

Biochemistry of Inflammation: Molecular Pathways and Therapeutic Targets

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Abstract

Inflammation is a complicated biological process of response to harmful factors; it is associated with a complex of molecular processes that include a great number of signalling pathways, mediators, and cellular interactions. The biochemical mechanisms of inflammation include activation of pattern recognition receptors, mobilisation of inflammatory cells and release of several mediators such as cytokines, chemokines and lipid derivatives. The knowledge in these molecular pathways has become crucial in coming up with specific treatment interventions. The paper reviews the most important biochemical pathways of inflammatory responses, major signalling cascades, inflammatory mediators, and new therapeutic targets. The latest progress in the research on the resolution phase of inflammation and the involvement of specific pro-resolving mediators is also discussed. Inflammatory networks are multifaceted: this has its own challenges and opportunities in terms of therapeutic intervention, and in the treatment of both acute and chronic inflammatory conditions, a variety of new targets are currently investigated.

Introduction

Inflammation is a basic defensive mechanism of the organism to tissue damage, infection, or other hostile factors. It is defined by a cascade of biochemical and cellular processes which set to work the primary cause of cell injury, destroy necrotic cells and tissues and trigger the process of tissue repair [1]. The inflammatory response is closely controlled by a complex of interconnected molecular

processes that involve different types of cells, signalling molecules and effector mechanisms [2]. Although acute inflammation is usually healthy and self-limiting, chronic inflammation is a causative factor in the pathogenesis of many disorders, such as cardiovascular diseases, metabolic syndrome, neurodegenerative diseases, and cancer [3].

Biochemical insights into inflammation have developed significantly throughout the last several decades, displaying complex signalling pathways and regulatory processes governing the inflammatory process. The developments have revealed many possible therapeutic targets and resulted in the generation of biologics and small-molecule inhibitors selectively regulating particular elements of the inflammatory pathway [4]. This review gives a broad overview of the molecular pathways underlying inflammation, including important signalling pathways, inflammatory mediators and the most up-to-date treatment methods.

Pattern Recognition Receptors and Inflammatory Signalling.

Pattern recognition receptors (PRRs) are the key mediators of the initiation of inflammation, sensing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [5]. These receptors can be identified as Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs) and C-type lectin receptors (CLRs) [6].

Toll-Like Receptors

TLRs are the most well-studied family of PRRs, and thirteen are known to exist in mammals. These transmembrane proteins identify a variety of molecular structures, such as lipopolysaccharide, peptidoglycan, flagellin, and nucleic acids [7]. TLRs also change their conformation upon binding a ligand, which allows the recruitment of adaptor proteins, including myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-2 (TRIF) [8].

Most TLRs use the MyD88-dependent pathway, which results in the activation of nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinases (MAPKs). This is mediated by the cascade recruitment of interleukin-1 receptor-associated kinases (IRAKs) and tumour necrosis factor receptor-associated factor 6 (TRAF6), which eventually leads to degradation of inhibitor of κ B (I κ B) proteins and translocation of NF- κ B to the nucleus [9]. The TRIF-dependent pathway, which is mostly used by TLR3 and TLR4, causes the activation of interferon regulatory factors (IRFs) and the synthesis of type I interferons [10].

Toll-Like Receptors and Inflammasomes.

NLRs are cytoplasmic PRRs which sense intracellular PAMPs and DAMPs. NOD1 and NOD2 receptors sense bacterial peptidoglycan fragments and stimulate NF- κ B activation of NOD1 and NOD2 by recruiting receptor-interacting serine/threonine protein kinase 2 (RIPK2) [11]. A number of NLRs, such as NLRP1, NLRP3 and NLRC4, may also form large multiprotein complexes referred to as inflammasomes [12].

The most widely studied of them is the NLRP3 inflammasome and can be triggered by a wide range of stimuli, such as ATP, crystalline substances, and reactive oxygen species (ROS). The activation of NLRP3 causes the adaptor protein, ASC (apoptosis-associated speck-like protein containing a CARD) and pro-caspase-1 to join to form an active inflammasome complex [13]. The caspase-1 is activated to process pro-interleukin-1 β (pro-IL-1 β) and pro-IL-18 into their mature and active forms, which are secreted to induce the inflammatory responses [14].

Nuclear Factor-kappaB Signalling Pathway.

The NF- κ B signalling pathway is one of the key regulators of inflammatory expression of genes. The NF- family consists of five members, namely p65 (RelA), RelB, c-Rel, p50/p105 (NF- κ B1) and p52/p100 (NF- κ B2) that form different homo- and heterodimeric complexes [15]. NF- κ B dimers are cytoplasmically trapped in I κ B proteins of resting cells. When stimulated, the IKK complex, comprising IKK α , IKK β and IKK γ (NEMO), phosphorylates I κ B proteins, which undergo ubiquitination and degradation in the proteasome [16].

Many stimuli, such as antigen receptors, TLR ligands and cytokines, activate the canonical NF- κ B pathway. The key pathway in this direction is that of IKK2-dependent activation of p65/p50 heterodimers [17]. The non-canonical pathway is triggered by certain members of the TNF family and includes IKK0 -dependent p100 cleavage to produce p52, which is capable of dimerising with RelB [18]. NF-, upon liberation, translocate to the nucleus, bind to κ B sites on the promoter and enhancer regions of the target genes and cause the expression of proinflammatory cytokines, chemokines, adhesion molecules and other inflammatory mediators [19].

Mitogen-Activated Protein Kinase Signalling.

MAPKs are a set of evolutionarily conserved serine /threonine kinases that mediate cellular responses to a range of stimuli. There are three key MAPK pathways, namely, extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK [20]. These routes are arranged as three-tier cascades of MAPK language-related kinases (MAP3Ks), MAPK language-related kinases (MAP2Ks), and MAPKs.

The p38 MAPK pathway is an especially significant one in the case of inflammation. Activated by MAP2Ks (MKK3 and MKK6), p38 MAPK can phosphorylate numerous different substrates, such as transcription factors (activating transcription factor 2 (ATF2)) and kinases (MAPK-activated protein kinase 2 (MK2)) [21]. These mediators control the activation and maintenance of inflammatory genes, such as those of TNF- α , IL-1 β , IL-6, and cyclooxygenase-2 (COX-2) [22].

MAP2Ks (MKK4 and MKK7) are activated by MAP2Ks when stimulated by stress stimuli and inflammatory cytokines. JNK is activated, and c-Jun, which is a subunit of the activator protein-1 (AP-1) transcription factor complex, is then phosphorylated, increasing its transcriptional activity [23]. Although the ERK pathway is linked with cell proliferation and differentiation, it also plays a part in the inflammatory responses involving transcriptional factors regulation and cPLA2 phosphorylation [24].

Cytokines and Chemokines

Cytokines are small proteins that are involved in cell-to-cell communication and control of immune and inflammatory reactions. These molecules fall in various categories, which are interleukins, tumour necrosis factors, interferons and colony-stimulating factors [25].

Proinflammatory Cytokines

IL-1b is a strong proinflammatory cytokine which is mainly generated by activated macrophages. It is produced as the inactive precursor (pro-IL-1 β), which can be activated by cleavage by caspase-1. IL-1 β attaches itself to the IL-1 receptor type I (IL-1R1), which triggers an IL-1R1-mediated signalling cascade involving the activation of NF- κ B and MAPKs, which cause the release of other inflammatory mediators [26]. IL-1 receptor antagonist (IL-1Ra) is a competitive inhibitor of the IL-1 biological activity that binds to IL-1R1 without initiating signalling, which is a natural competitive inhibitor [27].

The other important proinflammatory cytokine that is generated by the macrophages, T cells and other kinds of cells is the TNF- α . It is present in the form of a transmembrane protein as well as in a soluble form produced through proteolytic cleavage. TNF- α uses two receptors TNFR1 and TNFR2, to trigger various signalling pathways, such as NF- κ B, MAPKs and caspase cascades [28]. Pleiotropic effects of TNF- α are as follows: adhesion molecule expression, which induces an inflammatory reaction in neutrophils and endothelial cells, and stimulates acute phase protein synthesis [29].

IL-6 is secreted by different types of cells and has both proinflammatory and anti-inflammatory effects. It uses IL-6 receptor α (IL-6R α) and the signal-transducing protein gp130 to signal through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway [30]. The IL-6 is essential in acute phase responses, B cell differentiation, and T cell activation [31].

Chemokines

A family of small chemotactic cytokines called chemokines triggers the movement and localisation of the leukocytes. The conservation of cysteine residues is used to classify chemokines into four subfamilies, which include CXC, CC, CX3C, and C [32]. The chemokines interact with G protein-coupled receptors in the target cells and initiate signalling cascades that control cell migration, adhesion and activation [33].

CXCL8 (IL-8), CCL2 (MCP-1) and CCL5 (RANTES) are proinflammatory chemokines that are quickly released during an inflammatory response and attract neutrophils, monocytes and other leukocytes to inflammatory foci [34]. The concerted action of chemokines/chemokine receptors creates chemotactic gradients that regulate leukocyte migration across blood vessels into the inflamed tissue [35].

Lipid Mediators

Membrane-based lipid mediators are important in inflammatory reactions. These are eicosanoids (prostaglandins, leukotrienes, and thromboxanes) and specialised pro-resolving mediators (SPMs) [36].

Eicosanoids

The production of eicosanoids is based on the arachidonic acid, which is released by phospholipase A2 (PLA2) as it is produced from membrane phospholipids. Arachidonic acid is converted into bioactive lipid mediators by three main enzymatic pathways, which are the cyclooxygenase (COX), lipoxygenase (LOX), and the cytochrome P450 pathways [37].

COX pathway produces thromboxanes and prostaglandins. There are 2 COX isoforms; COX-1, which is constitutively expressed, thus participating in homeostatic functions and COX-2, which is induced in the inflammatory process [38]. COX transforms arachidonic acid into prostaglandin H2 (PGH2), which is then modified by the action of several synthases into various prostaglandins (PGE2, PGD2, PGF2 α , PGI2) and thromboxane A2 (TXA2) [39]. During inflammation, the most common prostaglandin is PGE2, which has a variety of actions involving four types of G protein-coupled receptors (EP1-EP4), among which are vasodilation, fever evolution, or regulation of the immune cells' functions [40].

5-lipoxygenase (5-LOX) is the pathway that synthesises leukotrienes, proinflammatory compounds that take part in both allergic and inflammatory reactions [41]. 5-LOX transforms arachidonic acid to leukotriene A4 (LTA4) that is converted to LTB4 by LTA4 hydrolase or to cysteinyl leukotrienes (LTC4, LTD4, LTE4) by LTC4 synthase. LTB4 is a potent neutrophil chemoattractant and enhances the leukocyte adhesion to endothelial cells, whereas cysteinyl leukotrienes have the effect of facilitating bronchoconstriction and vascular permeability [42].

Pro-Resolving Mediators are specialists who perform roles of arbitrators, facilitators, and reconcilers to help conflicting parties resolve their disputes peacefully. Pro-Resolving Mediators are professionals who play the roles of arbitrators, facilitators, and reconcilers to assist warring parties in settling their disputes amicably.

Recent studies have chosen a family of lipid mediators which actively support the healing of inflammation. These SPMs consist of lipoxins, resolvins, protectins and maresins, which are enzymatically generated out of omega-3 and omega-6 unsaturated fatty acids [43].

The transcellular biosynthesis entails the production of lipoxins by several types of cells. The production of Lipoxin A4 (LXA4) and Lipoxin B4 (LXB4) occurs as a consequence of the first stage metabolism of arachidonic acid involving 15-LOX and 5-LOX [44]. Lipoxins suppress neutrophil recruitment, induce the phagocytosis of cellular apoptosis by macrophages and accelerate inflammatory resolution [45].

Resolvins are formed out of the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA forms the precursors of e-series resolvins (RvE1, RvE2), whereas DHA forms the precursors of D-series resolvins (RvD1-RvD6) [46]. Such mediators are strong anti-inflammatory and pro-resolving, such as restriction of neutrophil entry, increase of macrophage efferocytosis and suppression of proinflammatory cytokines synthesis [47].

Oxidative Stress and Inflammation.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have multifaceted involvement in the inflammatory reactions. These molecules are produced by different enzymatic systems such as NADPH oxidases (NOX), mitochondrial electron transport chain, and nitric oxide synthases (NOS) [48].

Median amounts of ROS act as a signal molecule that controls the pathways of inflammation. NF- κ B and MAPKs can be activated by ROS, inflammasomes can have their activity increased by ROS, and transcription factors' activity can be altered by oxidative alteration of cysteine residues [49]. Nevertheless, when the level of the ROS is too high, it causes oxidative stress, which damages the proteins, lipids and DNA and also adds to the chronic inflammation [50].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is one of the most significant cell defences against oxidative stress. In the basal condition, Nrf2 is trapped in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1) and directed to proteasomal degradation [51]. When Nrf2 dissociates with Keap1 because of oxidative stress, it moves to the nucleus and alters the expression of antioxidant and cytoprotective genes by binding to antioxidant response elements (AREs) [52].

Resolution of Inflammation

Inflammatory resolution is an active process that is coordinated by particular molecular processes and cellular programs. This stage includes the elimination of the production of proinflammatory mediators, clearance of inflammatory cells by means of apoptosis and efferocytosis, and tissue homeostasis restoration [53].

Macrophages are also at the centre of the resolution because they can phenotypically switch. The proinflammatory M1 macrophages that prevail in the acute phase change to anti-inflammatory M2 macrophages that facilitate tissue repair and remodelling [54]. The phenotypic switch is also controlled by other factors, such as SPMs, glucocorticoids, IL-10 and transforming growth factor-2 (TGF-2) [55].

Efferocytosis is a phagocytic clearance of apoptotic cells and is an essential part of resolution. The apoptotic cells also have an eat-me signal (phosphatidylserine at the outer membrane), which is seen by the receptors on the phagocytes [56]. Efferocytosis causes anti-inflammatory effects in the macrophages, such as the release of TGF-b and IL-10 and the inhibition of proinflammatory cytokines [57].

Therapeutic Goals and Existing Strategies.

The comprehensive knowledge of inflammatory processes has helped in coming up with specific therapeutic interventions in the case of inflammatory ailments.

Nonsteroidal Anti-inflammatory Drugs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) continue to be the most popular anti-inflammatory drugs. These medications block COX enzymes, hence lowering the formation of prostaglandins [58]. Conventional NSAIDs block both COX-1 and COX-2, whereas selective COX-2 inhibitors (coxibs) have a more specific action on the inducible COX-2 isoform [59]. However, NSAIDs have side effects, especially gastrointestinal and cardiovascular, which do not allow the use of such drugs in the long term despite their effectiveness [60].

Corticosteroids

Corticosteroids are strong anti-inflammatory agents, and they have various mechanisms of action. These drugs, which bind to the glucocorticoid receptor, are translocated to the nucleus and suppress the expression of proinflammatory genes by interfering with NF- κ B and AP-1 [61]. The effect of corticosteroids is also the stimulation of the expression of anti-inflammatory proteins like lipocortin-1 and IL-10 [62]. Although chronic steroid therapy has been proven very efficient, chronic corticosteroids are linked to major negative consequences, such as immunosuppression, metabolic imbalances, and bone loss [63].

Biologic Therapies

The invention of the biologic agents has transformed the management of chronic inflammatory disorders. TNF- α is a potent drug whose use has been shown to be very effective in rheumatoid arthritis, inflammatory bowel disease, and psoriasis [64]. Such agents counter TNF- α by various ways, either by binding soluble and membrane-bound TNF- α and/or by decoying receptors [65].

In some inflammatory diseases, IL-1 blockage is also effective. Anakinra is a recombinant IL-1Ra that competes with IL-1 β , and canakinumab is a monoclonal antibody specifically binding to IL-1 β [66]. It has been demonstrated that these agents are effective in gout and autoinflammatory syndromes [67].

Another more effective treatment option is IL-6 pathway inhibition. Tocilizumab is an anti-IL-6 receptor humanised antibody that is used in the treatment of rheumatoid arthritis and other inflammatory diseases [68]. Tofacitinib and baricitinib are examples of JAK inhibitors that prevent downstream signalling of various cytokine receptors, including IL-6, and have been found to be effective in rheumatoid arthritis and other inflammatory diseases [69].

New Therapeutic modalities.

New treatment interventions against the NLRP3 inflammasome are being developed. Directly binding NLRP3 inhibitors that prevent the assembly of an inflammasome are promising in preclinical trials [70]. Such agents could be useful in conditions where there is aberrant activity of inflammasomes, such as metabolic diseases and neurodegenerative diseases [71].

Pro-resolving mediators are a new form of therapy that does not focus on the suppression of inflammation, but rather improves the endogenous resolving responses. There is the development of SPM analogues and mimetics that should encourage the resolution of chronic inflammatory conditions without compromising host defence mechanisms [72].

There is also a focus on targeting specific MAPK pathways. P38 MAPK inhibitors are widely investigated, but their clinical development has not been successful because of toxicity and poor efficacy [73]. Greater specificity of the p38 isoform or downstream targets of more selective inhibitors could have better therapeutic windows [74].

Conclusion

Inflammatory biochemistry is a complex of cellular interactions and regulatory mechanisms, as well as molecular pathways. Important breakthroughs in the knowledge of these processes have provided a large number of possible targets of therapy and have resulted in effective therapies for inflammatory disease. The identification of inflammation resolution as an active process, which can be controlled by certain molecular pathways, has created new opportunities in the treatment process. Further studies in the area of consolidating proinflammatory and pro-resolving inflammatory responses, the discovery of new regulatory mechanisms, and the creation of precision medicine practice will probably create better solutions to deal with acute and chronic inflammatory diseases. The difficulty now ahead is to find therapeutic options that are able to selectively regulate pathological inflammation without damaging useful inflammatory reactions essential to host defence and tissue healing.

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