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Expression of IL-1 Family in Immune System

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Abstract: The interleukin-1 (IL-1) family is closely related to natural inflammation and immune response. As an important component of innate immunity, IL-1 plays an important role in animals' organisms. The IL-1 family has 11 cytokines that induce the expression of pro-inflammatory factors and express their proteins through interactions between leukocytes and endothelial cells to regulate the bodys inflammatory response. IL-1 can also respond to non-specific induction of inflammatory cells and regulation of T lymphocytes. However, IL-1 family cytokines lack signal peptides and need a protein to hydrolyze them to activate them into active molecules.In this paper, the members of IL-1 family and the role of IL-1 will be discussed.

Keywords: Host Immunity; IL-1; Immunity; Inflammation

Introduction

Interleukin-1 (IL-1) mediator family is associated with acute and chronic inflammation and plays an important role in host response to infection. Members of the IL-1 family have the function of non-specifically enhancing antigen recognition and activating lymphocytes, and are called the basic characteristics of acquired immune response. In recent years, the significance of IL-1 family in diseases has become more important through therapeutic intervention against these molecules. Due to the role of IL-α and IL-β in self-inflammation, IL-α and IL-β are IL-1 families. The most studied member[1] of 35. When the body's defense system is impacted, IL-1 and β can assist the body's defense system to advance. Row evolution[2]. Therefore, basic inflammatory reactions such as the induction of cyclooxygenase 2 type, the production of various cytokines and chemokines increase the expression of adhesion molecules, or the synthesis of nitric oxide makes no difference between IL-1 and TLR ligands[3]. In the absence of neutrophil protection, the mice were supplemented with low dose of IL-1β to prevent the mice from being infected by dead bacteria[4]. Although we have now accepted the concept of cytokines such as IL-1β to protect the host, in today's antibiotics. In the 40 era of antiviral therapy, most people believe that cytokines are also the cause of diseases caused by acute or chronic inflammation. The role of IL-1 family members in the body is briefly described.

1. IL-1 and cytokines

1.1 IL-1 family

Cytokines and receptors of the 45 IL-1 family can widely affect the immune and inflammatory responses of the body. Members of the IL-1 family are closely related to the destruction of inflammatory cells. The 11 members of the IL-1 family are divided into 3 subfamily IL-1, IL-8 and IL-36 families. Each subfamily has its own members. The main mechanism of action is the binding of receptor and ligand. Only IL-Ra in the IL-1 family is[5] which carries signal peptide itself. Other members lack signal peptide and are not easy to secrete corresponding protein. They are found as diffuse precursors in the cytoplasm.

Each precursor of 50 has three conservative amino acid sequences AXD (consensus sequence, wherein a can

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represent any aliphatic amino acid, x represents any amino acid, and d represents aspartic acid). There are 9 N- terminal amino acids before the consensus sequence, which can provide the best folding form[6] for cytokines and receptors. However, the same family members also have the developmental effects of increasing non-specific anti-infection and anti-foreign immune response. The cytoplasmic domain[7] of the IL-1 receptor type I (IL-1R1) was found in the TOLL protein of Drosophila. The cytoplasmic component of the functional domain is called the Toll- interleukin -1 receptor (TIR) domain[8]. The functional domain of 55 has high homology with the functional domain of Toll like receptor (TLR).

1.2 Bifunctional cytokines

Dual-functional cytokines exist in the nucleus. Cytokines can bind to their cell membrane receptors and initiate signal transduction. Cytokines can also translocate to the nucleus as intracellular precursors and affect transcription. IL-1α and IL-33 are bifunctional cytokines. IL-1α can increase gene expression, and its function is similar to that of chemokine IL-8[9].

The N terminal amino acid of IL-1 contains nuclear localization sites. For example, the expression of N- terminal amino acid of IL-1β stimulates the production of IL-8 when the cell surface completely blocks IL-1RI.

2. IL-1 family transmission pathway

Members of the 65 interleukin 1 (IL-1) cytokine family are central mediators of immune response and inflammation, regulate many health and disease processes, and have extensive effects on immune and non-immune cells. Outpost cells of innate immune system (macrophages and monocytes) are the main sources of IL-1α and IL-1β, but many other cells such as epithelial cells, endothelial cells, fibroblasts, etc. can also produce IL-1α and IL-1β[10]. The signal transmission of IL-1 and α is mainly through membrane fixation, autocrine or signal transmission. The signaling system relies on the rapid transmission of multiple non-enzymatic adaptor proteins and enzymatic protein complexes[12].

When the conjugate of adaptor protein and enzyme protein is activated, phosphorylation and K48 linkage degradation reaction or K63 continuous non-degradation generalization reaction will take place. Because of its multidirectional nature, synthesis and release are mainly controlled by NALP3- inflammasome. Control of membrane receptor and regulation of signal transmission downstream of receptor, these three control levels limit the potent pro-inflammatory activity of IL-1.

The ligand-induced conformational change[13] in the first extracellular region of IL-1RI is beneficial to the combination of IL-1RACP (IL-1 receptor helper protein) with signaling proteins MyD88 and IL-1 receptor activated protein kinases (IRAK) 1 and 4 in the TIR domain of the cell, forming a trimeric complex and being activated by it, and then conducting signals to TRAF6 and MEKK3 in turn to form three conduction pathways. IRAK1 and IRAK2 also undergo phosphorylation reaction so as to undergo aggregation reaction with TRAF6 (tumor necrosis factor receptor-related factor and combine with functional adapters and protein kinases of IRAK1 and 2, and sequentially activate downstream conduction signals P62, PKC and TAK1 to act on pathway-dependent products into IKKβ-IKKγ (activation of nuclear factor inhibitor b phosphorylation reaction pathway[14]. When the multimeric complexes of IRAK1, 2 and TRAF6 are separated from the receptor complexes, cells lacking these proteins affect the activation of transcription factor nuclei, thus further activating NF-κB factor and activating protein -1 (AP-1)[15].

Therefore, TRAF6 in the cell intima is the key reaction factor, ubiquitin ligase (E3), and it conjugates with ubiquitin to perform its function. the ubiquitin E2 ligase complex is composed of protein conjugate synthase E2N and ubiquitin conjugate synthase E2 variant 1. the catalytic complex is combined with K63 linked polyubiquitin chain and IL-1 signaling intermediate[16]. Then the generalized TRAF6 and mapkkk7 (TAK1) form a complex that interacts with TAB1 and TAB2 proteins and tak1 and combines with MEKK3. When TRAF6 undergoes oligomerization reaction, it can directly combine with IRAK1 and IRAKK3 and undergo phosphorylation reaction, thus forming a necessary condition[17] for activating NF-κB and p38MAPK pathways.

Activation of the NF-κB pathway requires IL-1 to combine with activation of nuclear factor inhibitor B (I κ B) kinase 2 (IKK2), IK1 plus NF-κB essential modifier (NEMO) to form a core IKK complex. At the same time, NEMO can be combined with several upstream ubiquitin chain molecules, including IRAK1, Tak1, Tab2 and tab3[18]. The

activated IKK promotes phosphorylation of IκBα and further promotes degradation of the polyubiquitinated chain proteasome linked by K48. Subsequently, I, κ and B are destroyed and subunit p50 and p65 of NF-κB are released and nuclear translocation reaction occurs. This is the core step of activation of NF-κB. When TAK1 and MEKK3 are activated, MAPKK, mk3, MKK4, MKK6 and MKK7 are also activated

Will be activated. NKK4 and MKK7 activate JNK protein while MKK4, MKK3 and MKK6 activate P38 MAPK. The phosphorylated product of JNK is an important component of AP-1 protein and can activate transcription factor 2 (ATF-2)[19].

The signal transduction pathway of IL-1 is transient. When IL-1R and transcription interaction protein (TOLLIP) begin to combine, it will prevent the target of IRAK1 from transforming IL-1R into endosome, which is a necessary condition for the effective degradation of IL-1R. IL-1 can also activate several negative feedback inhibition signals of IL-1R, such as TAK1 inactivation caused by p38 MAPK mediated phosphorylation of TAK1, mRNA and protein synthesis of IκBα mediated by p65 NF-κB blocking the reaction of NF-κB, induced expression of gene encoding MAPK phosphorylase 1 (MKP1) dephosphorylation of active MAPK,etc. Some blocked molecular signals can also act as endogenous inhibitors[20]. When bacterial lipopolysaccharide (LPS) induces the generation of IRAK-M, a member of the IRAK family, this process does not activate the signal conduction mediated by IL-1R/TOLL like receptor, but blocks its signal conduction and causes its signal conduction to terminate.

3. Gene regulation of IL-1 and activation of IL-1 family members

3.1 IL-1 gene regulation of family

The main function of the P38 MAPK pathway is to stabilize the unstable IL-1 reactive mRNA containing adenine nucleoside rich elements (AREs). P38 MAPK can mediate the stable synthesis of mRNA and the translation process of transcription reaction, and can also activate the enzyme inhibition of downstream mRNA destabilization factor reaction. MAPK activated protein kinase 2)[21]. MK2 can make phosphorylated RNA and protein triproline (TTP).

Stable combination, while p 38MAPK can make KH splice regulatory protein (KSRP) undergo phosphorylation reaction, thus controlling the instability of IL-1 regulatory factor.

3.2 Activation of IL-1 α and IL-1 β

The IL-1α precursor does not have signal peptide, and can be an integrated membrane protein combined with nuclear DNA. When cells are exposed to apoptosis-promoting signals, IL-1α leaves the cytoplasm and rapidly migrates to the nucleus and rapidly combines with chromatin, but this process does not induce inflammation. IL-1α is used as unprocessed precursor or as processed protein and 1 type IL-1 receptor (IL-1R1) binding. The IL-1α on the cell surface has biological activity, so the IL-1α on the cell membrane is a complete membrane protein. Activation of the IL-1α precursor is accomplished by calcium-dependent protease II (Cystatic-1), while calcium influx induces secretion of the processed form of IL-1α. In addition, recent reports have reported the effect of inflammatory body-dependent IL-1α treatment of NOD like receptor P3 (NLRP 3), which also depends on calpain. Inflammation is proved to be related to the combination of MyD 88 and IL-1RI, but not to TLR[22]. In the cell culture of IL-1α, serine (Ser) was found, and the N- terminal was found at 113. Ser-113 was not the N- terminal predicted by consensus sequence. Calpain inhibited the precursor processing of IL-1α[23]. When S100A13 was used to treat mouse fibroblasts, it was found that the secretion of IL-1α increased[24].

IL-1β is mainly the product of monocytes, macrophages and dendritic cells (DC), although B lymphocytes and natural killer (NK) cells can also produce it in low amounts. There are many mechanisms for secretory maturation of IL-1β, including loss of membrane integrity, combination of phospholipase C and secretory lysosomes, and shedding of plasma membrane microbubbles or vesicles containing exosomes. In general, the release of active IL-1 occurs before the release of lactate dehydrogenase. The processing and secretion of IL-1β are carried out under the condition of activating inflammasome. Cells themselves can secrete proteins that form complexes with NLRP3 (inflammatory corpuscles), known as cryopyrin. NLRP forms a complex with inactive caspase-1 (caspase-1) and binds to potassium ions in the cell. After ATP binds to the P2X7 receptor, potassium in the cell rapidly leaves, and potassium in the cell begins to decrease, and the secretion of IL-1β begins to decrease. When the protein in the cell is oligomerized, caspase-1 will be activated

into an active enzyme and secreted into lysosomes or cytoplasm, which will stimulate the maturation of IL-1β and increase the expression of[25].

3.3 Expression of IL-18 and IL-37

IL-18 is first synthesized as an inactive precursor, has no signal peptide, and is still an intracellular cytokine. The IL-18 precursor is expressed in endothelial cells, keratinocytes and intestinal epithelial cells throughout the gastrointestinal tract. Macrophages and dendritic cells are the main sources of releasing active IL-18, while inactive precursors remain in the intracellular compartments of mesenchymal cells. The IL-18 precursor has a molecular weight of 24,000 and is processed by intracellular cysteine protease caspase-1, which cleaves the precursor into 17,200 active mature molecule[26]. Inactive caspase -1 is first activated into active caspase-1 by nucleotide binding domain and leucine-rich double pyrin protein-3 (nlrp3) inflammasome. After cleavage by active caspase -1, mature IL-18 is secreted from monocyte /macrophages, although more than 80 percent of IL-18 precursors remain unprocessed in the cells. Fas signal can activate caspase-8 in macrophages and dendritic cells, and can also induce the processing and release of IL-18. Vascular endothelial cell growth factor -D (VEGF-D) can also increase the secretion of IL-18[27]. IL-37 consists of blood mononuclear cells, tissue macrophages, synovial cells, tonsil B cells, plasma cells, T cells.

Expression of tumor cells and epithelial cells of skin, kidney and intestine. IL-37 cannot be expressed by blood mononuclear cells of healthy animals and requires activation of IL-1β and TLR agonists. The IL-37 precursor does not contain classical signal peptides. In endotoxin-stimulated human blood mononuclear cells, the addition of exogenous ATP leads to the release of processed IL-37, but most secreted IL-37 is still in precursor form. The precursor and processed form of IL-37 are both active. In keratinocytes, β-defensin -3 can induce the production of IL-37. When the body produces inflammation, monocytes in the blood are activated to produce IL-37 protein with a level of 10-20pg/ Million cells[28]. Despite the low production of endogenous IL-37, the use of recombinant IL-37 shows that cytokines have high activity.

4. IL-1 impact on the body

4.1 IL-1 effects of family factors on mice

The IL-1α on the cell membrane plays an important role in inflammation. When the IL-1α gene of the mouse is knocked out, it is found that the inflammatory state of the mouse itself is improved under the conditions of cell death and no release of the IL-1α in the cell. When the IL-1α gene of the newborn mouse is knocked out, the mouse develops normally. When injected subcutaneously with matsunitin, it can cause local inflammatory reaction in mice, thus causing fever in mice. However, after the IL-1β gene is knocked out, no spontaneous disease occurs in mice. In IL-1α deficient mice, the expression of IL-1βmRNA decreased by 1.5 times, while in IL-1β deficient mice, the expression of IL-1αmRNA decreased by 30 times or more. These data show that the regulatory expression of IL-1β on IL-1α is more obvious. When lipopolysaccharide (LPS) induces fever, the body temperature of mice lacking IL-1β is higher than that of other mice[29] compared with mice lacking IL-1α or IL-1β genes. When LPS is injected into mice lacking IL-1β gene, the expression of leptin mRNA in mice is little or no expression occurs.

The precursor of IL-18 exists in brain stroma and endothelial cells, so it is called the homeostasis regulator of IL-18 organism. Knock out the IL-18 gene of healthy mice, and at the 16th week, the mice began to suffer from obesity and abnormal insulin resistance[30]. Injection of IL-18 into mice or rabbits will not cause fever, and the concentration of IL-18 in blood will not increase after stimulating the body with bacterial products or endotoxin. IL-18 plays a specific immune role of IL-36 in immune-mediated diseases usually assisted by T in 1 type (Th1) diseases, and can also be used as a nonspecific adjuvant for T cell activation. In the asthma mouse model against airway sensitization, the response to antigen excitation makes bronchoconstrictor have enhanced response to airway, and the expression of IL-4 infiltrated by eosinophils in the lung increases. However, in mice that knocked out IL-1RI, the antibody response to inhaled antigen was significantly reduced. The T cells of IL-1R1 deficient mice cannot induce the production of IL-17[31] when challenged with antigen. Moreover, IL-23 cannot maintain the normal secretion of IL-17 in IL-1R1 defective T cells. In shock model, compared with wild-type mice, IL-37tg mice have less hepatitis, hypothermia and acidosis during endotoxemia[33].

4.2 IL-1 effects on human body

IL-1a and IL-1b are effective activators of DC subpopulations, including conventional (cDCs) and Langerhans cells (LCs), which are highly expressed phagocytes and are the first line of defense against skin pathogens. IL-1a can promote human mature mononuclear cells to produce DCs, enhance the response ability of CD4+T cells, and increase the secretion of interferon (IFN) -C and IL-13.

When the body produces brain injury or atherosclerosis, IL-1α also plays an important role[34]. IL-1b contributes to the activation of human DC mediated by CD40L and at the same time enhances its secretion of IFN-c in T cells to simultaneously produce IL-12 and IL-18 and perform the function of self-secretion. IL-18 can increase the expression of CCR7 in NK cells, which can produce high levels of IFN γ[35]. Several human autoimmune diseases are associated with increased production of IFN-γ and IL-18. Diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, type 1 diabetes, Crohn's disease, psoriasis and graft-versus-host disease are partially mediated by IL-18.

In trachea, IL-33 can promote the activation of DC and react to allergic inflammation, while in intestinal tract, IL-33 promotes the amplification of regulatory T cells. IL-33 also acts on macrophages, inducing M2 polarization and up-regulation of IL-13 in T cells, promoting the response of Th2 in vivo and secreting mature IL-6. IL-33 mainly acts as a pro-inflammatory cytokine in human rheumatoid arthritis, but IL-33 has anti-inflammatory properties. For example, IL-33 exerts anti-inflammatory properties in models of heart disease, obesity and uveitis. When the IL-33 precursor is overexpressed in cells, the IL-33 precursor can be combined with NF-κBp65 to induce a decrease in the secretion of tumor necrosis factor-α TNF-α[36]. When the body has inflammatory reactions and immune diseases, the content of IL-37 in the body will increase, thus playing the role of limiting inflammation. Compared with healthy people, the levels of IL-37 in patients with rheumatoid arthritis, patients with mandatory spondylitis and patients with psoriasis have increased.

5. Conclusion

When pathogens induce the body's immune system response, the most important thing is the mechanism by which inflammasome causes the addition and activation of IL-1 family cytokines. These findings can better be helpful to understand the process of inflammation and design and plan for treatment better. IL-1β and IL-18 activate caspase -1, which plays an important role in the regulation of innate immune system stimulation and adaptive immune response when inflammation occurs. However, activation of caspase -1 is not the only mechanism for processing IL-1β and IL-18 into bioactive cytokines. Neutrophil-derived serine protease and pathogen-released enzyme can also be treated to activate IL-1 cytokine.

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