Representative Components of Innate Immunity

Subjects: Others

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The breach of the host immune system by pathogenic microorganisms generates an array of immune reactions through the synergy between the diversified cluster of pathogen-based virulence factors and defensive immune processes of the host. The host–pathogen encounter usually launches immune reactions via identification of conserved molecular structures known as pathogen-associated molecular patterns (PAMPs). Active recognition of a PAMP immediately elicits an immune response in the host by stimulating multiplex signaling pathways that climax in the inflammatory responses regulated by numerous chemokines and cytokines, which consequently promote the elimination of the harmful microorganism carrying the PAMP, such as viral double-stranded ribonucleic acid (RNA) and lipopolysaccharides (LPS). Moreover, the innate immune system expands efficient defense against pathogenic microbes by initiating adaptive immunity, which involves immunological memory and is long-lasting. Adaptive immunity is characterized by the formation of antigen-specific T and B lymphocytes via gene rearrangement.

innate immune system | pattern recognition receptor | Toll-like receptor

1. Pattern Recognition Receptors

TLRs

TLRs are extensively studied and evolutionarily conserved proteins that detect PAMPs. They were initially identified in *Drosophila melanogaster* as an essential gene because of its vital role in ontogenesis and immunological effects against fungal infections [1]. To date, 10 TLR family members have been identified in humans (TLR1 to TLR10) [2]. They are type I integral membrane glycoproteins characterized by their (1) extracellular domains containing varying numbers of leucine-rich repeat (LRR) motifs that are required for PAMP recognition and (2) a cytoplasmic signaling domain homologous to that of interleukin 1 receptor (IL-1R), termed the Toll/IL-1R homology (TIR) domain, which is essential for the activation of downstream signaling. The TIR domain interacts with multiple adaptor molecules and brings about the activation of nuclear factor (NF)-κB through the signal transmission that culminates in the synthesis of proinflammatory cytokines [3]. Among TLRs, TLR1, TLR2, TLR4, TLR5, and TLR6 are mainly located on the surface of the cell and detect PAMPs from fungi, bacteria, and protozoa, whereas TLR3, TLR7, TLR8, and TLR9 are exclusively expressed within endocytic compartments and primarily recognize nucleic acids from various bacteria [4]. Diverse TLRs exclusively detect specific DAMPs and PAMPs [5]. TLR2 forms heterodimers with either TLR1 or TLR6, where TLR1 or TLR2 detects triacyl lipopeptides, while TLR2 or TLR6 specifically interacts with diacyl lipopeptides. TLR3 has high specificity for RNA ligands (double-stranded) that are products of viral replication at various stages. TLR4 recognizes LPS, i.e., the cell wall component of gram-negative bacteria; LPS

requires an interaction with coreceptor MD2 to bind to TLR4. TLR5 identifies bacterial-flagellin–based ligands by its extracellular homodimeric domain. Both TLR7 and TLR8 respond to single-stranded RNA, whereas TLR9 interacts with CpG motif–containing ligands [5]. TLRs switch on similar signaling components that are utilized for IL-1R signaling [6]. Signaling through TLRs proceeds essentially through a well-described pathway in which various receptor-binding domains (TIR domains) transmit a signal through adapter molecules such as MyD88, TRIF (TICAM-1), TIRAP (MAL), and TRAM [7]. These adaptor molecules stimulate specific transcription factors like IRF3/7, nuclear factor κB (NF-κB), and mitogen-activated protein kinases (MAPKs) to induce the expression of type I interferons and proinflammatory cytokines. All TLRs, except TLR3, engage MyD88, and launch MyD88-dependent signaling pathway to cause NF-κB and MAPKs to upregulate proinflammatory cytokines in dendritic cells and macrophages. On the other hand, TLR1, TLR2, TLR4, and TLR6 employ TIRAP to activate MyD88-dependent signaling. TLR3 and TLR4 initiate TRIF-dependent signaling to make NF-κB and IRF3 upregulate type I interferons and proinflammatory cytokines. TLR4 employs TRIF through a complementary adapter molecule, TRAM. Meanwhile, TLR4 triggers the TRIF-dependent signaling pathway together with MyD88 signaling by recruiting all four adapter molecules. First, TLR4 uses TIRAP, which enables MyD88 recruitment to induce MAPK and NF-κB activation. TLR4 is pushed to an endosome through dynamin-dependent endocytosis during TRIF-dependent signal transduction and forms a complex with TRIF and TRAM. This complex initiates TRIF-dependent signaling, which is essential for forcing IRF3 to upregulate a type 1 interferon and the second phase of NF-κB and MAPK stimulation to trigger the production of inflammatory cytokines [8]. In dendritic cells, a protein limited to the endoplasmic reticulum, UNC93B1, plays an integral part in the transport of endosome-localized TLRs, including TLR3, TLR7, and TLR9. Mice that carry a mutation in this protein show absolute absence of all cytokine production after encountering respective PAMPs [9][10][11].

NLRs

This group of molecules recognizes a broad range of ligands inside the cell cytoplasm. In the last few years, the vital role of the NLRP family was widely recognized [11][12]. This class of molecules consists of approximately 34 members in mice and 23 members in humans. NLRs respond to metabolic stress and microbial byproducts by causing inflammation with the inflammasome assembly: a huge cytoplasmic complex that stimulates various inflammatory caspases that bring about the synthesis of IL-1β and IL-18 [13]. NLRs are large multidomain tripartition proteins and usually possess an inner nucleotide-binding region designated as the NACHT domain (also frequently referred to as the NOD domain). A C-terminal domain incorporates a receptor domain that carries repeating LRRs, and N-terminal domains serve for attachment to downstream pathway molecules. It is believed that the oligomerization of the NACHT domain is critical for the triggering of NLRs; therefore, establishing an effective signaling platform, e.g., a NODosome or inflammasome, is necessary to attach to the effector protein subunits and adapter molecules in order to elicit an inflammatory response [14][15]. NLRs play a vital part in the protection of the body from various infectious diseases caused by viruses, bacteria [16], helminths [17], fungi, and protists [18][19]. The NLRs studied so far are categorized into four classes: (1) MAPK and NF kB activators, (2) activators of the inflammasome, (3) *trans*-activators of MHC expression, and (4) inflammatory-signal inhibitors. Meanwhile, various NLRs perform a certain function in several biological mechanisms, such as fetal development and embryogenesis [20]. Alternatively, some NLRs have an essential role in development and inflammation [21]. On the other hand, a

few NLRs, such as NLRP3, recognize DAMPs, e.g., side products of sterile cellular damage (like uric acid or pathogen invasions, such as extracellular ATP release or reactive oxygen species [22][23]. One group of NLRs that modulates MAPKs and NF kB includes NLRC1 and NLRC2. NLRC1 identifies iE-DAP, a peptidoglycan component and a building block of the bacterial walls [24]. NLRC2 identifies another peptidoglycan fragment called muramyl dipeptide [25][26]. Then, NLRC1 and NLRC2 proceed with the help of adaptor molecule RIPK2 to start up MAPK and NF kB signaling pathways [27].

Inflammasomes have an inherent capability to induce an innate immune response after recognition of a DAMP or PAMP. The molecular patterns are identified through PRRs or endosomal compartments (e.g., TLRs) or in the cytoplasm, i.e., RIG-I–like receptors (RLRs). Engagement of these PRRs stimulates downstream signaling pathways that drive a release of proinflammatory cytokines [28][29]. Among these cytokines, few are synthesized in their precursor state, which is mandatory to be converted into a functionally active mature form. Various cellular components (such as the inflammasome) are crucial for this activation, ultimately resulting in the secretion of cytokines in their active state (as inflammatory markers) from some cells. The innate immune system triggers the inflammasome's triggering through a mechanism recently analyzed in numerous studies [30][31][32]. In both mice and humans, the leading players of the inflammasome are PRRs such as NLRs and "not present in melanoma 2–like receptors" (AIM2-like receptors) [33]. Various inflammasomes have been investigated, including the NLR family pyrin domain–containing 3 (NLRP3), AIM2, NLRP1, and NLRC4 types. NLRP3 is a member of the NLRP subfamily and contains a pyrin domain (PYD) at its N terminus. NLRP3 has been widely studied due to its integral role in immunity and immune-system–related diseases. In addition, NLRP3 is involved in the pathogenesis of numerous neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and metabolic diseases, e.g., atherosclerosis, obesity, and type 2 diabetes mellitus [34][35].

NLRP3 Inflammasome

Various factors have been documented that activate the NLRP3 inflammasome, although the exact mechanism is still unknown and needs further research. A possible mechanism behind the triggering of the NLRP3 inflammasome involves the production of reactive oxygen species, impairment of mitochondrial function, discharge of mitochondrial DNA, K+ efflux, a release of cathepsin B from damaged lysosomes, an imbalance of extracellular Ca2+ concentration, and the emergence of transmembrane holes [36][37][1]. Furthermore, NIMA-related kinase 7 (NEK7) is believed to attach to the LRR domain of NLRP3 and hence to carry out its activation by oligomerization [3]. Post-translational modifications have been proved to be crucially engaged in the activation of NLRP3 [4]. Nevertheless, deubiquitination and dephosphorylation can also result in its activation [5][6].

Moreover, phosphorylation of protein kinase A–related NLRP3 on the Ser21 residue is critical for triggering the NLRP3 inflammasome [8]. Recent studies revealed the function of microRNAs, e.g., myeloid-derived miR-223, in activating the NLRP3 inflammasome, such as myeloid-derived miR 223 [9]. Additionally, miR-33 has been reported to perform an essential function in the pathogenesis of rheumatoid arthritis through the modulation of the NLRP3 inflammasome in macrophages [10]

This knowledge has further improved understanding of the phenomena caused by epigenetic regulators during inflammasome stimulation [35].

2. Costimulatory Molecules/Receptors

Costimulatory molecules are categorized into three major groups, namely (i) immunoglobulin (Ig) superfamily, (ii) tumor necrosis factor (TNF) receptor superfamily (TNFR), and the emerging T cell Ig and mucin (TIM) domain family. They cannot activate T cells independently; however, they are crucial to functional naïve T cell response, which ultimately depends upon the consequence of the union of these stimulatory or inhibitory signals [12]. T cells' activation needs a first signal from the integration of antigenic peptide major histocompatibility complex (MHC) with T-cell antigen receptor (TCR) and a second signal from antigen-independent co-signal, the 'costimulatory signal. Jenkins and Schwartz et al. reported that in the absence of a costimulatory signal, T cells' TCR-mediated activation comes out in the antigen-specific unresponsiveness a phenomenon called T-cell anergy. Therefore, costimulation is considered to have a central role in regulating the outcome of T-cell contact with the antigen, whether it results in anergy or activation. The essential role of costimulation to regulate the immune response has driven the researchers to study further about it from therapeutic point of view. Earlier studies demonstrated the role of cluster of differentiation (CD)28 receptor for the naive T cells and evaluated the role of B7 family members such as B7-1 (CD80) and B7-2 (CD86) by their respective ligands. The encounter of CD28 and B7-1/B7-2 satisfied many requirements to strengthen the postulates by Lafferty, Schwarz, and colleagues for costimulatory signaling. The interaction between CD28 and B7-1/B7-2 fulfilled many of the requirements for the costimulatory signal postulated by Lafferty, Schwarz, and colleagues. It was illustrated that the CD28 homolog cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) exhibited a greater binding affinity for B7-1 and B7-2 in comparison to CD28 [13]. There was also a consideration that CTLA-4 would also be a stimulatory receptor, but the lethal inflammatory phenotype of CTLA-4 lacking mice (−/−) depicted the inhibitory function of CTLA-4. Moreover, CTLA-4 (−/−) mice exhibited the T-cell costimulatory receptors to convey stimulatory and second inhibitory signal for T-cell responses and indicated that the second inhibitory signals (co-inhibitory) could regulate T-cell tolerance [14].

The first costimulatory molecule to be identified as a member of the TNFR/TNF superfamily was CD154 (also called CD40 ligand) has a critical role in the function of B cells and dendritic cells (DCs). CD40 transduces the signals to dendritic cells (DCs) and B cells along with other cell types, such as tumor cells. Noelle and colleagues discussed the downstream signaling pathways activated by CD40 through tumor necrosis factor receptor associated factor (TRAF) proteins. They also showed the fundamental role of CD4/CD40L interactions in regulating cellular, humoral, and tumor immunity [15]. The members of TNFR/TNF family members, CD27/CD70, CD30/CD30L, OX40/OX40L, 4-1BB/4-1BBL, glucocorticoid-induced TNF receptor (GITR)/GITR ligand (GITRL) provide necessary costimulatory signals. Among them, CD27 is expressed on naive T cells while others are expressed only upon T-cell activation. Recent work suggested that OX40/OX40L and 4-1BB/4-1BBL interactions have a significant role in controlling the balance between effector and T_{reg} responses. Croft et al. discussed that OX40 boost effector T-cell expansion, survival, maintenance, generation, and reactivation of memory T cells [16]. OX40 blocks T_{reg} activity along with antagonizing the generation of inducible T_{regs}. Consequently, OX40 stimulates effector and memory T cell responses directly by activating these cells and indirectly by inhibiting T_{regs}. Due to the

dual-functional capacity of OX40, while blockade can attenuate the inflammation and autoimmunity and stimulation can enhance anti-tumor immunity, it has become an attractive therapeutic target. The primary role of 4-1BB is the survival of activated and memory T cells with particular impact on CD8+ T cells. The 4-1BB signals can cooperate with TCR-induced signals to increase the development and proliferation of response when other costimulatory signals are limited. 4-1BB is expressed on T_{regs}, and their ligation could enhance CD8+ T-cell and interferon-γ (IFN-γ)-dependent suppression of CD4+ T-cell responses.

3. Complement System

The complement system is a significant part of the innate immune system's effector mechanism that works as a bridge between innate and acquired immunity. It mainly consists of a collection of proteins that are synthesized in the liver and circulate in the blood plasma and on cell surfaces in the form of inactive precursor zymogens [17]. The complement system plays a vital role in infections and involves a wide range of physiological and pathological processes [18]. There are three known pathways for complement activation: classical, alternative, and lectin pathway.

3.1. Classical Pathway

The classical pathway is activated by binding immunoglobulin G (IgG) or IgM antigen/antibody complexes to C1q (first protein of cascade), leading to the activation C1r and, in turn, cleaves C1s. This results in the activation of serine proteases that cause cleavage of C4 and C2. This leads to C4b2a (C3 convertase) development, cleaving the C3 into C3a, and C3b [19]. The C3a will cause the recruitment of the inflammatory cells (anaphylatoxin), and in contrast, C3b binds to the C4b2a complex to formulate C5 convertase (C4b2a3b). Besides, the C5 convertase will activate the formation of the Membrane Attack Complex (MAC), which will form pores in the bacterial membrane leading to its lysis (30). The classical pathway can also be initiated by other danger signals such as viral proteins, C-reactive protein, polyanions, amyloid, and apoptotic cells [20][21][22]. This shows that the classical pathway can be activated without antibodies.

3.2. Lectin Pathway

Like the classical pathway, the lectin pathway also leads to the formation of C4bC2aC3 convertase complex in its activation. However, the lectin pathway utilizes members of the collectin family of plasma proteins called mannose-binding lectins (MBLs) and ficolins to identify the ligands' carbohydrate patterns expressed on the surface of various microorganisms. In addition, the ficolins are homologous to MBL. When MBL or ficolins binds to sugar molecules expressed on pathogens' surface, MBL-associated serine proteases are activated, i.e., MBL-Associated Serine Proteases (MASP)-1, MASP-2, MASP-3. This, in turn, cleaves the C4 and C2 to generate C4bC2a in a similar way as in the classical pathway [23].

3.3. Alternative Pathway

In contrast to the classical and lectin pathways, the alternative pathway is activated at low levels of pathogenic microorganisms in the normal host. This is mainly referred to as a *tickover* mechanism that allows the system to remain primed for a fast and robust activation. The hydrolysis of a thioester bond within C3 initiates the alternative pathway, resulting in a conformational change of the C3 structure. It is referred to as C3(H_2O), which has similar binding functionality to factor B as C3b. This bound CFB will act as a substrate for serine proteases factor D (CFD). Moreover, the cleavage of CFB by the CFD leads to the formation of alternative pathway C3 convertase C3(H_2O)Bb process, which is similar to the classical pathway C3 convertase (C4bC2a) and can cleave C3 into C3a and C3b. Moreover, the C3b generation by forming the amplification loop of C3 convertase C3bBb allows complete activation of the alternative pathway in either fluid phase represented by fluid phase C3b or surface bound C3b on the activating surface [24].

4. Interleukins

Interleukins are type of cytokines, initially discovered in 1955, secreted by leukocytes and various other types of cells [25]. Interleukin-1 (IL-1) family contains 11 cytokines and 10 receptors that play an essential role in the regulation of immune and inflammatory responses to infections via activation and differentiation of immune cells in addition to maturation, proliferation, migration, and adhesion. Interleukins also show pro-inflammatory and anti-inflammatory activity after binding to high-affinity receptors on the cell surfaces. IL-1 family system is strictly regulated at different points by decoy receptors, antagonists, scavengers, and dominant-negative molecules. The excessive or unchecked activation of the IL-1 family is the leading cause of detrimental and dangerous local or systemic inflammatory, allergic or autoimmune reactions [26]. Therefore, IL-1 family therapies have an enormous beneficial influence in treatment of inflammatory diseases. IL-1 family system is further divided into three sub-families. These include the IL-1 sub-family (IL-1α, IL-1β, and IL-33, IL-1Ra), IL-18 sub-family (IL-18 and IL37), and IL-36 sub-family (IL-36-α, -β, -γ, and IL-38). Among the cytokines, the sub-families are characterized as “pro-inflammatory” and “anti-inflammatory” such as IL-1α, IL-1β, IL-18, IL-33, and IL-1Ra, IL-36Ra, IL-37, IL-38, respectively [27][28][29].

Among the IL-1 family, there are seven agonistic ligand molecules (IL-1α, IL-1β, IL-18, IL-33, IL-36-α, -β, and -γ), three receptor antagonists (IL-1Ra, IL-36Ra, and IL-38), and an anti-inflammatory cytokine (IL-37). In the common IL-1 family activation pathway, the receptor chains commonly consist of an extracellular portion having three Ig-like domains except for IL-18 binding protein and TIR8, which have a single Ig domain. The intracellular portion of these receptors is characterized by a TIR domain that conducts the signal through the MyD88 adaptor molecule. The IL-1 family cytokines mediate the intracellular signaling pathway by binding to a primary receptor subunit such as IL-1 RI/IL-1 R1, IL-18 R α /IL-1 R5, IL-1 Rrp2/IL-1 R6, or ST2/IL-1 R4 which subsequently recruits an accessory receptor to form an active receptor complex (such as IL-1 RAcP or IL-18 R β) to activate downstream signaling. IL-1α, IL-1β, IL-18, IL-33, IL-36-α, -β, and -γ activates the intracellular signaling pathway that recruits the NF-κB and AP-1-dependent expression of chemokines, pro-inflammatory cytokines, and secondary mediators of the inflammatory response. Furthermore, other members of the IL-1 family prevent inflammation by acting as antagonists of IL-1 or IL-36 signaling. The IL-1Ra negatively controls the IL-1 signaling pathway by binding to IL-1

RI and inhibits its ability to interact with IL-1α and IL-1β. Likewise, IL-36Ra binds to IL-1 Rrp2 and inhibits IL-36 signaling [30]. Moreover, the cytokine receptor IL-6R and cytokines such as IL-8, IL-10, and IL-11 have been targeted by aptamers for therapeutic applications. Thus, the detailed pathway of these interleukins is described below.

4.1. IL-8 Signaling Pathway

IL-8 is a small soluble protein and belongs to the CXC chemokine family [37]. IL-8 was originally identified as a potent chemotactic and neutrophil activator factor secreted by activated macrophages and monocytes [3][4][5]. Moreover, neutrophils, lymphocytes, endothelial cells [10] and fibroblasts, also secrete IL-8 [31][32][33][34]. IL-8 holds the pro-angiogenic property, confirmed by a Glu-Leu-Arg motif that precedes the first N-terminal cysteine residue [35]. The biological activities of IL-8 are mediated by rhodopsin-like guanine-protein-coupled receptors (GPCRs): CXCR1 (IL-8RA) and CXCR2 (IL-8RB). CXCR1 and CXCR2 are characterized by 7-transmembrane-spanning regions, an extracellular N-terminus, and an intracellular C-terminus [38]. CXCR1 is stimulated by IL-8 and granulocyte chemotactic protein-2 (GCP-2)/CXCL6 [39]. CXCR2 can be activated not only by IL-8 but by many other CXC chemokines, for example, neutrophil-activating protein-2 (NAP-2)/CXCL7 and growth-regulated oncogene. Various studies stated that the signaling of IL-8 requires interaction between the N-terminal region of IL-8 and the N-terminal extracellular domain of the receptors [40]. This ligand binding activates the exchange of guanosine diphosphate for guanosine triphosphate on the Gα subunit, which activates the release of this subunit from the receptor and the Gβγ subunits [41]. Subsequently, Gα and Gβγ subunits activate a variety of signaling pathways in different cell types. The major three pathways include phosphatidylinositol 3 kinase/Akt (PI3K/Akt), phospholipase C/protein kinase C (PLC/PKC), and Ras/Raf/extracellular signal-regulated protein kinases 1 and 2 (Erk1/2). Other signaling pathways include focal adhesion kinase, Rho, Rac, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) [42].

4.2. IL-10 Signaling Pathway

The binding of IL-10 to the receptor complex activates the Janus tyrosine kinases, JAK1 and Tyk2, associated with IL-10R1 and IL-10R22. The domain of STAT3 recruitment is shared by other STAT3-recruiting receptors, IL-20R1, IL-22R1, and including gp130 [43]. Homodimerization of STAT3 drives its release from the receptor and translocate the STAT homodimer into the nucleus, where it binds to the STAT-binding promotor region of various genes, e.g., IL-10 itself. In addition, STAT3 stimulates cytokine signaling 3 (SOCS3) suppressor and, consequently, regulates the quality and quantity of STAT activation. SOCS proteins are composed of two primary domains: one is the substrate-binding domain called Src homology 2 (SH2) domain and second Socs box that form a complex with belongings B and C, a cullin and Rbx2, to form an E3 ubiquitin ligase [44]. The roles of STAT3 and SOCS in IL-10 signal transduction have been well established [45]. Moreover, IL-10 activates another pathway, the phosphoinositide 3-kinase (PI3K) pathway. Inhibition of NF-κB by IL-10 well explains many genes that remain unresponsive to IL-10 treatment. Dendritic cell maturation is also inhibited by defective NF-κB activation, decreasing the antigen-presenting cell (APC) function. Moreover, the inhibition of Rel family members, like p65, is an example of IL-10 inhibitory functionality for inflammatory genes, but it activates other genes. It is reported that

IL-10 inhibition may not occur in human monocytes at the extent of NF-κB inhibition [46]. The possible causes may include activation of an inhibitory PI3K/AKT and/or inhibition of MAPKs [47]. Therapeutic aptamer for IL-10R has been developed, will be discussed in Section 6.5.

4.3. IL-6 Signaling Pathway

Interleukin-6 (IL-6) is a pleiotropic cytokine that plays a significant role in the immune system and various biological functions such as hematopoiesis, inflammation, and oncogenesis by controlling cell survival growth, proliferation, and differentiation [48]. IL-6 receptor is composed of two distinct subunits IL-6Rα (gp80 or CD126), an 80-kDa type I transmembrane protein, and IL-6Rβ (gp130 or CD130), a 130-kDa second signal transmembrane protein. The soluble IL-6R, which is cleaved from the cell membrane, can still bind its ligand IL-6. Interleukin-6 exerts its activity mainly through binding to the cell membrane IL-6 receptor. Upon binding of IL-6 to IL-6R, homodimerization of gp130 is induced and a high-affinity functional receptor complex of IL-6, IL-6R, and gp130 is formed which initiates cellular events including activation of Janus kinase (JAK) kinases and activation of Ras-mediated signaling [49]. Activated JAK kinases phosphorylate and activate STAT transcription factors, particularly STAT3 (Signal Transducers and Activators of Transcription-3) and SHP2 (SH2 (Src Homology-2) domain-containing Tyrosine Phosphatase). Phosphorylated STAT3 then forms a dimer and translocate into the nucleus to activate transcription of genes containing STAT3 response elements. STAT3 is essential for gp130-mediated cell survival and G1 to S cell-cycle-transition signals. Both c-Myc and Pim have been identified as target genes of STAT3 and together can compensate for STAT3 in cell survival and cell-cycle transition. SHP2 links the cytokine receptor to the Ras/Mitogen-Activated Protein (MAP) kinase pathway and is essential for mitogenic activity [50].

Therapeutic aptamers against Interferon γ and TNFα have also been developed. Interferon γ is primarily secreted by activated T cells and natural killer (NK) cells which can promote macrophage activation, mediate antiviral and antibacterial immunity, enhance antigen presentation, and coordinate lymphocyte–endothelium interaction [51]. TNFα plays an important role in various physiological and pathological processes, including cell proliferation, differentiation, apoptosis, and modulation of immune responses and induction of inflammation [52]. The detailed signaling pathways can be checked from their reference papers, respectively.

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