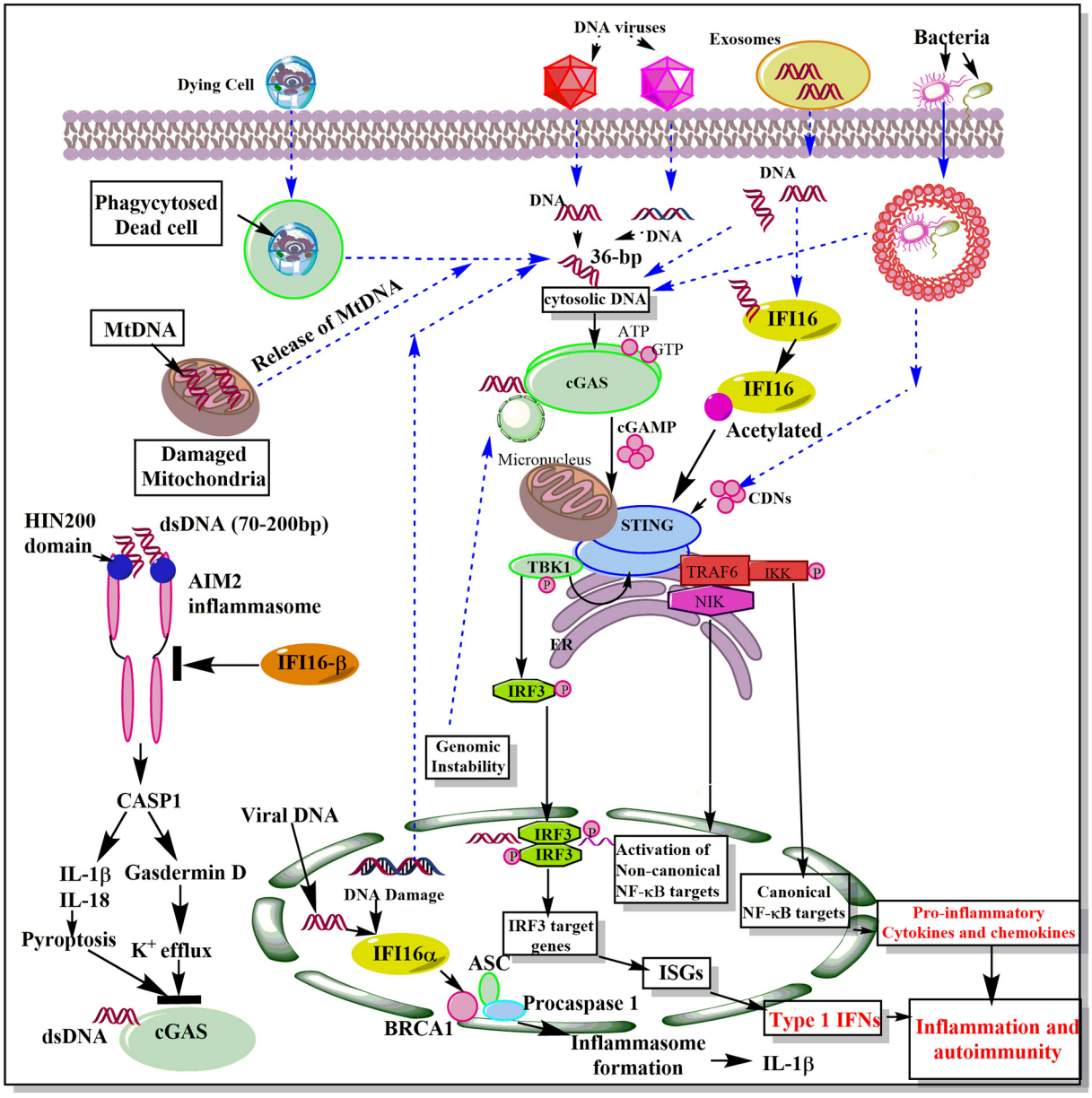

Fig. 2. Schematic representation of different cytosolic PRRs sensing host or pathogen-derived cytosolic or nuclear dsDNA as a PAMP or DAMP. ALRs including AIM2 and IFI16 recognize cytosolic and nuclear viral dsDNA to initiate the inflammatory immune response via the activation of AIM2 inflammasome and acetylation of IFI16 that activates STING downstream of cGAS to signal the synthesis and release of type 1 IFNs along with activating both canonical and non-canonical NF-κB-dependent release of pro-inflammatory cytokines, AIM2 activation also inhibits cGAS-STING signaling via directly binding to the cGAS. However, IFI16-β inhibits AIM2 inflammasome activation in response to cytosolic dsDNA. IFI16-α present in nucleus recognizes viral DNA entered into the nucleus to activate inflammasome-dependent IL-1β release. In addition to AIM2 and IFI16, intracellular dsDNAs are also recognized by cGAS that causes the formation of cGAMP (the second messenger) that activates STING. STING activation phosphorylates TBK1 that phosphorylates IRF3. The dimerized and phosphorylated IRF3 enters the nucleus to activate IRF3 target genes including ISGs that activate type 1 IFNs. In addition of viral and host-derived dsDNAs, cGAS-STING signaling is also activated by bacterial CDNs. The details are mentioned in the text.

(RICK or CARDIAK), RIPs are close members of the interleukin-1-receptor-associated kinase (IRAK) family, and belong to the family of serine/threonine kinases, play a crucial role in microbial infections, inflammation, and DNA damage) [49] and regulate the cell death mechanisms including necroptosis [46,49]. NLRC5 deficiency also impairs the basal expression of MHC class-1 in T, NKT, and NK cells and impairs the clearance of lymphocytes, intracellular pathogens (*L. monocytogenes*) and viruses (Influenza A virus (IAV)) by $CD8^+$ cytotoxic T cells [50–53].

Humans and laboratory mice have 22 and 34 NLR member proteins respectively [54]. The members of NLR protein family including NLRP1, 2, 3, 6, 12, NLRC4, and NOD2 form an inflammatory complex with caspase 1 (CASP1) and ASC (Apoptosis-associated speck-like protein containing a caspase recruitment domain) called inflammasome facilitating the activation of CASP1 and CASP11 causing maturation and release of pro-inflammatory cytokines IL-1β and IL-18 (major pro-inflammatory cytokines initiating neutrophil and monocyte influx at the site of infection or inflammation by increasing the expression of adhesion molecules on endothelial cells and leukocytes including monocytes and neutrophils) [55–57]. Activation of NLRs and inflammasomes further aggravates inflammation by inducing the cell death through pyroptosis and necroptosis (A regulated necrotic cell death involving RIPK1, RIPK3, and MLKL (mixed-lineage kinase domain-like pseudokinase)) [58–60]. The detailed mechanism of

necroptosis and its involvement in the inflammation and organ injury is beyond the scope of this article and is described somewhere else [58,61,62]. NOD1 and NOD2 also play a crucial role in the generation of endoplasmic-reticulum (ER) stress-induced inflammation via mediating the releasing IL-6 [63]. The detailed mechanisms of NLRs and inflammasomes signaling are discussed elsewhere [14,42,47,55,64]. Thus along with acting as individual PRRs, both TLRs and NLRs interact with each other in the process of pathogen, PAMP, and DAMP recognition to initiate the pro-inflammatory immune response to clear the invading pathogens and if this pro-inflammatory process is not controlled effectively may lead to the development of inflammatory diseases.

2.5. RLRs in inflammation

RLRs (RIG-I (Retinoic acid inducible gene-1) like receptors) or RIG-I like proteins are another class of PRRs involved in the recognition of intracellular viral nucleic acids including dsRNA, ssRNA or even host-derived self RNA and activate certain interferon-regulated factors (IRFs) (Fig. 1) [65–67]. MDA5 (Melanoma differentiation-associated gene -5) also belongs to the RLR family of proteins and recognize intracellular RNA [66,68,69]. The MDA-5 acts as a dsRNA-dependent ATPase containing both CARD and RNA helicase motifs [69]. RLRs are the family of DExD/H box RNA helicases [70]. The activation of RLRs in response to their corresponding PAMPs activates the CARD domain to downstream activation of CARD-containing adaptor protein, IFN-β promoter stimulator (IPS)-1 [or mitochondrial anti-viral signaling protein (MAVS) or virus-induced signaling adaptor (VISA) or CARD adaptor inducing IFN-β (Cardif)] to further activate NF-κB and IRF-3 to produce type 1 IFNs [67,71,72]. Under homeostasis, the expression of RLRs maintains at low levels but it increases during viral infections or exposure to the IFNs [67]. The detailed mechanism of pathogen and PAMP sensing by RLRs is described somewhere else [66,73–75].

2.6. Intracellular PRR for cytosolic pathogen-derived (bacteria and viruses) and host-derived DNA

2.6.1. Absent in melanoma 2 (AIM2)-like receptors (ALRs) in inflammation

AIM2 (p210), Interferon-γ-inducible protein 16 (IFI16), and the mouse orthologue of human IFI16, called p204 together form the new family of PRRs known as ALRs recognizing cytosolic viral dsDNA [37,76]. The human ALRs, AIM2 and IFI16 are encoded by the interferon (IFN)-inducible gene cluster located on the chromosome 1q23 [76]. AIM2 is a member of the PYHIN (Pyrin and HIN domain-containing protein) family, discovered in 2009 as a cytosolic PPR for cytosolic viral dsDNA (Fig. 2) [77,78]. The cytosolic viral dsDNA directly binds to the HIN200 (Hematopoietic IFN-inducible nuclear antigen of 200 amino acids) domain of the AIM2 (Fig. 2) [79]. The AIM2-mediated recognition of dsDNA occurs in a non-sequence-specific manner via electrostatic attraction between positively charged HIN domain residues and the dsDNA sugar phosphate backbone [80]. However, the dsDNAs with at least 70-bp have the potential to initiate AIM2-dependent inflammasome signaling pathway, and its optimal activation requires dsDNAs reaching the length of ~200-bp (Fig. 2) [80–82]. The assembly or disassembly dynamics of AIM2 filaments also depends on the dsDNA length, for example, assembly rate (k_{assm}) of AIM2 filaments increases nonlinearly approximately 700-fold depending on the length of dsDNA (Between 24- and 600-bp dsDNA) [83]. Thus AIM2 inflammasome activation optimally occurs upon the recognition of longer dsDNA as compared to the shorter one.

The binding of the cytosolic viral dsDNA to the HIN200 domain of the AIM2 liberates the autoinhibited state of the AIM2 Pyrin and HIN domains facilitating the inflammasome assembly along the DNA staircase via recruiting the ASC through homotypic PYRIN domain interaction to activate CASP1 [80,84,85]. Thus AIM2-mediated recognition of the cytosolic dsDNA stimulates synthesis and release of pro-inflammatory cytokines (IL-1β and IL-18) due to the formation and activation inflammasomes (Fig. 2) [86]. The AIM2-ASC interaction also forms ASC pyroptosome to induce the pyroptosis among infected cells [84]. The activation of AIM2 inflammasome signaling pathway in the presence of cytosolic dsDNA reduces the activation of cGAS-STING signaling pathway in vitro in murine macrophages and DCs by inducing the death of the immune cells in CASP-1-dependent manner [87]. The death of immune cells or their pyroptosis occurs due to cleavage of CASP-1-dependent gasdermin D in response to the activation of AIM2 inflammasome (Fig. 2) [88]. The gasdermin D depletes intracellular potassium (K^+) through membrane pores that serves as an essential step to inhibit cGAS-STING signaling pathway dependent type-1 IFN release (Fig. 2) [88].

IFI16 is constitutionally expressed in human lymphoid cells [89]. It recognizes both cytosolic and nuclear DNAs of viruses [HIV-1, Herpes-simplex virus-1 (HSV-1), Epstein Barr virus (EBV), and Kaposi's sarcoma-associated herpesvirus (KSHV)] and the generation of the pro-inflammatory immune response (Fig. 2) [90–93]. The recognition of intracellular viral DNA by IFI16 during KSHV infection causes its interaction with BRCA1 (Breast Cancer 1), ASC, and procaspase-1 to form the inflammasome in the nucleus and perinuclear region to induce the generation of IL-1β (Fig. 2) [92,94,95]. IFI16 has one extra dsDNA binding HIN200 domain [83]. HIN200 domain of the IFI16 binds dsDNA that induces the acetylation of IFI16 (Fig. 2) [96]. The acetylated IFI16 activates the stimulator of interferon genes (STING) that activates the TANK (TRAF family member-associated NF-κB activator)-binding kinase-1 (TBK1)-dependent phosphorylation of interferon regulatory factor (IRF) 3 and transcription of type I IFNs (IFN-β) and other related pro-inflammatory genes (Fig. 2) [95,96]. The involvement of TBK1 in the recognition of cytosolic artificial dsDNA Poly(dA:dT) and the induction of IRF3-dependent production of type 1 IFN (IFN-β) was first observed in the year 2006 [97]. The deletion of ASC and STING did not impact the acetylation of IFI16 as it occurs upstream of ASC assembly and STING activation [96]. The deletion of IFI16 severely attenuates IFN-α and the IFN-stimulated gene retinoic acid-inducible gene I (RIG-I) in response to cyclic GMP-AMP (cGAMP) that is synthesized by cyclic GMP-AMP synthase (cGAS) as well as RNA ligands and viruses [90]. The IFI16 knockout (KO) cells exhibit a compromised level of RNA polymerase II on the promoter region of the IFN-α that suggests the involvement of the IFI16 in the transcription of IFN-stimulated genes (ISGs) [90]. Thus IFI16 is involved in the generation of inflammatory immune response against the cytosolic viral DNA and RNA both in inflammasome-dependent and independent (the activation of cGAS-STING signaling) manner. The upregulation of IFI16 in the keratinocytes isolated from the patients of psoriasis aggravates the inflammation via producing the chemokines (CXCL10 and CCL20) [98]. The deletion of p204 (a mouse orthologue of human IFI16) in mice subjected to imiquimod-induced psoriasiform dermatitis inhibits the epidermal hyperplasia [98]. However, a recent study has indicated that ALRs are needless for the generation of type 1 IFNs in response to cytosolic DNA and also in *Trex1*$^{-/-}$ (Three Prime Repair Exonuclease 1) mice with Aicardi-Goutieres syndrome (AGS), an autoimmune disease, ALRs have negligible contribution [99]. IFI16-β is a transcript isoform of IFI16 that inhibits the AIM2 inflammasome activation by interacting with AIM2 to impede the formation of AIM2-ASC complex (Fig. 2) [100]. IFI16-β also sequesters the cytosolic dsDNA to prevent its recognition by AIM2. IFI16-α, the other transcript of IFI16 predominately resides in the nucleus, whereas IFI16-β co-localizes with AIM2 in cytoplasm [100]. IFI16-α is a homolog of mouse p202 and contains two HIN domains without any pyrin domain [100]. IFI16-α is present ubiquitously in various immune cells and its mRNA levels increases in the lymphocytes of patients with SLE, viral infections, and in cells treated with interferon-β or phorbol myristate (PMA) [100].

2.6.2. cGAS or Chromosome 6 open reading frame 150 (C60RF150)-STING signaling in inflammation

cGAS also serves as a cytosolic PRR for cytosolic DNAs (depending on their length) of both pathogen-originated or host-derived including retrotransposons (short interspersed nuclear elements (SINEs) and Alu elements). For example, DNA molecules equal to or more than 36 base-pairs (bps) serve as optimal inducers of cGAS-STING signaling to generate type 1 IFNs and other NF-κB-dependent pro-inflammatory molecules (Fig. 2) [101]. The recognition and binding of cytosolic DNA to cGAS synthesizes cGAMP that in turn activates STING to activate the IRF3 (Interferon regulatory factor 3) and IRF3 target genes including ISGs synthesizing type 1 IFNs (Fig. 2) [102]. The activation of STING also activates both canonical and non-canonical NF-κB targets to synthesize Pro-inflammatory cytokines and chemokines (Fig. 2). Of note, cGAS-STING activation releases the highest amount of type 1 IFNs by immune cells including macrophages and DCs in comparison to the activation of other cytosolic PRRs including TLR9 and ALRs [103]. cGAS also facilitates the recognition of extracellular cyclic dinucleotides (eCDNs) released by extracellular bacteria and dying cells as these eCDNs are endocytosed through endocytosis [104]. cGAS further enhances the perinuclear accumulation of eCDNs, and subsequent activation of STING to release type 1 IFNs [104].

cGAS and IFI16 cooperate to activate STING during cytosolic DNA sensing in human keratinocytes to fully activate the innate immune response [105]. IFI16 plays a crucial role in the production of cGAMP by cGAS and cGAMP-induced STING activation via interacting with STING to promote its phosphorylation by TBK1, and translocation from endoplasmic reticulum (ER) to ERGIC (ER-Golgi intermediate compartment) and clusters in membrane-bound peri-nuclear foci [105,106]. It also promotes the translocation of IRF3 into the nucleus [105]. The cGAMP produced due the activity of cGAS in the presence of cytosolic dsDNA serves as a second messenger to activate the STING signaling to generate IRF3-dependent type 1 IFNs and NF-κB-dependent pro-inflammatory cytokines (Fig. 2) [102]. Thus the recognition of cytosolic DNA (both, pathogen or host-derived) by intracellular PRRs including ALRs, cGAS, and TLR9 induces a potent pro-inflammatory immune response through the generation of type 1 IFNs and NF-κB-dependent pro-inflammatory cytokines, chemokines, and ROS or RNS.

A recent study has shown that ZCCHC3, a CCHC-type zinc-finger protein serves as a positive regulator of cGAS-STING signaling via directly binding to the cytosolic dsDNA to enhance its binding to the cGAS [107]. Thus ZCCHC3 serves as a co-sensor for cytosolic dsDNA recognized by cGAS. Also the damaged dsDNAs in the presence of PARP-1 [Poly [ADP-ribose] polymerase *1* or NAD^+ ADP-ribosyltransferase *1 (ADRT1)* or poly[ADP-ribose] synthase *1* (PARS-1)] and ATM (Ataxia-telangiectasia mutant) induce non-canonical STING signaling due the activation of IFI16 that binds to the damaged dsDNA and induces assembly of an alternative STING signaling complex with p53 (a tumor-suppressor protein) and E3 ubiquitin ligase TRAF6 (Tumor necrosis factor receptor-associated factor 6) [108]. The TRAF6 catalyzes K63-linked ubiquitin chain formation on STING to activating NF-κB and induce an alternative STING-dependent pro-inflammatory gene expression program [108]. Unlike human macrophages and DCs, human B cells do not produce type 1 IFNs in the presence of cytosolic dsDNA or cGAMP stimulation due to the lack of STING [109]. Even the reconstitution of the STING in human B cells is unable to induce the cGAS-dependent type 1 IFNs upon their exposure to dsDNA and cGAMP. Thus human B cells are defective in the recognition of cytosolic dsDNA and mounting a type 1 IFN-dependent pro-inflammatory immune response. The detailed pro-inflammatory signaling event involved in the cGAS-STING signaling during infection-induced or sterile inflammatory conditions including autoinflammation, autoimmunity, or cancer is beyond the scope and theme of the present article and is described somewhere else [103,110–113]. The released type 1 IFNs also act in an autocrine manner via type 1 IFN receptor (IFNR)-dependent pathway on plasmacytoid DCs (pDCs) and alter their immunometabolic stage via increasing the fatty-acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) [114]. Type 1 IFNs also induce FAO and OXPHOS in non-hematopoietic cells in virus-infected cells through the activation of PPAR-α. Thus targeting of FAO, OXPHOS and PPAR-α in cells infected with dsDNA or where host cytosolic dsDNAs serve to stimulate cytosolic PRRs may be used to target downstream pro-inflammatory action of type 1 IFNs [114].

Hence PRRs initiate the signaling events required for the pathogenesis of inflammation including the immune cell migration at the site of inflammation. These inflammatory signaling events induce immunometabolic reprogramming in activated immune cells for their survival, growth, proliferation, and release of pro-inflammatory mediators to contain the infection through inflammatory mediators. However, the dysregulation of the protective inflammatory process causes inflammatory tissue/organ damage or death of the person.

3. Immune cells involved in the process of inflammation

The recognition of pathogens/PAMPs/DAMPs at the mucosal surfaces covered by epithelial cells or by the endothelial cells lining the lymphatic or vascular blood vessels activates them to release several pro-inflammatory cytokines and chemokines. The release of cytokines and chemokines further causes the influx of neutrophils and monocytes at the site of infection or inflammation due to the expression of various adhesion molecules on endothelial cells. The apoptotic and necrotic death of epithelial, endothelial, and migrated inflammatory cells further aggravate it through tissue or organ failure. The following sections describe in detail the immune cell interaction taking place in the event of inflammation.

3.1. Neutrophil-epithelial cell and monocyte-epithelial cell interaction during inflammation

The epithelial neutrophil transmigration involves CD11b (Integrin alpha M (ITGAM) or macrophage-1 antigen (Mac-1))/CD18 (Integrin beta chain-2) interaction with epithelial cell ligands including fucosylated glycoproteins [115]. The neutrophil adherence to the epithelium is facilitated by HIF-1 (Hypoxia-inducible factor-1)-promoted β_2 integrin expression [116]. The epithelial neutrophil transmigration activates protease-activated receptors (PARs) PAR-1 and PAR-2, located on the basolateral surface of the epithelium inducing the GPCR-mediated signaling [115]. This GPCR signaling activates myosin light chain kinase (MLCK)–dependent contraction of the actomyosin ring associated with proteins in the apical epithelial tight and adherence junctions to disrupt epithelial barrier function [115,117,118]. The epithelial cell activation releases the monocyte chemo-attracting chemokines including CCL2 (Monocyte chemoattractant protein-1 (MCP-1)) and CCL5 (RANTES, Regulated upon Activation, normal T cell Expressed and Secreted) to induce the strong transepithelial monocyte migration [119]. The monocytic response depends on CCR2 but not on CCR5 [119]. The transepithelial migration of monocytes depends on adhesion molecules including ICAM-1 (intracellular adhesion molecule-1), VCAM-1 (Vascular cell adhesion molecule-1), CD47 (Integrin-associated protein), and junctional adhesion molecules expressed on epithelial cells that interact with monocyte β1 and β2 integrins and integrin-associated proteins [119–121]. Thus both neutrophil and monocyte interaction with epithelial cells plays a crucial role in inflammation or organ injury including intestinal epithelium (Inflammatory bowel disease, (IBD)), lung epithelium (Acute lung injury (ALI) or acute respiratory syndrome, (ARDS), cystic fibrosis) uroepithelium (pyelonephritis, Acute kidney injury (AKI) causing proteinuria), and gingival epithelium by damaging the epithelial barriers (Fig. 3) [115,121–124].

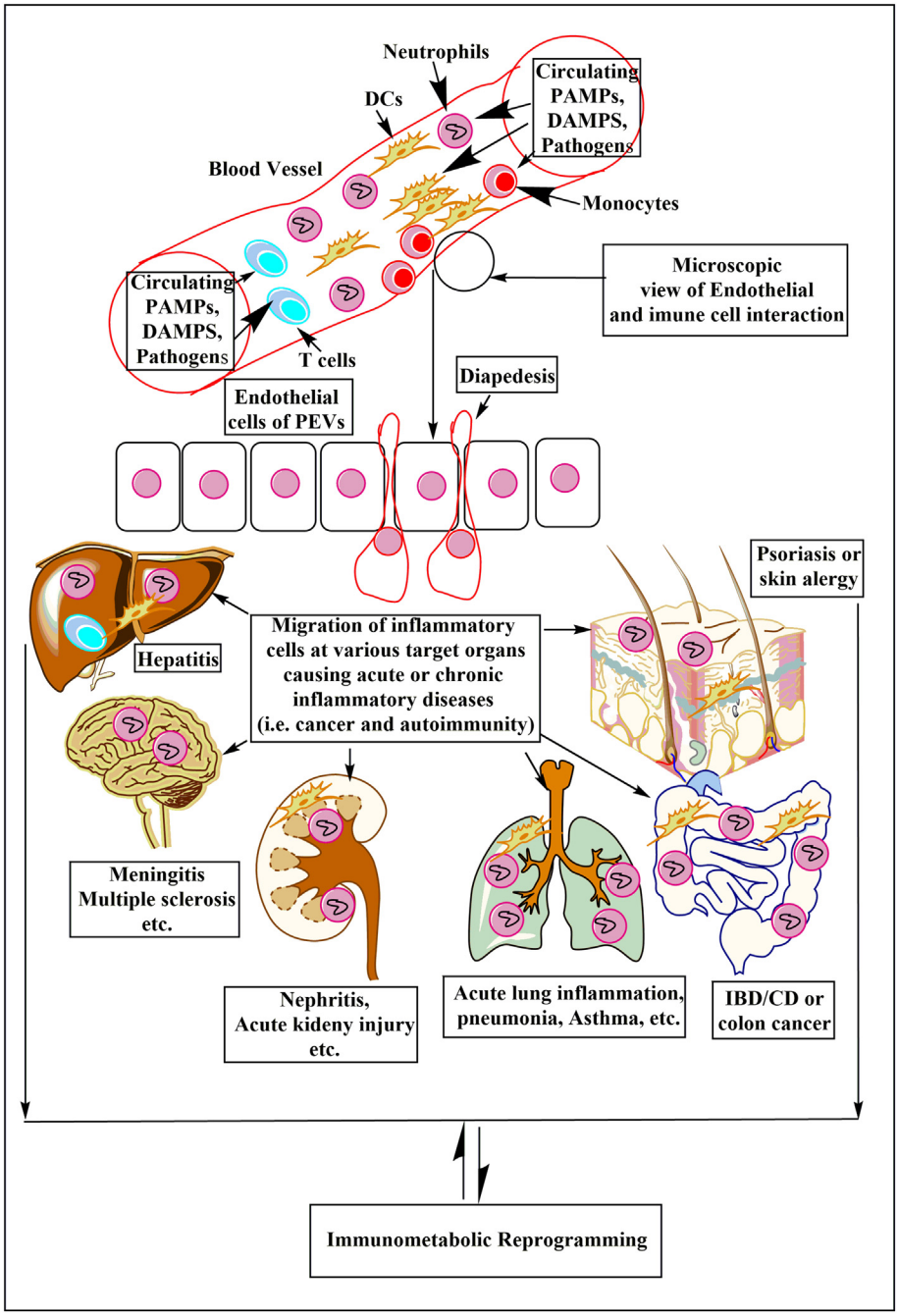

Fig. 3. Schematic representation of systemic activation of immune cells (neutrophils, monocytes, DCs, and T cells), their diapedesis, and migration to distant organs causing target organ inflammation or different organ-specific inflammatory diseases. The circulating PAMPs or DAMPs are recognized by their corresponding PRRs expressed by circulating immune cells as well as endothelial cells lining the blood vessels. This recognition reprograms these cells into their pro-inflammatory state and allows the interaction between endothelial cells and different immune cells to allow the process of diapedesis. Following diapedesis these immune cells are migrated to distant tissues and organs causing acute or chronic inflammatory diseases mentioned. See text for details.

3.2. Endothelial cell and leukocyte interaction during inflammation

The infiltration of inflammatory cells including neutrophils, monocytes (during acute inflammation) and sets of T cells (during chronic inflammation) into the target organs affected with infectious or sterile inflammatory inflammogens from the systemic circulation involves the process of diapedesis (a rapid transmigration of inflammatory cells across the endothelium via the formation of pseudopods) (Fig. 3) [125]. The process of diapedesis occurs at microvasculature of the affected tissue/organ principally known as the postcapillary venules (PCVs) (Fig. 3). The PCVs are the site of the histamine-induced vascular leakage occurring early during the inflammatory process. They serve as the site for leukocyte extravasation [125]. If the inflammatory insult is not very severe, then the endothelial junction regains its integrity. The endothelial-neutrophil interaction during diapedesis involves homophilic interaction followed by the Platelet–endothelial-cell adhesion molecule-1 (PECAM-1, CD31) and CD99 interaction during their transmigration [125,126]. The systemic inflammatory stimuli including, pathogens, PAMPs, and DAMPs induce the pro-inflammatory phenotype among circulating neutrophils and monocytes (an increase in phagocytosis, secretion of pro-inflammatory mediators and cytokines, and the formation of neutrophil or monocyte extracellular traps (NETs or METs)) along with stimulating the inflammatory signaling including Angiopoietin (Ang)/Tie2 signaling and the expression of several adhesion molecules including ICAM-1, VCAM-1, etc. on endothelial cells to promote their adhesion and migration to distant organs (Fig. 3) [127–129]. Furthermore circulating neutrophils and monocytes regulate each other's inflammatory function to contain the systemic infection or inflammation [10,129,130]. The loss of this regulatory network may lead to the uncontrolled inflammation and tissue or organ injury causing organ failure or death of the patient or chronic inflammatory conditions including cancer and autoimmunity

[129,131–133]. However, the irreversible loss in the functional and junctional integrity of the endothelium during severe inflammatory conditions including sepsis may lead to the development of vascular leakage and tissue and organ damage [134]. Thus epithelial cells, endothelial cells, neutrophils, monocytes, macrophages are the major immune cells playing important role in the pathogenesis of inflammation by secreting various pro-inflammatory molecules and cytokines. The different subsets of T cells come in action during chronic inflammatory conditions. However, the pro-inflammatory or anti-inflammatory action of these immune cells is determined by their immunometabolic stage governed by their immunometabolic reprogramming discussed later.

3.3. Endothelial cell and DC interaction during inflammation

DCs (professional APCs) express MHC-II molecules, CD80, CD86, different PRRs, and release various immunoregulatory cytokines and chemokines to impact the immune response [135–137]. In addition to their presence in various organs including mucosal surfaces, skin (Langerhans cells (LCs) and dermal DCs), and lymph nodes, they are also present in the circulation [136]. There are two major subtypes of DCs called myeloid or classical/conventional DCs (mDCs or cDCs), and plasmacytoid DCs (pDCs), the details of their phenotype and immunoregulatory roles are mentioned somewhere else [138,139]. The DCs involved in the process of inflammation are called inflammatory DCs (InfDCs) [140–142]. The inflammation-induced InfDCs ($CD64^+CD11c^+MHCII^+$) are of two types: (1) originates from cDCs called '$CD64^+$ cDCs' and, (2) monocyte-derived $CD64^+$ DCs in inflamed lymph nodes [143]. The $CD64^+$ cDCs are seen in *Listeria monocytogenes* infection in response to type 1 IFNs and activate T cells more potentially than monocyte-derived $CD64^+$ DCs [143]. The monocyte-derived InfDCs or TipDCs (TNFα- and iNOS-producing DCs) develop from monocytes *in situ* at the site of inflammation under the influence of inflammatory stimuli and activate $CD4^+$ and $CD8^+$ T cells along with the induction of Th17 subset of T cells in several infectious and inflammatory diseases including cancers and autoimmune diseases (Rheumatic arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis etc.) [140–142,144–148].

DCs interact with endothelial cells for their migration to the site of inflammation (Fig. 3) and subsequent migration to the secondary lymphoid organs (SLOs) including lymph nodes during autoimmunity, and angiogenesis, a process seen in the tumor microenvironment [149–153]. The DC migration from the site of inflammation to the SLOs (Lymph nodes, Peyer's patches (PP), spleen, tonsils etc.) is also required to present the antigens to T cells through interacting with endothelial cells of high endothelial venules (HEV) of lymphatic vessels [154,155]. These DCs migrating through endothelial layer are called interstitial DCs or migratory DCs [156,157]. The interaction of peripheral blood DCs with the vascular endothelium involves the ICAM-1, E- and P-selectin expressed by endothelial cells and this interaction increases by the stimuli increasing the atherogenesis or vascular inflammation or skin inflammation as rapid recruitment of DCs occurs during cutaneous inflammation [158,159]. However, the increased production of nitric oxide (NO·) by endothelial cells due to the enhanced endothelial nitric oxide synthase (eNOS) activity prevents this interaction. The CXCL12, CCL5, and CCL2 serve as major chemoattractants for cDCs for their transendothelial migration generated during inflammatory conditions [160,161]. LFA-1 (Leukocyte function-associated antigen-1) on DCs is involved in endothelial-DC interaction by binding to ICAM-1 during endothelial transmigration [162]. Immature DCs interact with brain endothelium during inflammatory conditions via ICAM-1, ICAM-2, platelet-EC adhesion molecule (PECAM)-1, VCAM-1, CD18, and DC-specific ICAM-3-grabbing nonintegrin (DC-SIGN), whereas mature DCs do the same by ICAM-1, CD18, DC-SIGN, and PECAM-1 [163]. The DC-endothelial cell interaction is also seen during cardiorenal syndrome (CRS) involving inflammatory cardiac and renal injury or failure [164]. Thus DC migration is a major step involved in both acute and chronic inflammatory conditions observed during acute trauma or infection-induced inflammation.

3.4. Endothelial and T cell interaction during inflammation

T cells ($CD4^+$ T cells, $CD8^+$ T cells, regulatory T cells (Tregs), and Th17 cells etc.) are mainly involved in chronic inflammation or inflammatory diseases along with autoimmune diseases causing autoinflammation or chronic infection-associated inflammation [165–167]. The migration of circulating T cells to the site of infection or inflammation also involves their interaction with vascular endothelial cells (Fig. 3) [168,169]. Endothelial cells stimulated with potent inflammogens including LPS, IFN-γ, and IL-1β induce the expression of CD69 on $CD8^+CD45RO^+$ T cells and this activation is blocked by inhibiting the ICAM-1 and CD18 expression of endothelial cells [170]. Thus, ICAM-1 and CD18-meidated interaction of T cells with endothelial cells during inflammatory conditions activates their pro-inflammatory action including the production of IFN-γ. IL-15 is also involved in the endothelial transmigration of peripheral blood T cells (PBTLs) [170]. The E- and P-selectin expressed on endothelial cells promote the migration of T effector cells (Teffs) grown in the presence of IL-12 during acute inflammation or skin inflammation [171]. While, ICAM-1 and VAP-1 (Vascular adhesion protein-1) expressed on endothelial cells promote the adherence and migration of $CD8^+$ T cells. The intestinal T cells highly express $\alpha_4\beta_7$-integrin migrate to the sites high in mucosal addressin cell adhesion molecule-1 or MAdCAM-1 (gut mucosa) and vascular cell adhesion molecule-1 or VCAM-1 (Synovial tissues) [172]. It should be noted that both the nature of SLOs including LNs and Peyer's patches (PPs) and their anatomic location impact the endothelial (HEV) transmigration of T cells [173]. Hence T cell and endothelial cell interaction is also crucial during the process of inflammation under diverse conditions.

4. Immunometabolic reprogramming and inflammation

Immunometabolism is an interdisciplinary area of research comprising metabolism and immune system [174]. Immunometabolism further divides into two branches: (1) Cellular immunometabolism and (2) Tissue Immunometabolism. The cellular immunometabolism involves the immunometabolic reprogramming of the immune cells that governs their phenotype and function (Pro-inflammatory or anti-inflammatory action) under different condition (homeostasis or pathological conditions including inflammation, infection or cancer) [174,175]. The tissue Immunometabolism deals with the impact of immune cells and their immunometabolic reprogramming on the tissue/organ and systemic metabolism favoring the transformation required to environmental changes in an individual [174].

4.1. Metabolic reprogramming in epithelial cells during inflammation or inflammatory disease

The inflammatory diseases involving the epithelial cells influence or reprogram their metabolic process or immunometabolism as epithelial cells are also considered as innate immune cells [33,176,177]. For example, an increase in glycolysis in intestinal epithelial cells (IECs) is observed during chronic colitis, inflammatory bowel disease (IBD)/Crohn's disease (CD) or colon cancer [178]. During chronic inflammation of colon an upregulation of key glycolytic enzymes in response to the activation of STAT3/c-Myc signaling pathway is observed like immunometabolic programing observed during early activation of T cells (Fig. 4A) [178]. Furthermore, DUOX (Dual Oxidase), a member of the NADPH oxidase family acts as a first line of defence against enteric pathogens by producing ROS [179]. Also, the increased tumorigenesis of epithelial prostate cancer cells regulates cellular redox mechanisms via mTORC1/c-Myc pathways of stromal glucose and amino acid (AA)

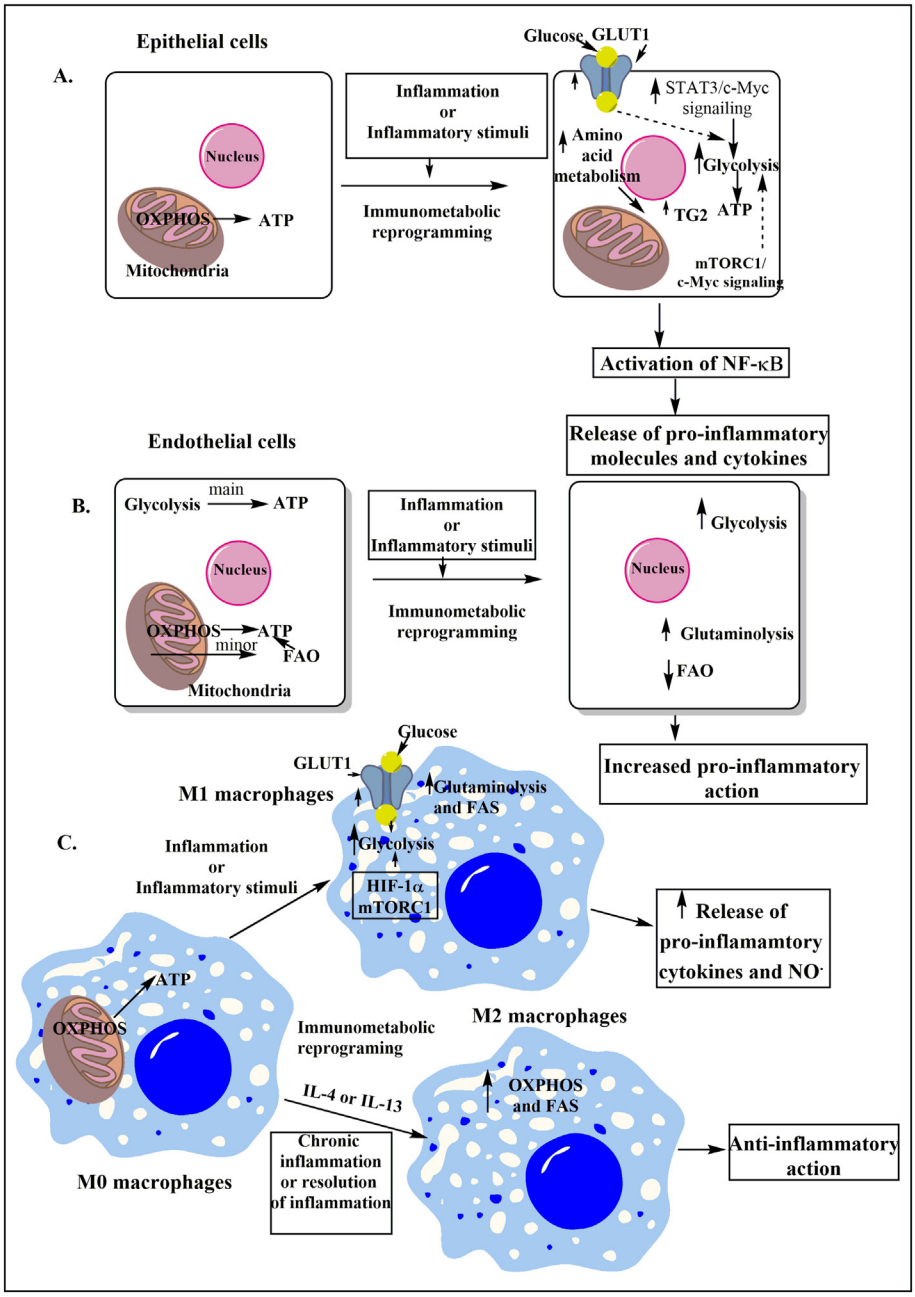

Fig. 4. Schematic representation of immunometabolic reprogramming among epithelial cells (A), endothelial cells (B), and macrophages (C). (A). For example, under normal homeostatic conditions epithelial cells fulfil their energy demand by solely depending on OXPHOS but inflammatory stimuli or inflammatory diseases reprogram their immunometabolic stage. The activated epithelial cells now depend on glycolysis and increased amino acid metabolism for their energy demand. (B). On the other hand, endothelial cells during normal physiological conditions mainly depend on glycolysis as their main energy source and OXPHOS serves as minor source of energy. The inflammatory stimuli induce immunometabolic reprogramming among endothelial cells and the increased glycolysis along with an increased amino acid metabolism is observed. However, the decreased FAO is observed in activated endothelial cells. (C). M0 macrophages or naïve macrophages are dependent on OXPHOS for their ATP demand inflammatory environment reprograms into two different phenotypes: M1 macrophages are pro-inflammatory in nature and exhibit an increased expression of GLUT1 expression for increased glucose intake to support increased glycolysis. In addition to the increased glycolysis, M1 macrophages also show an increased glutaminolysis and FAS. While, M2 macrophages generated during chronic inflammation or resolution of inflammation show increased OXPHOS and FAS. The detailed mechanisms are mentioned in the text.

metabolism to increase the production of IL-6 to promote tumorigenesis in the prostate epithelial cells [180]. TNF-α also induces a Warburg effect (a shift from OXPHOS to glycolysis), increases expression of GLUT1, and facilitates lactate export in breast epithelial cells to further promote inflammation and tumorigenesis [181]. The aberrant expression of transglutaminase 2 (TG2) regulates the Warburg effect responsible for metabolic reprogramming. Hence TG2 by acting as a master regulator of epithelial cell metabolic reprogramming promotes the inflammation by constitutively activating NF-κB [182] (Fig. 4A). NF-κB further activates HIF-1α to increase the glucose uptake (glycolysis), lactate synthesis and decreases the oxygen consumption by mitochondria [182].

The gastrointestinal infection induces “pro-catabolic” signaling in intestinal epithelial cells initiating the metabolic reprogramming of enterocytes towards lipid catabolism or FAO that governs homeostasis of DUOX [179]. The infection initiates the signaling events involving TRAF3 (TNF receptor-associated factor), AMPK (5′adenosine monophosphate kinase), and WTS (Serine/threonine-protein kinase WARTS homolog or Warts kinase) kinases regulating the TOR kinase for controlling the balance between lipogenesis and lipolysis [179]. Tubulointerstitial fibrosis or renal fibrosis both in mice and humans show decreased FAO causing a higher deposition of intracellular lipids [183]. The FAO inhibition severely depletes ATP molecules, induces cell death, dedifferentiation and intracellular lipid deposition in epithelial cells and restoration of metabolic defect or FAO prevents the disease [183]. Thus inflammation-induced metabolic reprogramming among epithelial cells plays a crucial role in infection generated or sterile inflammation.

4.2. Immunometabolic reprogramming among endothelial cells during inflammation

Endothelial cells are one of the major derivers of the inflammation as described earlier. During inflammatory process the

immunometabolic reprogramming of endothelial cells controls their pro-inflammatory function. The endothelial cells highly express pyruvate kinase M2 (PKM2) isoform in comparison to pyruvate kinase M1 (PKM1) that suppresses the activity of tumor suppressor gene p53 and maintains cell cycle of endothelial cells undergoing the process of cell proliferation [184]. The inhibition of PKM2 causes inflammatory endothelial cell damage and the onset of vascular leakage during sepsis. Endothelial cells are mainly dependent on glycolysis instead of OXPHOS for their energy supply during normal conditions (Fig. 4B) [185]. A further increase in the glycolysis fulfils the increased energy demand of ECs during inflammation [185]. The glucose, glutamine, and fatty acid (FA) oxidation contribute to about 15% of the ATP synthesis in endothelial cells by serving as a substrate for the Krebs or tricarboxylic acid (TCA) cycle [186]. FAO acts as another source of the energy to endothelial cells due to the increased expression of CPT1A involved in the transportation of FAs into the mitochondria for FAO and dNTP production [187]. Hypoxia in endothelial cells during inflammation promotes glycolysis, fatty acid synthesis (FAS), and glutaminolysis [188]. However, endothelial cells undergoing inflammatory changes during hypoxia show a decreased FAO [188]. Thus an increased rate of glycolysis and glutaminolysis in endothelial cells subjected to inflammatory stimulus provides an increased energy demand to these cells for their pro-inflammatory action. Further studies in the direction will prove beneficial for therapeutic targeting of inflammation via endothelial cell-specific immunometabolic reprogramming to target endothelial vascular leakage in several inflammatory conditions including sepsis [189].

4.3. Immunometabolic reprogramming among macrophages during inflammation

Monocytes/macrophages during homeostasis or in the absence of any infection or inflammogen do not require frequent and high energy supply, therefore are dependent on OXPHOS for their energy demand by utilizing glucose as the energy source (Fig. 4C) [190]. However, to mount an effective pro-inflammatory immune response (ROS production, phagocytosis, increased migration, and the release of pro-inflammatory cytokines etc.) the energy demand of macrophages increases in the presence of infection or the potent inflammogen that is met by shifting from OXPHOS to a very quick but not a very efficient metabolic pathway called glycolysis [190–192]. For example, glycolysis produces only two ATP molecules per molecule of glucose at a much faster rate in comparison to the OXPHOS. This phenomenon of shifting of OXPHOS to glycolysis is known as Warburg effect [193]. The increase in glycolysis is supported by the increased influx of the glucose due to the increased glucose transporter 1 (GLUT1) expression, causing an increased production of pro-inflammatory molecules including nitric oxide free radical (NO·) (Fig. 4C) [194]. The increased glycolysis in macrophages during inflammatory conditions is accompanied by increased glutaminolysis and FAS (Fig. 4C) [194]. Thus the pro-inflammatory M1 or classically activated macrophages (CAMs) are generated due to the immunometabolic reprogramming in response to the infection or inflammogens and show an increase in glycolysis, FAS, and glutaminolysis [192,194,195].

The immunometabolic shift from OXPHOS to glycolysis in M1 macrophages is induced by HIF-1α and mammalian target of rapamycin (mTOR, a serine/threonine protein kinase) or more precisely mTORC1 (Fig. 3C) [196,197]. The inflammatory stimuli including LPS activate Akt and mTORC1 via B-cell adapter for PI3K (phosphatidyl inositol 3 kinase) (BCAP, an adaptor domain) that increases the surface expression of GLUT1 in M1 macrophages to increase the influx of glucose to further increase the glycolysis [198,199]. Hypoxia is one of the several inducers of the inflammation and HIF (a transcription factor) induced due to tissue or organ hypoxia plays a crucial role in the generation of inflammation and the regulation of the immune response [200–203]. This transcription factor is a heterodimeric protein having two subunits: HIF-1α (its stability is determined by oxygen levels) or HIF-2α and HIF-1 β (also called aryl hydrocarbon receptor nuclear translocator (ARNT) protein) [201]. HIF-1α is present ubiquitously, while HIF-2α is restricted to only certain tissues [202,204]. HIF-1α generated by macrophages during inflammation causes the increased production of IL-1β by increasing the concentration of succinic acid or succinate [205].

PKM2 in macrophages further upregulates the HIF-1α by acting as its cofactor and induces the production of IL-1β to further aggravate the inflammation [206]. HIF-1α also induces the pyruvate dehydrogenase kinase isoform 1 (PDK1) activation to further promote the glycolysis in M1 macrophages and thus the inflammation [207]. Thus HIF-1α in macrophages shows a defective immunometabolic reprogramming towards the generation of M1 macrophages and thus the decreased inflammation. Serine metabolism in macrophages exposed to the inflammogens including LPS is required for the optimal generation of IL-1β mRNA, but not the inflammasome activation [208]. The mechanism involves the generation of glycine from serine that is required for the synthesis of glutathione (GSH) that regulates the induction of IL-1β I macrophages upon exposure to the LPS. The serine is synthesized in macrophages de novo during glycolysis [208]. Furthermore, the inhibition of de novo serine synthesis decreases the LPS-induced IL-1β secretion by macrophages and increases the survival of mice subjected to the sepsis [208]. Thus de novo serine synthesis in macrophages as result of increased glycolysis increases the synthesis of GSH that favors the IL-1β synthesis.

The M2 macrophages or alternatively activated macrophages (AAMs) are anti-inflammatory in nature. These are generated during the resolution phase of inflammation or in response to IL-4 and IL-13, or during the pathogenesis of cancer as cancer-promoting cells. Due to their role in immunosuppression of inflammatory immune response and angiogenesis, these M2 macrophages show an increased OXPHOS and FAO along with a decrease in mTOR signaling (Fig. 4C) [209]. Thus both the Warburg effect (a shift from OXPHOS to glycolysis) and metabolic processes occurring in the cytosol and mitochondria regulate the inflammatory phenotype and function of the macrophages by controlling the genes involved in the activation of macrophages during infection and inflammation [210–212]. The detailed mechanism of immunometabolic regulation of macrophages is described somewhere else [209,213,214].

4.4. Immunometabolic reprogramming among neutrophils during inflammation

Neutrophils are first immune cells migrating towards the site of infection and trauma leading to the development of the inflammation. To phagocytose invading pathogens and kill them via their intracellular killing (ICK) mechanisms (production of ROS and RNS etc.) and to further send the chemotactic signal to chemo-attract further neutrophils and monocytes they require a high energy supply to cope with higher metabolic rate. To overcome the high energy demand for their immunological function neutrophils are dependent on increased glycolysis along with pentose phosphate pathway (PPP) by the high influx of glucose due to the low number of mitochondria [215,216]. The NET formation during inflammation is also dependent on the glycolysis and PPP [217,218]. The defective glycolysis in neutrophils is shown to decrease their pro-inflammatory action, NET formation (called NETosis), antimicrobial action, and phagocytosis [219]. Neutrophils are independent of OXPHOS for their pro-inflammatory function due to a low number of mitochondria instead, show increased glycolysis and PPP. HIF-1α serves as one of the several regulators of glycolysis in neutrophils by increasing the expression of GLUT1 and GLUT3 required for increased uptake of glucose (Fig. 5A) [220,221]. However, mTOR signaling occurring as result of TLR signaling also regulates neutrophil glycolysis by increasing the HIF-1α expression [222,223]. Thus neutrophils immunometabolic reprogramming controls its immunological and inflammatory function.

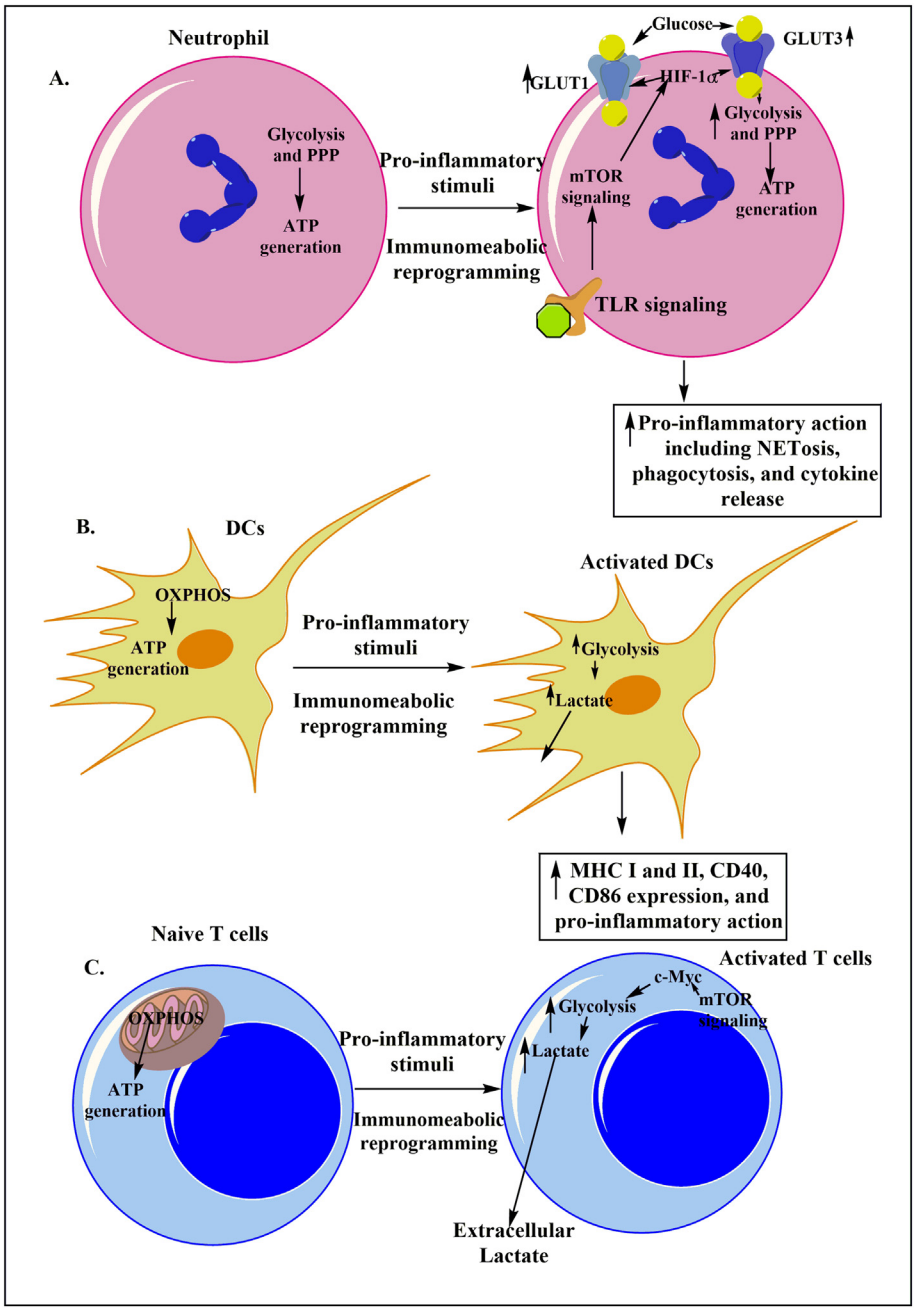

Fig. 5. The schematic representation of immunometabolic reprogramming among neutrophils (A), DCs (B), and T cells (C) during inflammation or inflammatory diseases. (A). Neutrophils during homeostasis use glycolysis and PPP to generate ATP for their energy demand. However, the immunometabolic reprogramming among neutrophils during inflammatory conditions further increase the rate of glycolysis and PPP due to the induction of mTOR signaling and HIF-α induction. (B). DCs during inflammation undergo immunometabolic reprogramming and exhibit increased rate of glycolysis as compared to the DCs not exposed to pro-inflammatory conditions. (C). Naïve T cells mainly depend on OXPHOS for their energy demand inflammatory conditions induce immunometabolic reprogramming among them via increasing the rate of glycolysis and lactate accumulation. The details are mentioned in the text.

4.5. Immunometabolic reprogramming among DCs during inflammation

DCs also depend on OXPHOS for their energy requirement under normal conditions in the absence of infection or any other inflammatory condition or inflammogen to maintain their normal homeostatic function [190,224]. FAO plays a crucial role in OXPHOS of bone marrow-derived dendritic cells (BMDCs), but its role in cDCs and pDCs is not yet clear [225]. Hypoxic conditions develop in inflammatory environment and also exposure of inflammogens to DCs induces transcription and translation of genes inducing HIFs and inflammatory cytokines and chemokines. This transition from their normal steady sate phenotype to the pro-inflammatory phenotype requires steady and frequent supply of energy that is attained by immunometabolic reprogramming inducing transition from OXPHOS to glycolysis (Fig. 5B) [139]. Furthermore, the transition from OXHOS to glycolysis among DCs during inflammation causes the conversion of pyruvate or pyruvic acid (generated during glycolysis) into lactate or lactic acid that gets secreted into extracellular environment (Fig. 5B) [223,225]. The inhibition of glycolysis among DCs inhibits their inflammatory action by inhibiting MHC I and II, CD40, and CD86 expression along with the inhibition of IL-6, IL-12p70, and TNF-α [224]. Thus the inflammatory function of DCs under inflammatory conditions reprograms their immunometabolism into an enhanced glycolysis that further fuels TCA cycle, increases FAS to fuel increased FAO and supports the PPP for their complete activation [139]. The TLR stimulated an early induction of glycolysis among DCs mediated by TBK1, IKKε (I-kappa-B kinase epsilon), and Akt promotes interaction between hexokinase II (HKII) and mitochondria [226]. It is noteworthy that both mouse and human cDCs do not express iNOS and thus are unable to produce NO· and do not exhibit the Warburg effect or the transition from OXPHOS to glycolysis [227]. However, both mTOR signaling and HIF-1α do not play a significant role in the early induction of glycolysis from OXPHOS in DCs that is an AKT-dependent process [226,228]. The loss of AMPK in DCs under inflammatory conditions also supports the

immunometabolic reprogramming from OXPHO to glycolysis [223,229]. Thus drugs or molecules or forceful induction of AMPK may prove as a therapeutic approach to target immune cells including DCs to counter the inflammation or inflammatory diseases. The details of DCs immunometabolic reprogramming are described somewhere else [139,224].

4.6. T cell immunometabolic reprogramming during inflammation

The naïve and quiescent CD4+, CD8+, and CD4 + CD8+ T cells like myeloid cells (neutrophils, monocyte/macrophages, etc.) are also mainly dependent on OXPHOS for their energy requirement [230–232]. For example, 96% of the ATP molecules of naïve T cells are generated by OXPHOS and remaining 4% are generated by glycolysis (Fig. 5C) [233]. The glucose undergone glycolysis, FAO, and AA metabolism including glutaminolysis provide the pyruvate for the process of OXPHOS [230,231]. This glucose influx into the naïve T cells is regulated by the tonic TCR signaling (A low-level TCR signaling occurring in response to self-peptide/MHC molecules and IL-7/IL-7receptor signaling required for the survival of naïve T cells) involving the cell surface trafficking of GLUT1 modulated by PI3K/Akt/mTOR signaling pathway [230,234]. Thus the absence of glucose influx due to the dysregulation of tonic TCR signaling may cause their apoptotic death due to the impaired or decreased expression of GLUT1 [235]. The IL-7/IL-7R signaling maintains normal GLUT1 expression through STAT5 activation causing a sustained activation of Akt-signaling for glucose uptake to prevent naïve T cell apoptosis [234].

It is noteworthy that the deletion of *Glut1* gene selectively limits glycolysis in $CD4^+$, but not in $CD8^+$ T cells that also specifically affects their cellular proliferation accordingly [236,237]. Thus, GLUT family of glucose transporters is important for glucose uptake in $CD8^+$ T cells. However, under chronic inflammatory conditions or during antigenic stimulation and co-stimulation the immunometabolic reprogramming among T cells takes place. Thus a shift from OXPHOS to glycolysis is observed that further increases lactate production and its transport into external cellular environment, FAS or lipid synthesis, nucleotides synthesis, and amino acid (AA) synthesis required for their growth and proliferation (Fig. 5C) [231]. However, FAO or lipid oxidation is decreased but the glutamine oxidation (glutaminolysis) like glycolysis is increased [231]. The immunometabolic reprogramming towards aerobic glycolysis is mainly induced by the induction of c-Myc transcription factor in response to mTOR signaling during early T cell growth and proliferation (Fig. 5C) [238]. The induction of c-Myc in response to the mTOR signaling within the first 24 h following the activation of naive T cells and their transition into Teffs is a very crucial signaling event [239]. The effector $CD4^+$ T cells show increased OXPHOS (up to two fold increase) as compared to the effector $CD8^+$ T cells after activation as these cells do not increase the OXPHOS beyond their resting stage [240]. Thus effector $CD4^+$ T cells can be distinguished from effector $CD8^+$ T cells on the basis of their OXPHOS status and $CD4^+$ effector T cells survive better than $CD8^+$ T cells under conditions limited by pro-glycolytic signals seen during acute lymphocytic choriomeningitis virus (LCMV) infection [241].

The major immunometabolic pathway in Th1, Th2, and Th17 cells generated from $CD4^+$ T cells during inflammatory conditions including cancer and autoimmunity comprises of aerobic glycolysis [231]. The immunometabolic pathway involved in the generation of Th17

cells involves the PI3K-Akt-mTORC1-S6K1 signaling axis suppressing the Gfi1 (a zinc finger protein) that acts as a transcriptional repressor protein [242]. Additionally, S6K1 by binding to the RORγt transports it into the nucleus for inducing the genes responsible for the functional phenotype of Th17 cells [242]. The absence of mTORC1 signaling in $CD4^+$ T cells prevents their transition into Th1 and Th17 cells without affecting their differentiation into Th2 immune cells [243,244]. However, the induction of Th2 cells from $CD4^+$ T cells in the absence of mTORC2 is inhibited [243]. Thus the induction of HIF-1α, mTORC1 signaling pathway due to the increased glycolysis, glutaminolysis in $CD4^+$T cells may induce the generation of Th17 cells during inflammation including sepsis [245]. The pro-inflammatory action of Th17 cells depends on TCR engagement causing the influx of calcium (Ca^{2+}) from endoplasmic reticulum (ER) due the action of second messenger called inositol-1,4,5-triphosphate (IP3). The intracellular Ca^{2+} activates stromal interaction molecule 1 (STIM1) and STIM2 localized in ER membrane [246]. The activated STIM1 binds to and opens ORAI1 (CRACM1,), the pore forming subunit of the Ca^{2+} influx through Ca^{2+}-release-activated Ca^{2+} channel (CRAC) providing the Ca^{2+} influx in bulk (called store-operated Ca^{2+} entry, or SOCE) after TCR stimulation [247–249]. The STIM1-mediated influx of Ca^{2+} upregulates mitochondrial ETC and OXPHOS and decreases the ROS generation enhancing the pro-inflammatory function of Th17 in the inflammatory environment [247]. Thus Ca^{2+} influx in Th17 cells regulates their pro-inflammatory function by inducing immunometabolic reprogramming towards their inflammatory phenotype and function.

The regulatory T cells (Tregs) are generated during inflammatory conditions to suppress the severity of the inflammation, and their deficiency or inhibition of their generation from $CD4^+$ T cells aggravates the inflammatory immune response. Due to the low expression of GLUT1 by Tregs as compared to the other Teffs, Tregs are not dependent on aerobic glycolysis for their energy demand instead use lipid oxidation or FAO for this process [250–253]. Resolution of the inflammation causes the apoptotic death of the majority of Teffs. The leftover Teffs become memory T cells (Tmems) and enhance immunity upon re-exposure to the same antigen including tumor antigens, inflammogen or pathogen [254–256]. Tmems are long living cells with lower turnover rates requiring a unique metabolic demand. Therefore Tmems exhibit a decreased mTOR signaling and exhibit FAO or lipid oxidation for their immunometabolic demand [257]. Tmems also have great number of spare respiratory capacity (SRC) in their mitochondria to produce a rapid and high number of ATP molecules upon secondary exposure to the same antigen or inflammogen [258–260]. IL-15 is a critical cytokine for $CD8^+$ Tmems regulating SRC and oxidative metabolism of FAs by promoting the mitochondrial biogenesis and the expression of carnitine palmitoyltransferase (CPT1a), a metabolic enzyme regulating the rate limiting step of FAO [258,259,261]. Tmems can increase their use of FAs for energy via OXPHOS decreasing their dependency on aerobic glycolysis due to increased number of mitochondria [238,261]. Hence Tmems show a higher survival rate as compared to Teffs in the absence of pro-glycolysis signals including the stage where the initial priming antigen is absent or eliminated and cytokines including IL-2 dissipate. Thus immunometabolic reprogramming of different sets of T cells including Tmems is an essential step in their immunoregulatory or immunopathogenic role during inflammation and various inflammatory diseases. Hence immunometabolic reprogramming among immune cells is a crucial event to mount an inflammatory immune response.

5. Therapeutic targeting of inflammation/inflammatory diseases via immunometabolism

The immunometabolic reprogramming among immune cells in the event of inflammation or inflammatory diseases is an essential process to regulate their pro- or anti-inflammatory action. Rheumatic inflammatory diseases including RA, osteoarthritis (OA), and SLE also involve immunometabolic reprogramming among immune cells responsible for the inflammatory phenotype [262–264]. Thus targeting their immunometabolic stage may prove as a novel therapeutic approach to control the inflammation or inflammatory organ damage or its failure observed during sepsis or other inflammatory diseases. For example, methotrexate (belongs to the class of drug called antimetabolites) used in cancer and autoimmune diseases including psoriasis and RA acts by inhibiting Janus kinase (JAK)–STAT (Signal transducer and activator) signaling pathway involved in the

inflammation and associated immune response [265]. However, it also exerts its anti-inflammatory action by altering the immunometabolic stage of immune cells involved in the process by targeting one-carbon metabolism involved in AA metabolism and nucleotide biosynthesis [266,267]. The targeting of AA metabolism in inflammatory immune cells by methotrexate potentially inhibits their growth, the redox balance (involved in inflammasome activation that further aggravates inflammation), and epigenetic reprogramming supporting inflammatory immune response [266].

The targeting of immunometabolic reprogramming (OXPHOS → Glycolysis) among $CD4^+$ T cells by 2-deoxy-D-glucose (2-DG) in combination with metformin has inhibited the release of pro-inflammatory IFN-γ and autoantibody production in the animal model of SLE [268]. The metformin restores the production of defective IL-12 by $CD4^+$ T cell in lupus-prone B6.Sle1.Sle2.Sle3 (TC) mice by impacting mitochondrial oxidative metabolism [268]. Thus 2-DG and metformin overcome the inflammatory phenotype of SLE by normalizing the pro-inflammatory T cell immunometabolism. The combination of 2-DG and metformin in the presence of an inhibitor of glutaminolysis called 6-diazo-5-oxo-L-norleucine (DON) inhibits the T cell-mediated inflammatory mechanism involved in organ transplantation [269]. The process involves the immunometabolic reprogramming among $CD4^+$ T cells towards the anti-inflammatory phenotype notably regulatory T cells (Tregs) and the inhibition of Teffs [269,270]. In addition to targeting inflammation associated with autoimmune diseases, targeting immunometabolic reprogramming may serve as a novel approach to manage systemic inflammation or sepsis [189,209,271]. For example, a plant-derivative plumbagin extracted from the roots of the plant called *Plumbago zeylanica* exerts anti-inflammatory action by inhibiting the enzyme PKM2 responsible for the glycolysis-induced pro-inflammatory action of the macrophages [272].

AMPK is a conserved serine/threonine kinase and its decreased activity in M1 macrophages and Th17 cells is associated with their pro-inflammatory phenotype during inflammation and tumorigenesis [273]. The decreased AMPK activity in pathogenic or pro-inflammatory T cells is associated with the defective function of N-myristoyltransferase 1 (NMT1) [274]. The NMT1 attaches fatty acid myristate to the N-terminal glycine of the protein for sorting them into soluble and membrane-bound fractions and AMPK works in a myristoylation-dependent manner [274]. The defective NMT1 function prevents AMPK activation and overly activates unopposed mTORC1 signaling shifting T cells towards their pro-inflammatory phenotype (Th1 and Th17 cells) and function [274]. The protective action of NMT1 involves lipidic modification of the AMPK (myristoylation) to its lysosomal recruitment for its activation. Thus deficiency of NMT1 causes severe inflammation (synovial tissue inflammation) by suppressing the function of AMPK and unopposed activation of mTORC1 signaling in T cells. Thus forced expression of NMT1 may serve as an anti-inflammatory approach by directly affecting immunometabolic reprogramming through impacting AMPK and mTORC1 signaling in T cells.

AMPK promotes the anti-inflammatory action of M2 macrophages and Tregs by modulating the pro-inflammatory immunometabolic reprogramming that is inhibiting the transition from OXPHOS to glycolysis to induce the stage of pseudostarvation and arresting the cell cycle [273]. Thus drugs with a potential to increase the AMPK levels and activity in immune cells during inflammation have a potential to target immunometabolism. The AMPK is activated by several anti-inflammatory agents including 2-DG, AICA riboside (AICAR or Acadesine or 5-Aminoimidazole-4-carboxamide-1-β–ribofuranoside), metformin, berberine (a natural plant-derivative used in traditional Chinese medicine), and A-769662, derived from a high-throughput screen for AMPK activator [275–277]. For example, AICAR, an AMP analog has a potential to use in severe inflammatory conditions including sepsis and associated organ injury [278,279]. Thus activation of AMPK may serve as a potential strategy to target inflammation via modulating immunometabolic reprogramming. The immunomodulatory action of recombinant human IL-7 (rhIL-7 or CYT107) also involves its impact on immunometabolism involving mTOR signaling, GLUT1 expression and glucose uptake by conventional ($CD4^+$ and $CD8^+$) T cells [280]. The clinical trial of rhIL-7 in sepsis has shown promising results as an immunoadjuvant approach for sepsis by targeting the immunometabolism of conventional T cells to increase their number [281]. Thus immunometabolism has a great potential for designing therapeutics to target inflammation and inflammatory diseases.

6. Conclusion

Inflammation is a very complex and diverse immunological process depending on the involvement of immune cells in the pathogenesis, its severity, inducing agent including infections, trauma or cancerous environment etc., and the duration of its pathogenesis (Acute versus chronic inflammation). The immune cells are first line of defence and their activation is the major player in the induction of inflammatory immune response and the pathogenesis of various inflammatory diseases including sterile inflammatory diseases, autoimmunity, and cancer. However, the induction pro-inflammatory or anti-inflammatory action of immune cells depends on their immunometabolic stage governed by the process of immunometabolic reprogramming. For example, inflammatory signals support anabolic metabolic processes required to the generate pro-inflammatory immune response [282]. However, naïve and Tmems depend on catabolic metabolic process (OXPHOS and FAO) for their energy requirement [282]. The TLR9 agonist called CpG-ODN-mediated stimulation of macrophages alters their immunometabolic stage and increases their antitumor action and phagocytic action against $CD47^+$ cancer cells [283]. For example, this increases the FAO among macrophages shunts the TCA cycle intermediates towards the de novo production of FAs through the activation of CPT1A and ATP citrate lyase imparting these macrophages as antitumor potential [283]. Targeting immunometabolic reprogramming of immune cells comprises a novel therapeutic approach for inflammation and inflammatory diseases including autoimmunity. The present article is written in a way to introduce the concept of immunometabolism, its involvement in the regulation of inflammation by describing the immunometabolic reprogramming of different immune cells serving as sentinel inflammatory cells in the pathogenesis of both acute and chronic inflammation and inflammatory diseases. Thus the long journey of inflammation research has sailed the sea of immunology to get ashore called immunometabolism for better cell-specific immunotherapeutic or immunomodulatory approach.

Declaration of competing interest

Author declares no conflict of interest.

Disclosure statement

Author generated the idea, searched for the literature, developed the concept, and wrote the manuscript independently.

References

[1] V. Ballakur, Inflammation in ayurveda and modern medicine, International Ayurvedic Medical Journal 1 (4) (2013).
[2] K.V.S. Rao, Immunology in India: an emerging story, Nature immunology 9 (2008) 1319.
[3] V.N. Sumantran, G. Tillu, Cancer, inflammation, and insights from ayurveda, Evidence-based Complementary and Alternative Medicine : eCAM 2012 (2012) (306346-306346).
[4] M. Rocha, e Silva, A brief survey of the history of inflammation. 1978, Agents and actions 43 (3–4) (1994) 86–90.
[5] K. Ley, History of inflammation research, in: K. Ley (Ed.), Physiology of Inflammation, Springer New York, New York, NY, 2001, pp. 1–10.
[6] A. Scott, K.M. Khan, J.L. Cook, V. Duronio, What is "inflammation"? Are we ready to move beyond Celsus? British Journal of Sports Medicine 38 (3) (2004) 248–249.
[7] J.N. Fullerton, D.W. Gilroy, Resolution of inflammation: a new therapeutic

frontier, Nature Reviews Drug Discovery 15 (2016) 551.
[8] V. Kumar, A. Ahmad, Role of MAIT cells in the immunopathogenesis of inflammatory diseases: new players in old game, Int Rev Immunol (2017) 1–21.
[9] V. Kumar, Innate lymphoid cells: new paradigm in immunology of inflammation, Immunology Letters 157 (1–2) (2014) 23–37.
[10] V. Kumar, A. Sharma, Neutrophils: Cinderella of innate immune system, International Immunopharmacology 10 (11) (2010) 1325–1334.
[11] V. Kumar, A. Sharma, Mast cells: emerging sentinel innate immune cells with diverse role in immunity, Molecular Immunology 48 (1–3) (2010) 14–25.
[12] E. Weiss, D. Kretschmer, Formyl-peptide receptors in infection, inflammation, and cancer, Trends in Immunology 39 (10) (2018) 815–829.
[13] T. Kawai, S. Akira, The roles of TLRs, RLRs and NLRs in pathogen recognition Int Immunol. 21:313, International Immunology 21 (4) (2009) 317–337.
[14] T.-D. Kanneganti, M. Lamkanfi, G. Núñez, Intracellular NOD-like receptors in host defense and disease, Immunity 27 (4) (2007) 549–559.
[15] N. Munoz-Wolf, E.C. Lavelle, Innate immune receptors, Methods in Molecular Biology (Clifton, N.J.) 1417 (2016) 1–43.
[16] R.D. Ye, F. Boulay, J.M. Wang, C. Dahlgren, C. Gerard, M. Parmentier, C.N. Serhan, P.M. Murphy, International union of basic and clinical pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family, Pharmacological Reviews 61 (2) (2009) 119–161.
[17] H.Q. He, R.D. Ye, The formyl peptide receptors: diversity of ligands and mechanism for recognition, Molecules (Basel, Switzerland) 22 (3) (2017).
[18] H. Forsman, M. Winther, M. Gabl, S.L. Skovbakke, F. Boulay, M.J. Rabiet, C. Dahlgren, Structural changes of the ligand and of the receptor alters the receptor preference for neutrophil activating peptides starting with a formylmethionyl group, Biochimica et Biophysica Acta 1853 (1) (2015) 192–200.
[19] M. Liu, K. Chen, T. Yoshimura, Y. Liu, W. Gong, Y. Le, J.L. Gao, J. Zhao, J.M. Wang, A. Wang, Formylpeptide receptors mediate rapid neutrophil mobilization to accelerate wound healing, PloS One 9 (6) (2014) e90613.
[20] D.A. Dorward, C.D. Lucas, M.K. Doherty, G.B. Chapman, E.J. Scholefield, A. Conway Morris, J.M. Felton, T. Kipari, D.C. Humphries, C.T. Robb, A.J. Simpson, P.D. Whitfield, C. Haslett, K. Dhaliwal, A.G. Rossi, Novel role for endogenous mitochondrial formylated peptide-driven formyl peptide receptor 1 signalling in acute respiratory distress syndrome, Thorax 72 (10) (2017) 928–936.
[21] D. Kretschmer, M. Rautenberg, D. Linke, A. Peschel, Peptide length and folding state govern the capacity of staphylococcal beta-type phenol-soluble modulins to activate human formyl-peptide receptors 1 or 2, Journal of Leukocyte Biology 97 (4) (2015) 689–697.
[22] D. Kretschmer, N. Nikola, M. Durr, M. Otto, A. Peschel, The virulence regulator Agr controls the staphylococcal capacity to activate human neutrophils via the formyl peptide receptor 2, Journal of Innate Immunity 4 (2) (2012) 201–212.
[23] D. Kretschmer, A.K. Gleske, M. Rautenberg, R. Wang, M. Koberle, E. Bohn, T. Schoneberg, M.J. Rabiet, F. Boulay, S.J. Klebanoff, K.A. van Kessel, J.A. van Strijp, M. Otto, A. Peschel, Human formyl peptide receptor 2 senses highly pathogenic *Staphylococcus aureus*, Cell Host & Microbe 7 (6) (2010) 463–473.
[24] M. Liu, K. Chen, T. Yoshimura, Y. Liu, W. Gong, A. Wang, J.L. Gao, P.M. Murphy, J.M. Wang, Formylpeptide receptors are critical for rapid neutrophil mobilization in host defense against *Listeria monocytogenes*, Scientific Reports 2 (2012) 786.
[25] D.A. Bloes, M. Otto, A. Peschel, D. Kretschmer, *Enterococcus faecium* stimulates human neutrophils via the formyl-peptide receptor 2, PloS One 7 (6) (2012) e39910.
[26] A. Betten, J. Bylund, T. Christophe, F. Boulay, A. Romero, K. Hellstrand, C. Dahlgren, A proinflammatory peptide from Helicobacter pylori activates monocytes to induce lymphocyte dysfunction and apoptosis, J Clin Invest 108 (8) (2001) 1221–1228.
[27] X. Deng, H. Ueda, S.B. Su, W. Gong, N.M. Dunlop, J.L. Gao, P.M. Murphy, J.M. Wang, A synthetic peptide derived from human immunodeficiency virus type 1 gp120 downregulates the expression and function of chemokine receptors CCR5 and CXCR4 in monocytes by activating the 7-transmembrane G-protein-coupled receptor FPRL1/LXA4R, Blood 94 (4) (1999) 1165–1173.
[28] S.B. Su, W.H. Gong, J.L. Gao, W.P. Shen, M.C. Grimm, X. Deng, P.M. Murphy, J.J. Oppenheim, J.M. Wang, T20/DP178, an ectodomain peptide of human immunodeficiency virus type 1 gp41, is an activator of human phagocyte N-formyl peptide receptor, Blood 93 (11) (1999) 3885–3892.
[29] S. Oldekamp, S. Pscheidl, E. Kress, O. Soehnlein, S. Jansen, T. Pufe, J.M. Wang, S.C. Tauber, L.O. Brandenburg, Lack of formyl peptide receptor 1 and 2 leads to more severe inflammation and higher mortality in mice with of pneumococcal meningitis, Immunology 143 (3) (2014) 447–461.
[30] A. Kantarci, N. Aytan, I. Palaska, D. Stephens, L. Crabtree, C. Benincasa, B.G. Jenkins, I. Carreras, A. Dedeoglu, Combined administration of resolvin E1 and lipoxin A4 resolves inflammation in a murine model of Alzheimer's disease, Experimental Neurology 300 (2018) 111–120.
[31] N. Prevete, F. Liotti, G. Marone, R.M. Melillo, A. de Paulis, Formyl peptide receptors at the interface of inflammation, angiogenesis and tumor growth, Pharmacological Research 102 (2015) 184–191.
[32] H.Y. Lee, M. Lee, Y.S. Bae, Formyl peptide receptors in cellular differentiation and inflammatory diseases, Journal of Cellular Biochemistry 118 (6) (2017) 1300–1307.
[33] R.P. Schleimer, A. Kato, R. Kern, D. Kuperman, P.C. Avila, Epithelium: at the interface of innate and adaptive immune responses, The Journal of Allergy and Clinical Immunology 120 (6) (2007) 1279–1284.
[34] T. Kawai, S. Akira, The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors, Nature Immunology 11 (5) (2010) 373–384.
[35] V. Kumar, Toll-like receptors in immunity and inflammatory diseases: past, present, and future, International Immunopharmacology 59 (2018) 391–412.
[36] H. Hemmi, O. Takeuchi, T. Kawai, T. Kaisho, S. Sato, H. Sanjo, M. Matsumoto, K. Hoshino, H. Wagner, K. Takeda, S. Akira, A Toll-like receptor recognizes bacterial DNA, Nature 408 (6813) (2000) 740–745.
[37] S.E. Keating, M. Baran, A.G. Bowie, Cytosolic DNA sensors regulating type I interferon induction, Trends in Immunology 32 (12) (2011) 574–581.
[38] T. Kawasaki, T. Kawai, Toll-like receptor signaling pathways, Front Immunol 5 (2014) 461.
[39] M.K. Vidya, V.G. Kumar, V. Sejian, M. Bagath, G. Krishnan, R. Bhatta, Toll-like receptors: significance, ligands, signaling pathways, and functions in mammals, Int Rev Immunol (2017) 1–17.
[40] S. Akira, K. Takeda, Toll-like receptor signalling, nature reviews. Immunology 4 (7) (2004) 499–511.
[41] V. Kumar, Toll-like receptors in the pathogenesis of neuroinflammation, Journal of Neuroimmunology 332 (2019) 16–30.
[42] B.K. Davis, H. Wen, J.P. Ting, The inflammasome NLRs in immunity, inflammation, and associated diseases, Annual Review of Immunology 29 (2011) 707–735.
[43] J.P. Ting, B.K. Davis, CATERPILLER: a novel gene family important in immunity, cell death, and diseases, Annual Review of Immunology 23 (2005) 387–414.
[44] J. Tschopp, F. Martinon, K. Burns, NALPs: a novel protein family involved in inflammation, nature reviews. Molecular Cell Biology 4 (2) (2003) 95–104.
[45] Inohara, Chamaillard, C. McDonald, G. Nunez, NOD-LRR proteins: role in host-microbial interactions and inflammatory disease, Annual Review of Biochemistry 74 (2005) 355–83.
[46] J.P.Y. Ting, J.A. Duncan, Y. Lei, How the noninflammasome NLRs function in the innate immune system, Science (New York, N.Y.) 327 (5963) (2010) 286–290.
[47] M.H. Shaw, T. Reimer, Y.G. Kim, G. Nunez, NOD-like receptors (NLRs): bona fide intracellular microbial sensors, Current Opinion in Immunology 20 (4) (2008) 377–382.
[48] F. Martinon, J. Tschopp, NLRs join TLRs as innate sensors of pathogens, Trends in Immunology 26 (8) (2005) 447–454.
[49] X.M. Wu, W.Q. Chen, Y.W. Hu, L. Cao, P. Nie, M.X. Chang, RIP2 is a critical regulator for NLRs signaling and MHC antigen presentation but not for MAPK and PI3K/Akt pathways, Front Immunol 9 (2018) 726.
[50] F. Staehli, K. Ludigs, L.X. Heinz, Q. Seguin-Estevez, I. Ferrero, M. Braun, K. Schroder, M. Rebsamen, A. Tardivel, C. Mattmann, H.R. MacDonald, P. Romero, W. Reith, G. Guarda, J. Tschopp, NLRC5 deficiency selectively impairs MHC class I- dependent lymphocyte killing by cytotoxic T cells, Journal of immunology (Baltimore, Md.: 1950) 188 (8) (2012) 3820–3828.
[51] S.T. Chelbi, A.T. Dang, G. Guarda, Emerging major histocompatibility complex class I-related functions of NLRC5, Advances in Immunology 133 (2017) 89–119.
[52] C.R. Lupfer, K.L. Stokes, T. Kuriakose, T.D. Kanneganti, Deficiency of the NOD-like receptor NLRC5 results in decreased CD8(+) T cell function and impaired viral clearance, Journal of Virology 91 (17) (2017).
[53] Y. Yao, Y. Wang, F. Chen, Y. Huang, S. Zhu, Q. Leng, H. Wang, Y. Shi, Y. Qian, NLRC5 regulates MHC class I antigen presentation in host defense against intracellular pathogens, Cell Res 22 (5) (2012) 836–847.
[54] J.P. Ting, R.C. Lovering, E.S. Alnemri, J. Bertin, J.M. Boss, B.K. Davis, R.A. Flavell, S.E. Girardin, A. Godzik, J.A. Harton, H.M. Hoffman, J.P. Hugot, N. Inohara, A. Mackenzie, L.J. Maltais, G. Nunez, Y. Ogura, L.A. Otten, D. Philpott, J.C. Reed, W. Reith, S. Schreiber, V. Steimle, P.A. Ward, The NLR gene family: a standard nomenclature, Immunity 28 (3) (2008) 285–287.
[55] V. Kumar, Inflammasomes: Pandora's box for sepsis, J Inflamm Res 11 (2018) 477–502.
[56] H. Guo, J.B. Callaway, J.P. Ting, Inflammasomes: mechanism of action, role in disease, and therapeutics, Nature Medicine 21 (7) (2015) 677–687.
[57] H. Wen, Edward A. Miao, Jenny P.Y. Ting, Mechanisms of NOD-like receptor-associated inflammasome activation, Immunity 39 (3) (2013) 432–441.
[58] R. Weinlich, A. Oberst, H.M. Beere, D.R. Green, Necroptosis in development, inflammation and disease, Nature reviews. Molecular Cell Biology 18 (2) (2017) 127–136.
[59] B. Shan, H. Pan, A. Najafov, J. Yuan, Necroptosis in development and diseases, Genes & development 32 (5–6) (2018) 327–340.
[60] J.P.Y. Ting, S.B. Willingham, D.T. Bergstralh, NLRs at the intersection of cell death and immunity, Nature Reviews Immunology 8 (2008) 372.
[61] H. Zhao, T. Jaffer, S. Eguchi, Z. Wang, A. Linkermann, D. Ma, Role of necroptosis in the pathogenesis of solid organ injury, Cell Death & Disease 6 (2015) e1975.
[62] K. Newton, G. Manning, Necroptosis and Inflammation, Annual Review of Biochemistry 85 (2016) 743–763.
[63] A.M. Keestra-Gounder, M.X. Byndloss, N. Seyffert, B.M. Young, A. Chavez-Arroyo, A.Y. Tsai, S.A. Cevallos, M.G. Winter, O.H. Pham, C.R. Tiffany, M.F. de Jong, T. Kerrinnes, R. Ravindran, P.A. Luciw, S.J. McSorley, A.J. Baumler, R.M. Tsolis, NOD1 and NOD2 signalling links ER stress with inflammation, Nature 532 (7599) (2016) 394–397.
[64] D. Corridoni, A. Simmons, Innate immune receptors for cross-presentation: the expanding role of NLRs, Molecular Immunology (2017), https://doi.org/10.1016/j.molimm.2017.11.028 (in press).
[65] E.M. Creagh, L.A.J. O'Neill, TLRs, NLRs and RLRs: a trinity of pathogen sensors that co-operate in innate immunity, Trends in Immunology 27 (8) (2006) 352–357.
[66] Y.-M. Loo, M. Gale, Jr., Immune signaling by RIG-I-like receptors, Immunity 34 (5) (2011) 680–692.
[67] M. Yoneyama, M. Kikuchi, T. Natsukawa, N. Shinobu, T. Imaizumi, M. Miyagishi, K. Taira, S. Akira, T. Fujita, The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses, Nat Immunol 5 (7) (2004) 730–737.
[68] H.-Y. Guo, X.-C. Zhang, R.-Y. Jia, Toll-like receptors and RIG-I-like receptors play

important roles in resisting flavivirus, Journal of Immunology Research 2018 (2018) 7.
[69] D.C. Kang, R.V. Gopalkrishnan, Q. Wu, E. Jankowsky, A.M. Pyle, P.B. Fisher, mda-5: an interferon-inducible putative RNA helicase with double-stranded RNA-dependent ATPase activity and melanoma growth-suppressive properties, Proceedings of the National Academy of Sciences of the United States of America 99 (2) (2002) 637–642.
[70] K. Onoguchi, M. Yoneyama, T. Fujita, Retinoic acid-inducible gene-I-like receptors, Journal of Interferon & Cytokine Research 31 (1) (2011) 27–31.
[71] R.B. Seth, L. Sun, Z.J. Chen, Antiviral innate immunity pathways, Cell Res 16 (2) (2006) 141–147.
[72] B. Qi, Y. Huang, D. Rowe, G. Halliday, VISA–a pass to innate immunity, The International Journal of Biochemistry & Cell Biology 39 (2) (2007) 287–291.
[73] K. Eisenacher, A. Krug, Regulation of RLR-mediated innate immune signaling–it is all about keeping the balance, European Journal of Cell Biology 91 (1) (2012) 36–47.
[74] A.M. Kell, M. Gale Jr., RIG-I in RNA virus recognition, Virology 479–480 (2015) 110–121.
[75] J.S. Errett, M. Gale, Emerging complexity and new roles for the RIG-I-like receptors in innate antiviral immunity, Virologica Sinica 30 (3) (2015) 163–173.
[76] D.J. Connolly, A.G. Bowie, The emerging role of human PYHIN proteins in innate immunity: Implications for health and disease, Biochemical Pharmacology 92 (3) (2014) 405–414.
[77] A. Dempsey, A.G. Bowie, Innate immune recognition of DNA: a recent history, Virology 479–480 (2015) 146–152.
[78] L. Unterholzner, S.E. Keating, M. Baran, K.A. Horan, S.B. Jensen, S. Sharma, C.M. Sirois, T. Jin, E. Latz, T.S. Xiao, K.A. Fitzgerald, S.R. Paludan, A.G. Bowie, IFI16 is an innate immune sensor for intracellular DNA, Nature Immunology 11 (2010) 997.
[79] T.L. Roberts, A. Idris, J.A. Dunn, G.M. Kelly, C.M. Burnton, S. Hodgson, L.L. Hardy, V. Garceau, M.J. Sweet, I.L. Ross, D.A. Hume, K.J. Stacey, HIN-200 proteins regulate caspase activation in response to foreign cytoplasmic DNA, Science 323 (5917) (2009) 1057–1060.
[80] T. Jin, A. Perry, J. Jiang, P. Smith, J.A. Curry, L. Unterholzner, Z. Jiang, G. Horvath, V.A. Rathinam, R.W. Johnstone, V. Hornung, E. Latz, A.G. Bowie, K.A. Fitzgerald, T.S. Xiao, Structures of the HIN domain:DNA complexes reveal ligand binding and activation mechanisms of the AIM2 inflammasome and IFI16 receptor, Immunity 36 (4) (2012) 561–571.
[81] S.R. Morrone, M. Matyszewski, X. Yu, M. Delannoy, E.H. Egelman, J. Sohn, Assembly-driven activation of the AIM2 foreign-dsDNA sensor provides a polymerization template for downstream ASC, Nat Commun 6 (2015) 7827.
[82] N. Shaw, Z.J. Liu, Role of the HIN domain in regulation of innate immune responses, Mol. Cell. Biol. 34 (1) (2014) 2–15, https://doi.org/10.1128/MCB.00857-13.
[83] M. Matyszewski, S.R. Morrone, J. Sohn, Digital signaling network drives the assembly of the AIM2-ASC inflammasome, Proceedings of the National Academy of Sciences 115 (9) (2018) E1963–E1972.
[84] T. Fernandes-Alnemri, J.W. Yu, P. Datta, J. Wu, E.S. Alnemri, AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA, Nature 458 (7237) (2009) 509–513.
[85] V. Hornung, A. Ablasser, M. Charrel-Dennis, F. Bauernfeind, G. Horvath, D.R. Caffrey, E. Latz, K.A. Fitzgerald, AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC, Nature 458 (7237) (2009) 514–518.
[86] T. Burckstummer, C. Baumann, S. Bluml, E. Dixit, G. Durnberger, H. Jahn, M. Planyavsky, M. Bilban, J. Colinge, K.L. Bennett, G. Superti-Furga, An orthogonal proteomic-genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome, Nat Immunol 10 (3) (2009) 266–272.
[87] L. Corrales, S.R. Woo, J.B. Williams, S.M. McWhirter, T.W. Dubensky Jr., T.F. Gajewski, Antagonism of the STING pathway via activation of the AIM2 inflammasome by intracellular DNA, Journal of Immunology (Baltimore, Md.: 1950) 196(7) (2016) 3191–8.
[88] I. Banerjee, B. Behl, M. Mendonca, G. Shrivastava, A.J. Russo, A. Menoret, A. Ghosh, A.T. Vella, S.K. Vanaja, S.N. Sarkar, K.A. Fitzgerald, V.A.K. Rathinam, Gasdermin D restrains type I interferon response to cytosolic DNA by disrupting ionic homeostasis, Immunity 49 (3) (2018) 413–426.e5.
[89] J.A. Trapani, K.A. Browne, M.J. Dawson, R.G. Ramsay, R.L. Eddy, T.B. Show, P.C. White, B. Dupont, A novel gene constitutively expressed in human lymphoid cells is inducible with interferon-gamma in myeloid cells, Immunogenetics 36 (6) (1992) 369–376.
[90] M.R. Thompson, S. Sharma, M. Atianand, S.B. Jensen, S. Carpenter, D.M. Knipe, K.A. Fitzgerald, E.A. Kurt-Jones, Interferon γ-inducible protein (IFI) 16 transcriptionally regulates type I interferons and other interferon-stimulated genes and controls the interferon response to both DNA and RNA viruses, Journal of Biological Chemistry 289 (34) (2014) 23568–23581.
[91] G. Pisano, A. Roy, M. Ahmed Ansari, B. Kumar, L. Chikoti, B. Chandran, Interferon-γ-inducible protein 16 (IFI16) is required for the maintenance of Epstein-Barr virus latency, Virology Journal 14 (1) (2017) 221.
[92] N. Kerur, M.V. Veettil, N. Sharma-Walia, V. Bottero, S. Sadagopan, P. Otageri, B. Chandran, IFI16 acts as a nuclear pathogen sensor to induce the inflammasome in response to Kaposi Sarcoma-associated herpesvirus infection, Cell host & microbe 9 (5) (2011) 363–375.
[93] H.-R. Lee, R. Amatya, J.U. Jung, Multi-step regulation of innate immune signaling by Kaposi's sarcoma-associated herpesvirus, Virus Research 209 (2015) 39–44.
[94] J. Iqbal, M.A. Ansari, B. Kumar, D. Dutta, A. Roy, L. Chikoti, G. Pisano, S. Dutta, S. Vahedi, M.V. Veettil, B. Chandran, Histone H2B-IFI16 recognition of nuclear herpesviral genome induces cytoplasmic interferon-beta responses, PLoS Pathogens 12 (10) (2016) e1005967.
[95] D. Dutta, S. Dutta, M.V. Veettil, A. Roy, M.A. Ansari, J. Iqbal, L. Chikoti, B. Kumar, K.E. Johnson, B. Chandran, BRCA1 regulates IFI16 mediated nuclear innate sensing of herpes viral DNA and subsequent induction of the innate inflammasome and interferon-beta responses, PLoS Pathogens 11 (6) (2015) e1005030.
[96] M.A. Ansari, S. Dutta, M.V. Veettil, D. Dutta, J. Iqbal, B. Kumar, A. Roy, L. Chikoti, V.V. Singh, B. Chandran, Herpesvirus genome recognition induced acetylation of nuclear IFI16 Is essential for its cytoplasmic translocation, inflammasome and IFN-beta responses, PLoS Pathogens 11 (7) (2015) e1005019.
[97] K.J. Ishii, C. Coban, H. Kato, K. Takahashi, Y. Torii, F. Takeshita, H. Ludwig, G. Sutter, K. Suzuki, H. Hemmi, S. Sato, M. Yamamoto, S. Uematsu, T. Kawai, O. Takeuchi, S. Akira, A Toll-like receptor-independent antiviral response induced by double-stranded B-form DNA, Nat Immunol 7 (1) (2006) 40–48.
[98] T. Cao, S. Shao, B. Li, L. Jin, J. Lei, H. Qiao, G. Wang, Up-regulation of Interferon-inducible protein 16 contributes to psoriasis by modulating chemokine production in keratinocytes, Scientific Reports 6 (2016) 25381.
[99] E.E. Gray, D. Winship, J.M. Snyder, S.J. Child, A.P. Geballe, D.B. Stetson, The AIM2-like receptors are dispensable for the interferon response to intracellular DNA, Immunity 45 (2) (2016) 255–266.
[100] P.H. Wang, Z.W. Ye, J.J. Deng, K.L. Siu, W.W. Gao, V. Chaudhary, Y. Cheng, S.Y. Fung, K.S. Yuen, T.H. Ho, C.P. Chan, Y. Zhang, K.H. Kok, W. Yang, C.P. Chan, D.Y. Jin, Inhibition of AIM2 inflammasome activation by a novel transcript isoform of IFI16, EMBO Rep 19 (10) (2018).
[101] P. Gao, M. Ascano, Y. Wu, W. Barchet, B.L. Gaffney, T. Zillinger, A.A. Serganov, Y. Liu, R.A. Jones, G. Hartmann, T. Tuschl, D.J. Patel, Cyclic [G(2′,5′)pA(3′,5′)p] is the metazoan second messenger produced by DNA-activated cyclic GMP-AMP synthase, Cell 153 (5) (2013) 1094–1107.
[102] K. Kato, H. Omura, R. Ishitani, O. Nureki, Cyclic GMP-AMP as an endogenous second messenger in innate immune signaling by cytosolic DNA, Annual Review of Biochemistry 86 (2017) 541–566.
[103] X. Cai, Y.H. Chiu, Z.J. Chen, The cGAS-cGAMP-STING pathway of cytosolic DNA sensing and signaling, Molecular Cell 54 (2) (2014) 289–296.
[104] H. Liu, P. Moura-Alves, G. Pei, H.J. Mollenkopf, R. Hurwitz, X. Wu, F. Wang, S. Liu, M. Ma, Y. Fei, C. Zhu, A.B. Koehler, D. Oberbeck-Mueller, K. Hahnke, M. Klemm, U. Guhlich-Bornhof, B. Ge, A. Tuukkanen, M. Kolbe, A. Dorhoi, S.H. Kaufmann, cGAS facilitates sensing of extracellular cyclic dinucleotides to activate innate immunity, EMBO Rep 20 (4) (2019).
[105] J.F. Almine, C.A. O'Hare, G. Dunphy, I.R. Haga, R.J. Naik, A. Atrih, D.J. Connolly, J. Taylor, I.R. Kelsall, A.G. Bowie, P.M. Beard, L. Unterholzner, IFI16 and cGAS cooperate in the activation of STING during DNA sensing in human keratinocytes, Nat Commun 8 (2017) 14392.
[106] K.L. Jonsson, A. Laustsen, C. Krapp, K.A. Skipper, K. Thavachelvam, D. Hotter, J.H. Egedal, M. Kjolby, P. Mohammadi, T. Prabakaran, L.K. Sorensen, C. Sun, S.B. Jensen, C.K. Holm, R.J. Lebbink, M. Johannsen, M. Nyegaard, J.G. Mikkelsen, F. Kirchhoff, S.R. Paludan, M.R. Jakobsen, IFI16 is required for DNA sensing in human macrophages by promoting production and function of cGAMP, Nat Commun 8 (2017) 14391.
[107] H. Lian, J. Wei, R. Zang, W. Ye, Q. Yang, X.N. Zhang, Y.D. Chen, Y.Z. Fu, M.M. Hu, C.Q. Lei, W.W. Luo, S. Li, H.B. Shu, ZCCHC3 is a co-sensor of cGAS for dsDNA recognition in innate immune response, Nat Commun 9 (1) (2018) 3349.
[108] G. Dunphy, S.M. Flannery, J.F. Almine, D.J. Connolly, C. Paulus, K.L. Jønsson, M. R. Jakobsen, M.M. Nevels, A.G. Bowie, L. Unterholzner, Non-canonical activation of the DNA sensing adaptor STING by ATM and IFI16 mediates NF-κB signaling after nuclear DNA damage, Molecular Cell 71(5) (2018) 745–760.e5.
[109] A.M. Gram, C. Sun, S.L. Landman, T. Oosenbrug, H.J. Koppejan, M.J. Kwakkenbos, R.C. Hoeben, S.R. Paludan, M.E. Ressing, Human B cells fail to secrete type I interferons upon cytoplasmic DNA exposure, Molecular Immunology 91 (2017) 225–237.
[110] A. Ablasser, Z.J. Chen, cGAS in action: Expanding roles in immunity and inflammation, Science 363(6431) (2019) eaat8657.
[111] Q. Chen, L. Sun, Z.J. Chen, Regulation and function of the cGAS-STING pathway of cytosolic DNA sensing, Nat Immunol 17 (10) (2016) 1142–1149.
[112] V. Kumar, A STING to inflammation and autoimmunity, Journal of Leukocyte Biology (2019) 1–15.
[113] L.T. Khoo, L.Y. Chen, Role of the cGAS-STING pathway in cancer development and oncotherapeutic approaches, EMBO Rep 19 (12) (2018).
[114] D. Wu, D.E. Sanin, B. Everts, Q. Chen, J. Qiu, M.D. Buck, A. Patterson, A.M. Smith, C.-H. Chang, Z. Liu, M.N. Artyomov, E.L. Pearce, M. Cella, E.J. Pearce, Type 1 interferons induce changes in core metabolism that are critical for immune function, Immunity 44 (6) (2016) 1325–1336.
[115] C.A. Parkos, Neutrophil-epithelial interactions: a double-edged sword, The American Journal of Pathology 186 (6) (2016) 1404–1416.
[116] T. Kong, H.K. Eltzschig, J. Karhausen, S.P. Colgan, C.S. Shelley, Leukocyte adhesion during hypoxia is mediated by HIF-1-dependent induction of beta2 integrin gene expression, Proceedings of the National Academy of Sciences of the United States of America 101 (28) (2004) 10440–10445.
[117] A.C. Chin, W.Y. Lee, A. Nusrat, N. Vergnolle, C.A. Parkos, Neutrophil-mediated activation of epithelial protease-activated receptors-1 and -2 regulates barrier function and transepithelial migration, Journal of Immunology (Baltimore, Md. : 1950) 181(8) (2008) 5702–10.
[118] A.C. Chin, C.A. Parkos, Neutrophil transepithelial migration and epithelial barrier function in IBD: potential targets for inhibiting neutrophil trafficking, Annals of the New York Academy of Sciences 1072 (2006) 276–287.
[119] S. Herold, W. von Wulffen, M. Steinmueller, S. Pleschka, W.A. Kuziel, M. Mack, M. Srivastava, W. Seeger, U.A. Maus, J. Lohmeyer, Alveolar epithelial cells direct

monocyte transepithelial migration upon Influenza virus infection: impact of chemokines and adhesion molecules, The Journal of Immunology 177 (3) (2006) 1817–1824.
[120] Q. Chen, A.A. Luo, H. Qiu, B. Han, B.H.-K. Ko, A.S. Slutsky, H. Zhang, Monocyte interaction accelerates HCl-induced lung epithelial remodeling, BMC Pulmonary Medicine 14 (2014) (135-135).
[121] H. Ishii, S. Hayashi, J.C. Hogg, T. Fujii, Y. Goto, N. Sakamoto, H. Mukae, R. Vincent, S.F. van Eeden, Alveolar macrophage-epithelial cell interaction following exposure to atmospheric particles induces the release of mediators involved in monocyte mobilization and recruitment, Respiratory Research 6 (1) (2005) (87-87).
[122] K.N. Lai, J.C.K. Leung, L.Y.Y. Chan, H. Guo, S.C.W. Tang, Interaction between proximal tubular epithelial cells and infiltrating monocytes/T cells in the proteinuric state, Kidney International 71 (6) (2007) 526–538.
[123] M.S. Tonetti, M.A. Imboden, N.P. Lang, Neutrophil migration into the gingival sulcus is associated with transepithelial gradients of interleukin-8 and ICAM-1, Journal of Periodontology 69 (10) (1998) 1139–1147.
[124] J.C. Brazil, C.A. Parkos, Pathobiology of neutrophil-epithelial interactions, Immunological Reviews 273 (1) (2016) 94–111.
[125] W.A. Muller, Leukocyte-endothelial-cell interactions in leukocyte transmigration and the inflammatory response, Trends in Immunology 24 (6) (2003) 327–334.
[126] D. Vestweber, Adhesion and signaling molecules controlling the transmigration of leukocytes through endothelium, Immunological Reviews 218 (2007) 178–196.
[127] A. Leligdowicz, M. Richard-Greenblatt, J. Wright, V.M. Crowley, K.C. Kain, Endothelial activation: the Ang/Tie axis in sepsis, Frontiers in Immunology 9 (2018) (838-838).
[128] C. Rosales, Neutrophil: a cell with many roles in inflammation or several cell types? Frontiers in Physiology 9 (2018) (113-113).
[129] K. Prame Kumar, A.J. Nicholls, C.H.Y. Wong, Partners in crime: neutrophils and monocytes/macrophages in inflammation and disease, Cell and Tissue Research 371 (3) (2018) 551–565.
[130] P. Scapini, M.A. Cassatella, Social networking of human neutrophils within the immune system, Blood 124 (5) (2014) 710–719.
[131] M. Finsterbusch, P. Hall, A. Li, S. Devi, C.L. Westhorpe, A.R. Kitching, M.J. Hickey, Patrolling monocytes promote intravascular neutrophil activation and glomerular injury in the acutely inflamed glomerulus, Proceedings of the National Academy of Sciences of the United States of America 113 (35) (2016) E5172–E5181.
[132] P.H. Leliefeld, C.M. Wessels, L.P. Leenen, L. Koenderman, J. Pillay, The role of neutrophils in immune dysfunction during severe inflammation, Critical Care (London, England) 20 (2016) 73.
[133] K.R. Dobbs, P. Embury, J. Vulule, P.S. Odada, B.A. Rosa, M. Mitreva, J.W. Kazura, A.E. Dent, Monocyte dysregulation and systemic inflammation during pediatric falciparum malaria, JCI insight 2 (18) (2017) e95352.
[134] C. Ince, P.R. Mayeux, T. Nguyen, H. Gomez, J.A. Kellum, G.A. Ospina-Tascón, G. Hernandez, P. Murray, D. De Backer, A.X. Workgroup, The endothelium in sepsis, Shock (Augusta, Ga.) 45(3) (2016) 259–270.
[135] J. Banchereau, R.M. Steinman, Dendritic cells and the control of immunity, Nature 392 (6673) (1998) 245–252.
[136] A. Agrawal, S. Agrawal, S. Gupta, Role of dendritic cells in inflammation and loss of tolerance in the elderly, Frontiers in Immunology 8 (2017) (896-896).
[137] C. Qian, X. Cao, Dendritic cells in the regulation of immunity and inflammation, Seminars in Immunology 35 (2018) 3–11.
[138] P. Blanco, A.K. Palucka, V. Pascual, J. Banchereau, Dendritic cells and cytokines in human inflammatory and autoimmune diseases, Cytokine & Growth Factor Reviews 19 (1) (2008) 41–52.
[139] V. Kumar, Dendritic cells in sepsis: Potential immunoregulatory cells with therapeutic potential, Molecular Immunology 101 (2018) 615–626.
[140] K. Shortman, S.H. Naik, Steady-state and inflammatory dendritic-cell development, nature reviews. Immunology 7 (1) (2007) 19–30.
[141] E. Segura, S. Amigorena, Inflammatory dendritic cells in mice and humans, Trends in Immunology 34 (9) (2013) 440–445.
[142] C. Hespel, M. Moser, Role of inflammatory dendritic cells in innate and adaptive immunity, European Journal of Immunology 42 (10) (2012) 2535–2543.
[143] J. Min, D. Yang, M. Kim, K. Haam, A. Yoo, J.-H. Choi, B.U. Schraml, Y.S. Kim, D. Kim, S.-J. Kang, Inflammation induces two types of inflammatory dendritic cells in inflamed lymph nodes, Experimental & Molecular Medicine 50 (2018) e458.
[144] A. Said, G. Weindl, Regulation of dendritic cell function in inflammation, Journal of Immunology Research 2015 (2015) 15.
[145] M. Fei, S. Bhatia, T.B. Oriss, M. Yarlagadda, A. Khare, S. Akira, S. Saijo, Y. Iwakura, B.A. Fallert Junecko, T.A. Reinhart, O. Foreman, P. Ray, J. Kolls, A. Ray, TNF-alpha from inflammatory dendritic cells (DCs) regulates lung IL-17A/IL-5 levels and neutrophilia versus eosinophilia during persistent fungal infection, Proceedings of the National Academy of Sciences of the United States of America 108 (13) (2011) 5360–5365.
[146] E. Segura, M. Touzot, A. Bohineust, A. Cappuccio, G. Chiocchia, A. Hosmalin, M. Dalod, V. Soumelis, S. Amigorena, Human inflammatory dendritic cells induce Th17 cell differentiation, Immunity 38 (2) (2013) 336–348.
[147] T.P. Singh, H.H. Zhang, I. Borek, P. Wolf, M.N. Hedrick, S.P. Singh, B.L. Kelsall, B.E. Clausen, J.M. Farber, Monocyte-derived inflammatory Langerhans cells and dermal dendritic cells mediate psoriasis-like inflammation, Nat Commun 7 (2016) 13581.
[148] N.V. Serbina, T.P. Salazar-Mather, C.A. Biron, W.A. Kuziel, E.G. Pamer, TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection, Immunity 19 (1) (2003) 59–70.
[149] S. Sozzani, M. Rusnati, E. Riboldi, S. Mitola, M. Presta, Dendritic cel-endothelial cell cross-talk in angiogenesis, Trends in Immunology 28(9) (2007) 385–392.
[150] G.G. Pendl, C. Robert, M. Steinert, R. Thanos, R. Eytner, E. Borges, M.K. Wild, J.B. Lowe, R.C. Fuhlbrigge, T.S. Kupper, D. Vestweber, S. Grabbe, Immature mouse dendritic cells enter inflamed tissue, a process that requires E- and P-selectin, but not P-selectin glycoprotein ligand 1, Blood 99 (3) (2002) 946–956.
[151] A. Del Prete, M. Locati, K. Otero, E. Riboldi, A. Mantovani, A. Vecchi, S. Sozzani, Migration of dendritic cells across blood and lymphatic endothelial barriers, Thrombosis and Haemostasis 95 (1) (2006) 22–28.
[152] E. Russo, M. Nitschké, C. Halin, Dendritic cell interactions with lymphatic endothelium, Lymphatic Research and Biology 11 (3) (2013) 172–182.
[153] C.L. Schlichting, W.D. Schareck, M. Weis, Dendritic cell endothelium interaction in autoimmunity, Current Pharmaceutical Design 10 (2) (2004) 171–181.
[154] A. Martin-Fontecha, A. Lanzavecchia, F. Sallusto, Dendritic cell migration to peripheral lymph nodes, Handbook of Experimental Pharmacology (188) (2009) 31–49.
[155] G.J. Randolph, V. Angeli, M.A. Swartz, Dendritic-cell trafficking to lymph nodes through lymphatic vessels, nature reviews. Immunology 5 (8) (2005) 617–628.
[156] G.J. Randolph, G. Sanchez-Schmitz, R.M. Liebman, K. Schakel, The CD16(+) (FcgammaRIII(+)) subset of human monocytes preferentially becomes migratory dendritic cells in a model tissue setting, The Journal of Experimental Medicine 196 (4) (2002) 517–527.
[157] G.J. Randolph, S. Beaulieu, S. Lebecque, R.M. Steinman, W.A. Muller, Differentiation of monocytes into dendritic cells in a model of transendothelial trafficking, Science 282 (5388) (1998) 480–483.
[158] C. Robert, R.C. Fuhlbrigge, J.D. Kieffer, S. Ayehunie, R.O. Hynes, G. Cheng, S. Grabbe, U.H. von Andrian, T.S. Kupper, Interaction of dendritic cells with skin endothelium: a new perspective on immunosurveillance, The Journal of Experimental Medicine 189 (4) (1999) 627–636.
[159] M. Weis, C.L. Schlichting, E.G. Engleman, J.P. Cooke, Endothelial determinants of dendritic cell adhesion and migration: new implications for vascular diseases, Arteriosclerosis, Thrombosis, and Vascular Biology 22 (11) (2002) 1817–1823.
[160] G. de la Rosa, N. Longo, J.L. Rodriguez-Fernandez, A. Puig-Kroger, A. Pineda, A.L. Corbi, P. Sanchez-Mateos, Migration of human blood dendritic cells across endothelial cell monolayers: adhesion molecules and chemokines involved in subset-specific transmigration, Journal of Leukocyte Biology 73 (5) (2003) 639–649.
[161] D.A. Bleijs, T.B. Geijtenbeek, C.G. Figdor, Y. van Kooyk, DC-SIGN and LFA-1: a battle for ligand, Trends in Immunology 22 (8) (2001) 457–463.
[162] C.L. Schlichting, W.D. Schareck, M. Weis, Dendritic cell adhesion is enhanced on endothelial cells preexposed to calcineurin inhibitors, Journal of Cardiovascular Pharmacology 46 (3) (2005) 250–254.
[163] A. Arjmandi, K. Liu, K. Dorovini-Zis, Dendritic cell adhesion to cerebral endothelium: role of endothelial cell adhesion molecules and their ligands, Journal of Neuropathology and Experimental Neurology 68 (3) (2009) 300–313.
[164] G.M. Virzì, J. Zhang, F. Nalesso, C. Ronco, P.A. McCullough, The role of dendritic and endothelial cells in cardiorenal syndrome, Cardiorenal Medicine 8 (2) (2018) 92–104.
[165] A. Skapenko, J. Leipe, P.E. Lipsky, H. Schulze-Koops, The role of the T cell in autoimmune inflammation, Arthritis Research & Therapy 7 (Suppl. 2) (2005) S4–S14.
[166] A.P. Cope, Studies of T-cell activation in chronic inflammation, Arthritis Research 4 Suppl 3(Suppl 3) (2002) S197-S211.
[167] S. Huber, N. Gagliani, W. Connor, J. Geginat, F. Caprioli, CD4+ T helper cell plasticity in infection, inflammation, and autoimmunity, Mediators of Inflammation 2017 (2017) 2.
[168] C.V. Carman, R. Martinelli, T lymphocyte-endothelial interactions: emerging understanding of trafficking and antigen-specific immunity, Frontiers in Immunology 6 (2015) (603-603).
[169] J. Choi, D.R. Enis, K.P. Koh, S.L. Shiao, J.S. Pober, T lymphocyte-endothelial cell interactions, Annual Review of Immunology 22 (2004) 683–709.
[170] D. Sancho, M.a. Yáñez-Mó, R. Tejedor, F. Sánchez-Madrid, Activation of peripheral blood T cells by interaction and migration through endothelium: role of lymphocyte function antigen-1/intercellular adhesion molecule-1 and interleukin-15, Blood 93 (3) (1999) 886–896.
[171] V. D., Austrup F, Borges E, Lohning M, Brauer R, et al., P- and Eselectin mediate recruitment of T-helper-1 but not T-helper-2 cells into inflammed tissues, Nature 385 (1997) 81–83.
[172] A. Hamann, U. Syrbe, T-cell trafficking into sites of inflammation, Rheumatology 39 (7) (2000) 696–699.
[173] B. Ludewig, S. Firner, L. Onder, V. Nindl, Tight control – decision-making during T cell–vascular endothelial cell interaction, Frontiers in Immunology 3 (279) (2012).
[174] L.A. O'Neill, R.J. Kishton, J. Rathmell, A guide to immunometabolism for immunologists, nature reviews. Immunology 16 (9) (2016) 553–565.
[175] G.D. Norata, G. Caligiuri, T. Chavakis, G. Matarese, M.G. Netea, A. Nicoletti, L.A. O'Neill, F.M. Marelli-Berg, The cellular and molecular basis of translational immunometabolism, Immunity 43 (3) (2015) 421–434.
[176] D.J. Philpott, S.E. Girardin, P.J. Sansonetti, Innate immune responses of epithelial cells following infection with bacterial pathogens, Current Opinion in Immunology 13 (4) (2001) 410–416.
[177] Epithelial Cells: Immunological Aspects, eLS.
[178] D. Qu, L. Shen, S. Liu, H. Li, Y. Ma, R. Zhang, K. Wu, L. Yao, J. Li, J. Zhang, Chronic inflammation confers to the metabolic reprogramming associated with tumorigenesis of colorectal cancer, Cancer Biology & Therapy 18 (4) (2017) 237–244.
[179] K.-A. Lee, K.-C. Cho, B. Kim, I.-H. Jang, K. Nam, Y.E. Kwon, M. Kim, D.Y. Hyeon, D. Hwang, J.-H. Seol, W.-J. Lee, Inflammation-modulated metabolic reprogramming is required for DUOX-dependent gut immunity in *Drosophila*, Cell Host &

Microbe 23(3) (2018) 338–352.e5.
[180] T. Valencia, Ji Y. Kim, S. Abu-Baker, J., Moscat-Pardos, Christopher S. Ahn, M. Reina-Campos, A. Duran, Elias A. Castilla, Christian M. Metallo, Maria T. Diaz-Meco, J. Moscat, Metabolic reprogramming of stromal fibroblasts through p62-mTORC1 signaling promotes inflammation and tumorigenesis, Cancer Cell 26 (1) (2014) 121–135.
[181] R.A. Vaughan, R. Garcia-Smith, J. Dorsey, J.K. Griffith, M. Bisoffi, K.A. Trujillo, Tumor necrosis factor alpha induces Warburg-like metabolism and is reversed by anti-inflammatory curcumin in breast epithelial cells, International Journal of Cancer 133 (10) (2013) 2504–2510.
[182] S. Kumar, T.R. Donti, N. Agnihotri, K. Mehta, Transglutaminase 2 reprogramming of glucose metabolism in mammary epithelial cells via activation of inflammatory signaling pathways, International Journal of Cancer 134 (12) (2014) 2798–2807.
[183] H.M. Kang, S.H. Ahn, P. Choi, Y.-A. Ko, S.H. Han, F. Chinga, A.S.D. Park, J. Tao, K. Sharma, J. Pullman, E.P. Bottinger, I.J. Goldberg, K. Susztak, Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development, Nature Medicine 21 (2014) 37.
[184] B. Kim, C. Jang, H. Dharaneeswaran, J. Li, M. Bhide, S. Yang, K. Li, Z. Arany, Endothelial pyruvate kinase M2 maintains vascular integrity, The Journal of Clinical Investigation 128 (10) (2018) 4543–4556.
[185] G. Eelen, P. de Zeeuw, M. Simons, P. Carmeliet, Endothelial cell metabolism in normal and diseased vasculature, Circulation Research 116 (7) (2015) 1231–1244.
[186] K. De Bock, M. Georgiadou, S. Schoors, A. Kuchnio, B.W. Wong, A.R. Cantelmo, A. Quaegebeur, B. Ghesquiere, S. Cauwenberghs, G. Eelen, L.K. Phng, I. Betz, B. Tembuyser, K. Brepoels, J. Welti, I. Geudens, I. Segura, B. Cruys, F. Bifari, I. Decimo, R. Blanco, S. Wyns, J. Vangindertael, S. Rocha, R.T. Collins, S. Munck, D. Daelemans, H. Imamura, R. Devlieger, M. Rider, P.P. Van Veldhoven, F. Schuit, R. Bartrons, J. Hofkens, P. Fraisl, S. Telang, R.J. Deberardinis, L. Schoonjans, S. Vinckier, J. Chesney, H. Gerhardt, M. Dewerchin, P. Carmeliet, Role of PFKFB3-driven glycolysis in vessel sprouting, Cell 154 (3) (2013) 651–663.
[187] G. Eelen, P.d. Zeeuw, L. Treps, U. Harjes, B.W. Wong, P. Carmeliet, Endothelial cell metabolism, Physiological Reviews 98(1) (2018) 3–58.
[188] B.W. Wong, E. Marsch, L. Treps, M. Baes, P. Carmeliet, Endothelial cell metabolism in health and disease: impact of hypoxia, EMBO J. 36 (15) (2017) 2187–2203.
[189] V. Kumar, Immunometabolism: another road to sepsis and its therapeutic targeting, Inflammation (2018), https://doi.org/10.1007/s10753-018-0939-8.
[190] L.A. O'Neill, E.J. Pearce, Immunometabolism governs dendritic cell and macrophage function, The Journal of Experimental Medicine 213 (1) (2016) 15–23.
[191] L.E. Gleeson, F.J. Sheedy, Metabolic reprogramming & inflammation: fuelling the host response to pathogens, Seminars in Immunology 28 (5) (2016) 450–468.
[192] H.R. Griffiths, D. Gao, C. Pararasa, Redox regulation in metabolic programming and inflammation, Redox Biology 12 (2017) 50–57.
[193] W.H. Koppenol, P.L. Bounds, C.V. Dang, Otto Warburg's contributions to current concepts of cancer metabolism, nature reviews. Cancer 11 (5) (2011) 325–337.
[194] J. Tur, T. Vico, J. Lloberas, A. Zorzano, A. Celada, Macrophages and mitochondria: a critical interplay between metabolism, signaling, and the functional activity, Advances in Immunology 133 (2017) 1–36.
[195] J.-C. Rodríguez-Prados, P.G. Través, J. Cuenca, D. Rico, J. Aragonés, P. Martín-Sanz, M. Cascante, L. Boscá, Substrate fate in activated macrophages: a comparison between innate, classic, and alternative activation, The Journal of Immunology 185 (1) (2010) 605–614.
[196] K. Ganeshan, A. Chawla, Metabolic regulation of immune responses, Annual Review of Immunology 32 (1) (2014) 609–634.
[197] L. Zhu, Q. Zhao, T. Yang, W. Ding, Y. Zhao, Cellular metabolism and macrophage functional polarization, Int Rev Immunol 34 (1) (2015) 82–100.
[198] T.D. Troutman, W. Hu, S. Fulenchek, T. Yamazaki, T. Kurosaki, J.F. Bazan, C. Pasare, Role for B-cell adapter for PI3K (BCAP) as a signaling adapter linking Toll-like receptors (TLRs) to serine/threonine kinases PI3K/Akt, Proc Natl Acad Sci U S A 109 (1) (2012) 273–278.
[199] R.G. Jones, E.J. Pearce, MenTORing immunity: mTOR signaling in the development and function of tissue-resident immune cells, Immunity 46(5) 730–742.
[200] H.K. Eltzschig, P. Carmeliet, Hypoxia and inflammation, The New England Journal of Medicine 364 (7) (2011) 656–665.
[201] C.T. Taylor, S.P. Colgan, Regulation of immunity and inflammation by hypoxia in immunological niches, Nature Reviews Immunology 17 (2017) 774.
[202] J. Biddlestone, D. Bandarra, S. Rocha, The role of hypoxia in inflammatory disease (review), International Journal of Molecular Medicine 35 (4) (2015) 859–869.
[203] T. McGarry, M. Biniecka, D.J. Veale, U. Fearon, Hypoxia, oxidative stress and inflammation, Free Radical Biology and Medicine 125 (2018) 15–24.
[204] S.A. Patel, M.C. Simon, Biology of hypoxia-inducible factor-2alpha in development and disease, Cell Death Differ 15 (4) (2008) 628–634.
[205] G.M. Tannahill, A.M. Curtis, J. Adamik, E.M. Palsson-McDermott, A.F. McGettrick, G. Goel, C. Frezza, N.J. Bernard, B. Kelly, N.H. Foley, L. Zheng, A. Gardet, Z. Tong, S.S. Jany, S.C. Corr, M. Haneklaus, B.E. Caffrey, K. Pierce, S. Walmsley, F.C. Beasley, E. Cummins, V. Nizet, M. Whyte, C.T. Taylor, H. Lin, S.L. Masters, E. Gottlieb, V.P. Kelly, C. Clish, P.E. Auron, R.J. Xavier, L.A. O'Neill, Succinate is an inflammatory signal that induces IL-1beta through HIF-1alpha, Nature 496 (7444) (2013) 238–242.
[206] E.M. Palsson-McDermott, A.M. Curtis, G. Goel, M.A.R. Lauterbach, F.J. Sheedy, L.E. Gleeson, M.W.M. van den Bosch, S.R. Quinn, R. Domingo-Fernandez, D.G.W. Johnson, J.-k. Jiang, W.J. Israelsen, J. Keane, C. Thomas, C. Clish, M.V. Heiden, R.J. Xavier, L.A.J. O'Neill, Pyruvate Kinase M2 regulates Hif-1α activity and IL-1β induction, and is a critical determinant of the Warburg Effect in LPS-activated macrophages, Cell Metabolism 21 (1) (2015) 65–80.
[207] H. Semba, N. Takeda, T. Isagawa, Y. Sugiura, K. Honda, M. Wake, H. Miyazawa, Y. Yamaguchi, M. Miura, D.M. Jenkins, H. Choi, J.W. Kim, M. Asagiri, A.S. Cowburn, H. Abe, K. Soma, K. Koyama, M. Katoh, K. Sayama, N. Goda, R.S. Johnson, I. Manabe, R. Nagai, I. Komuro, HIF-1alpha-PDK1 axis-induced active glycolysis plays an essential role in macrophage migratory capacity, Nat Commun 7 (2016) 11635.
[208] A.E. Rodriguez, G.S. Ducker, L.K. Billingham, C.A. Martinez, N. Mainolfi, V. Suri, A. Friedman, M.G. Manfredi, S.E. Weinberg, J.D. Rabinowitz, N.S. Chandel, Serine metabolism supports macrophage IL-1β production, Cell Metabolism 29(4) (2019) 1003–1011.e4.
[209] V. Kumar, Targeting macrophage immunometabolism: dawn in the darkness of sepsis, International Immunopharmacology 58 (2018) 173–185.
[210] E.L. Mills, B. Kelly, L.A.J. O'Neill, Mitochondria are the powerhouses of immunity, Nature Immunology 18 (5) (2017) 488–498.
[211] J. Garaude, R. Acin-Perez, S. Martinez-Cano, M. Enamorado, M. Ugolini, E. Nistal-Villan, S. Hervas-Stubbs, P. Pelegrin, L.E. Sander, J.A. Enriquez, D. Sancho, Mitochondrial respiratory-chain adaptations in macrophages contribute to antibacterial host defense, Nature Immunology 17 (9) (2016) 1037–1045.
[212] P.-S. Liu, P.-C. Ho, Mitochondria: a master regulator in macrophage and T cell immunity, Mitochondrion 41 (2018) 45–50.
[213] C. Diskin, E.M. Palsson-McDermott, Metabolic modulation in macrophage effector function, Frontiers in Immunology 9 (2018) 270.
[214] J. Van den Bossche, L.A. O'Neill, D. Menon, Macrophage immunometabolism: where are we (going)?, Trends in Immunology 38(6) (2017) 395–406.
[215] S.K. Biswas, Metabolic reprogramming of immune cells in cancer progression, Immunity 43 (3) (2015) 435–449.
[216] C.C. Winterbourn, A.J. Kettle, M.B. Hampton, Reactive oxygen species and neutrophil function, Annual Review of Biochemistry 85 (2016) 765–792.
[217] D.W. Park, J.W. Zmijewski, Mitochondrial dysfunction and immune cell metabolism in sepsis, Infection & Chemotherapy 49 (1) (2017) 10–21.
[218] E.P. Azevedo, N.C. Rochael, A.B. Guimaraes-Costa, T.S. de Souza-Vieira, J. Ganilho, E.M. Saraiva, F.L. Palhano, D. Foguel, A metabolic shift toward pentose phosphate pathway is necessary for amyloid fibril- and phorbol 12-myristate 13-acetate-induced neutrophil extracellular Trap (NET) formation, The Journal of Biological Chemistry 290 (36) (2015) 22174–22183.
[219] O. Rodriguez-Espinosa, O. Rojas-Espinosa, M.M. Moreno-Altamirano, E.O. Lopez-Villegas, F.J. Sanchez-Garcia, Metabolic requirements for neutrophil extracellular traps formation, Immunology 145 (2) (2015) 213–224.
[220] H. Lu, R.A. Forbes, A. Verma, Hypoxia-inducible factor 1 activation by aerobic glycolysis implicates the Warburg effect in carcinogenesis, The Journal of Biological Chemistry 277 (26) (2002) 23111–23115.
[221] D.N. Halligan, S.J. Murphy, C.T. Taylor, The hypoxia-inducible factor (HIF) couples immunity with metabolism, Seminars in Immunology 28 (5) (2016) 469–477.
[222] J.J. Howell, B.D. Manning, mTOR couples cellular nutrient sensing to organismal metabolic homeostasis, Trends in Endocrinology and Metabolism: TEM 22 (3) (2011) 94–102.
[223] C.M. Krawczyk, T. Holowka, J. Sun, J. Blagih, E. Amiel, R.J. DeBerardinis, J.R. Cross, E. Jung, C.B. Thompson, R.G. Jones, E.J. Pearce, Toll-like receptor-induced changes in glycolytic metabolism regulate dendritic cell activation, Blood 115 (23) (2010) 4742–4749.
[224] B. Everts, E.J. Pearce, Metabolic control of dendritic cell activation and function: recent advances and clinical implications, Frontiers in Immunology 5 (2014) 203.
[225] E.J. Pearce, B. Everts, Dendritic cell metabolism, nature reviews. Immunology 15 (1) (2015) 18–29.
[226] B. Everts, E. Amiel, S.C. Huang, A.M. Smith, C.H. Chang, W.Y. Lam, V. Redmann, T.C. Freitas, J. Blagih, G.J. van der Windt, M.N. Artyomov, R.G. Jones, E.L. Pearce, E.J. Pearce, TLR-driven early glycolytic reprogramming via the kinases TBK1-IKKvarepsilon supports the anabolic demands of dendritic cell activation, Nature Immunology 15 (4) (2014) 323–332.
[227] B. Everts, E. Amiel, G.J. van der Windt, T.C. Freitas, R. Chott, K.E. Yarasheski, E.L. Pearce, E.J. Pearce, Commitment to glycolysis sustains survival of NO-producing inflammatory dendritic cells, Blood 120 (7) (2012) 1422–1431.
[228] R. Spirig, S. Djafarzadeh, T. Regueira, S.G. Shaw, C. von Garnier, J. Takala, S.M. Jakob, R. Rieben, P.M. Lepper, Effects of TLR agonists on the hypoxia-regulated transcription factor HIF-1alpha and dendritic cell maturation under normoxic conditions, PloS One 5 (6) (2010) e0010983.
[229] K.C. Carroll, B. Viollet, J. Suttles, AMPKalpha1 deficiency amplifies proinflammatory myeloid APC activity and CD40 signaling, Journal of Leukocyte Biology 94 (6) (2013) 1113–1121.
[230] N.M. Chapman, S. Shrestha, H. Chi, Metabolism in immune cell differentiation and function, Advances in Experimental Medicine and Biology 1011 (2017) 1–85.
[231] N.J. MacIver, R.D. Michalek, J.C. Rathmell, Metabolic regulation of T lymphocytes, Annu Rev Immunol 31 (2013) 259–283.
[232] G.R. Bantug, L. Galluzzi, G. Kroemer, C. Hess, The spectrum of T cell metabolism in health and disease, nature reviews. Immunology 18 (1) (2018) 19–34.
[233] M. Guppy, E. Greiner, K. Brand, The role of the Crabtree effect and an endogenous fuel in the energy metabolism of resting and proliferating thymocytes, European Journal of Biochemistry 212 (1) (1993) 95–99.
[234] J.A. Wofford, H.L. Wieman, S.R. Jacobs, Y. Zhao, J.C. Rathmell, IL-7 promotes Glut1 trafficking and glucose uptake via STAT5-mediated activation of Akt to support T-cell survival, Blood 111 (4) (2008) 2101–2111.
[235] J.C. Rathmell, M.G. Vander Heiden, M.H. Harris, K.A. Frauwirth, C.B. Thompson, In the absence of extrinsic signals, nutrient utilization by lymphocytes is insufficient to maintain either cell size or viability, Molecular Cell 6 (3) (2000) 683–692.
[236] A.N. Macintyre, V.A. Gerriets, A.G. Nichols, R.D. Michalek, M.C. Rudolph, D. Deoliveira, S.M. Anderson, E.D. Abel, B.J. Chen, L.P. Hale, J.C. Rathmell, The glucose transporter Glut1 is selectively essential for CD4 T cell activation and

effector function, Cell Metabolism 20 (1) (2014) 61–72.
[237] Y. Cao, J.C. Rathmell, A.N. Macintyre, Metabolic reprogramming towards aerobic glycolysis correlates with greater proliferative ability and resistance to metabolic inhibition in CD8 versus CD4 T cells, PloS one 9 (8) (2014) e104104.
[238] M.B. Mockler, M.J. Conroy, J. Lysaght, Targeting T cell immunometabolism for cancer immunotherapy; understanding the impact of the tumor microenvironment, Frontiers in Oncology 4 (2014) 107.
[239] R. Wang, C.P. Dillon, L.Z. Shi, S. Milasta, R. Carter, D. Finkelstein, L.L. McCormick, P. Fitzgerald, H. Chi, J. Munger, D.R. Green, The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation, Immunity 35 (6) (2011) 871–882.
[240] D.R. Wahl, C.A. Byersdorfer, J.L. Ferrara, A.W. Opipari Jr., G.D. Glick, Distinct metabolic programs in activated T cells: opportunities for selective immunomodulation, Immunological Reviews 249 (1) (2012) 104–115.
[241] R.J. De Boer, D. Homann, A.S. Perelson, Different dynamics of CD4+ and CD8+ T cell responses during and after acute lymphocytic choriomeningitis virus infection, Journal of Immunology (Baltimore, Md.: 1950) 171 (8) (2003) 3928–3935.
[242] Y. Kurebayashi, S. Nagai, A. Ikejiri, M. Ohtani, K. Ichiyama, Y. Baba, T. Yamada, S. Egami, T. Hoshii, A. Hirao, S. Matsuda, S. Koyasu, PI3K-Akt-mTORC1-S6K1/2 axis controls Th17 differentiation by regulating Gfi1 expression and nuclear translocation of RORgamma, Cell Reports 1 (4) (2012) 360–373.
[243] G.M. Delgoffe, K.N. Pollizzi, A.T. Waickman, E. Heikamp, D.J. Meyers, M.R. Horton, B. Xiao, P.F. Worley, J.D. Powell, The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2, Nature Immunology 12 (4) (2011) 295–303.
[244] C.Y. Sasaki, G. Chen, R. Munk, E. Eitan, J. Martindale, D.L. Longo, P. Ghosh, p70S6K1 in the TORC1 pathway is essential for the differentiation of Th17 Cells, but not Th1, Th2, or Treg cells in mice, European Journal of Immunology 46 (1) (2016) 212–222.
[245] V. Kumar, T cells and their immunometabolism: a novel way to understanding sepsis immunopathogenesis and future therapeutics, Eur J Cell Biol 97 (6) (2018) 379–392.
[246] S. Feske, E.Y. Skolnik, M. Prakriya, Ion channels and transporters in lymphocyte function and immunity, nature reviews. Immunology 12 (7) (2012) 532–547.
[247] U. Kaufmann, S. Kahlfuss, J. Yang, E. Ivanova, S.B. Koralov, S. Feske, Calcium signaling controls pathogenic Th17 cell-mediated inflammation by regulating mitochondrial function, Cell Metabolism 29 (5) (2019) 1104–1118.
[248] P.G. Hogan, R.S. Lewis, A. Rao, Molecular basis of calcium signaling in lymphocytes: STIM and ORAI, Annual Review of Immunology 28 (2010) 491–533.
[249] I. Derler, I. Jardin, C. Romanin, Molecular mechanisms of STIM/Orai communication, American Journal of Physiology. Cell Physiology 310 (8) (2016) C643–C662.
[250] D.J. Coe, M. Kishore, F. Marelli-Berg, Metabolic regulation of regulatory T cell development and function, Frontiers in Immunology 5 (2014) 590.
[251] M.O. Johnson, P.J. Siska, D.C. Contreras, J.C. Rathmell, Nutrients and the microenvironment to feed a T cell army, Seminars in Immunology 28 (5) (2016) 505–513.
[252] R.D. Michalek, V.A. Gerriets, S.R. Jacobs, A.N. Macintyre, N.J. MacIver, E.F. Mason, S.A. Sullivan, A.G. Nichols, J.C. Rathmell, Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets, Journal of Immunology (Baltimore, Md.: 1950) 186 (6) (2011) 3299–3303.
[253] N. Tanimine, L.A. Turka, B. Priyadharshini, Navigating T-cell immunometabolism in transplantation, Transplantation 102 (2) (2018) 230–239.
[254] J.T. Harty, V.P. Badovinac, Shaping and reshaping CD8+ T-cell memory, nature reviews. Immunology 8 (2) (2008) 107–119.
[255] A. Shaulov, K. Murali-Krishna, CD8 T cell expansion and memory differentiation are facilitated by simultaneous and sustained exposure to antigenic and inflammatory milieu, Journal of Immunology (Baltimore, Md.: 1950) 180 (2) (2008) 1131–1138.
[256] L.E. Harrington, K.M. Janowski, J.R. Oliver, A.J. Zajac, C.T. Weaver, Memory CD4 T cells emerge from effector T-cell progenitors, Nature 452 (7185) (2008) 356–360.
[257] A.T. Waickman, J.D. Powell, mTOR, metabolism, and the regulation of T-cell differentiation and function, Immunological Reviews 249 (1) (2012) 43–58.
[258] G.J. van der Windt, E.L. Pearce, Metabolic switching and fuel choice during T-cell differentiation and memory development, Immunological Reviews 249 (1) (2012) 27–42.
[259] G.J. van der Windt, B. Everts, C.H. Chang, J.D. Curtis, T.C. Freitas, E. Amiel, E.J. Pearce, E.L. Pearce, Mitochondrial respiratory capacity is a critical regulator of CD8+ T cell memory development, Immunity 36 (1) (2012) 68–78.
[260] G.J. van der Windt, D. O'Sullivan, B. Everts, S.C. Huang, M.D. Buck, J.D. Curtis, C.H. Chang, A.M. Smith, T. Ai, B. Faubert, R.G. Jones, E.J. Pearce, E.L. Pearce, CD8 memory T cells have a bioenergetic advantage that underlies their rapid recall ability, Proc Natl Acad Sci U S A 110 (35) (2013) 14336–14341.
[261] B. Raud, P.J. McGuire, R.G. Jones, T. Sparwasser, L. Berod, Fatty acid metabolism in CD8(+) T cell memory: challenging current concepts, Immunological Reviews 283 (1) (2018) 213–231.
[262] J.P. Rhoads, A.S. Major, J.C. Rathmell, Fine tuning of immunometabolism for the treatment of rheumatic diseases, nature reviews. Rheumatology 13 (5) (2017) 313–320.
[263] L. Morel, Immunometabolism in systemic lupus erythematosus, nature reviews. Rheumatology 13 (5) (2017) 280–290.
[264] A. Perl, Review: metabolic control of immune system activation in rheumatic diseases, Arthritis & Rheumatology (Hoboken, N.J.) 69 (12) (2017) 2259–2270.
[265] S. Thomas, K.H. Fisher, J.A. Snowden, S.J. Danson, S. Brown, M.P. Zeidler, Methotrexate is a JAK/STAT pathway inhibitor, PloS One 10 (7) (2015) e0130078.
[266] O. Shuvalov, A. Petukhov, A. Daks, O. Fedorova, E. Vasileva, N.A. Barlev, One-carbon metabolism and nucleotide biosynthesis as attractive targets for anticancer therapy, Oncotarget 8 (14) (2017) 23955–23977.
[267] A.C. Newman, O.D.K. Maddocks, One-carbon metabolism in cancer, British Journal of Cancer 116 (12) (2017) 1499–1504.
[268] Y. Yin, S.C. Choi, Z. Xu, D.J. Perry, H. Seay, B.P. Croker, E.S. Sobel, T.M. Brusko, L. Morel, Normalization of CD4+ T cell metabolism reverses lupus, Science Translational Medicine 7 (274) (2015) 274ra18.
[269] C.F. Lee, Y.C. Lo, C.H. Cheng, G.J. Furtmuller, B. Oh, V. Andrade-Oliveira, A.G. Thomas, C.E. Bowman, B.S. Slusher, M.J. Wolfgang, G. Brandacher, J.D. Powell, Preventing Allograft rejection by targeting immune metabolism, Cell Rep 13 (4) (2015) 760–770.
[270] B. Priyadharshini, L.A. Turka, T-cell energy metabolism as a controller of cell fate in transplantation, Current Opinion in Organ Transplantation 20 (1) (2015) 21–28.
[271] V. Kumar, T cells and their immunometabolism: a novel way to understanding sepsis immunopathogenesis and future therapeutics, European journal of cell biology 97 (6) (2018) 379–392.
[272] Z. Zhang, W. Deng, R. Kang, M. Xie, T. Billiar, H. Wang, L. Cao, D. Tang, Plumbagin protects mice from lethal sepsis by modulating immunometabolism upstream of PKM2, Molecular Medicine (Cambridge, Mass.) 22 (2016) 162–172.
[273] L.A. O'Neill, D.G. Hardie, Metabolism of inflammation limited by AMPK and pseudo-starvation, Nature 493 (7432) (2013) 346–355.
[274] Z. Wen, K. Jin, Y. Shen, Z. Yang, Y. Li, B. Wu, L. Tian, S. Shoor, N.E. Roche, J.J. Goronzy, C.M. Weyand, N-myristoyltransferase deficiency impairs activation of kinase AMPK and promotes synovial tissue inflammation, Nature Immunology 20 (3) (2019) 313–325.
[275] G. Zhou, R. Myers, Y. Li, Y. Chen, X. Shen, J. Fenyk-Melody, M. Wu, J. Ventre, T. Doebber, N. Fujii, N. Musi, M.F. Hirshman, L.J. Goodyear, D.E. Moller, Role of AMP-activated protein kinase in mechanism of metformin action, J Clin Invest 108 (8) (2001) 1167–1174.
[276] Y.S. Lee, W.S. Kim, K.H. Kim, M.J. Yoon, H.J. Cho, Y. Shen, J.M. Ye, C.H. Lee, W.K. Oh, C.T. Kim, C. Hohnen-Behrens, A. Gosby, E.W. Kraegen, D.E. James, J.B. Kim, Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states, Diabetes 55 (8) (2006) 2256–2264.
[277] B. Cool, B. Zinker, W. Chiou, L. Kifle, N. Cao, M. Perham, R. Dickinson, A. Adler, G. Gagne, R. Iyengar, G. Zhao, K. Marsh, P. Kym, P. Jung, H.S. Camp, E. Frevert, Identification and characterization of a small molecule AMPK activator that treats key components of type 2 diabetes and the metabolic syndrome, Cell Metabolism 3 (6) (2006) 403–416.
[278] D.A. Escobar, A.M. Botero-Quintero, B.C. Kautza, J. Luciano, P. Loughran, S. Darwiche, M.R. Rosengart, B.S. Zuckerbraun, H. Gomez, Adenosine monophosphate-activated protein kinase activation protects against sepsis-induced organ injury and inflammation, The Journal of Surgical Research 194 (1) (2015) 262–272.
[279] W. Zhao, L. Zhang, R. Chen, H. Lu, M. Sui, Y. Zhu, L. Zeng, SIRT3 protects against acute kidney injury via AMPK/mTOR-regulated autophagy, Frontiers in Physiology 9 (2018) 1526.
[280] F. Venet, J. Demaret, B.J. Blaise, C. Rouget, T. Girardot, E. Idealisoa, T. Rimmele, F. Mallet, A. Lepape, J. Textoris, G. Monneret, IL-7 Restores T Lymphocyte immunometabolic failure in septic shock patients through mTOR activation, Journal of Immunology (Baltimore, Md.: 1950) 199 (5) (2017) 1606–1615.
[281] B. Francois, R. Jeannet, T. Daix, A.H. Walton, M.S. Shotwell, J. Unsinger, G. Monneret, T. Rimmele, T. Blood, M. Morre, A. Gregoire, G.A. Mayo, J. Blood, S.K. Durum, E.R. Sherwood, R.S. Hotchkiss, Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial, JCI Insight 3 (5) (2018).
[282] A. Wang, H.H. Luan, R. Medzhitov, An evolutionary perspective on immunometabolism, Science 363 (6423) (2019) eaar3932.
[283] M. Liu, R.S. O'Connor, S. Trefely, K. Graham, N.W. Snyder, G.L. Beatty, Metabolic rewiring of macrophages by CpG potentiates clearance of cancer cells and overcomes tumor-expressed CD47−mediated 'don't-eat-me' signal, Nature Immunology 20 (2019) 265–275.