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EDITORIAL

INTERRELATIONSHIP BETWEEN INFLAMMATORY CYTOKINES (IL-1, IL-6, IL-33, IL-37) AND ACQUIRED IMMUNITY

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It is now well-known that interleukins (ILs) play a pivotal role in shaping innate immunity: inflammatory ILs are responsible for all innate aspects of immune response, from the very first vascular reactions to the chronic non-specific response to inflammation; while anti-inflammatory ILs are responsible for keeping adaptive immunity at bay. The interactions between ILs and adaptive immunity have been long considered secondary to the effects on the innate immune system, but in recent years it has appeared more clearly that IL direct interactions with adaptive immunity are extremely important both in physiologic and pathologic immune response. In the present review we analyze the role of inflammatory ILs (IL-1, IL-6, IL-33 and IL-37) on adaptive immunity and briefly discuss the possible therapeutic perspectives of IL-blockade in adaptive immunity disorders.

Inflammatory cytokines are a heterogeneous group which comprises the interleukin (IL)-1 family. The IL-1 family is made up of 11 different cytokines: IL-1α, IL-1β, IL-1Rantagonist (IL-1Ra), IL-18, IL-36Ra, IL-36α, IL-37, IL-36β, IL-36γ, IL-38 and IL-33 (1). Cytokines belonging to the IL-1 family present the same structure at the C-terminus, a β-trefoil fold made up of 12-β-strands connected by 11 loops. The pathways through which they are produced and activated are quite different from one another, ranging from nuclear expression and activation, to caspase-depending activation (2). Their functions also differ considerably, as some of these cytokines are involved in inflammatory pathways (IL-1α, IL-1β,IL-18, IL-36α,IL-36β, IL-36γ and IL-33), others have anti-inflammatory properties (IL-37) and others work as antagonists of other IL belonging to the IL-1 family (IL-1Ra and IL-36Ra). Yet, the differences in their function appear to be primarily associated to the different IL-receptors (IL-R) (3). The IL-R family is made up of 10 different receptors of which IL-1R8, IL-1R9 and IL-1R10 are anti-inflammatory pathway

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activators, while the others work as inflammatory receptors (1).

The role of the IL-1 family has been explored particularly in the pathogenesis of auto-inflammatory diseases, as it seems that alterations of the balance between the different members of the family and the expression of IL-R are key factors in the pathogenesis of these diseases. However, the role of the IL-1 family has been studied also in other immunological diseases and disorders; for example, psoriasis, rheumatoid arthritis, gout, systemic lupus erythematosus and Crohn's disease have been specifically linked to IL-36, IL-37 and IL-38 (4), while autoimmune hepatitis has been linked to IL-1 (5). IL-36 also activates mast cells (6). Targeting members of the IL-1 family is now a common therapeutic strategy in hematologic malignancies and disorders (7) and it is being examined also in septic patients (8).

The role of the IL-1 family in human pathology has prevalently been linked to its effects on the innate immune system, promoting the activity of neutrophils, eosinophils, basophils, mast cells and natural killer cells. Yet, it appears that the IL-1 family also acts on the adaptive immune system, not only through its effects on the innate components of the system, but also directly (9).

IL-6 is another important inflammatory cytokine that is often linked to various different diseases and that may be synergic with the IL-1 family in the development of different diseases, such as macrophage activation syndrome (10) and different forms of cancer (11). It also appears to interact with the IL-1 family in the direct regulation of the adaptive immune system (12).

In this review, our main focus is to discuss the role of the IL-1 family, IL-1 and IL-33 particularly, and of IL-6 in the shaping of adaptive immunity and the possible practical consequences there could be in terms of therapies (13).

The IL-1 family in adaptive immunity: IL-1, IL-33 and IL-37

The IL-1 family plays a key role in innate immune response, sharing a similar function with Toll-like receptors (TLRs). They both stimulate the same aspecific inflammatory pathways, through cycloxigenase-2, production of cytokines and chemokines, expression of adhesion molecules and synthesis of nitric oxide. Many of these ILs present a so-called dual function, as in the case of IL-1α. The term dual-function indicates a situation in which a cytokine is expressed both as a membrane protein and as a nuclear protein, through which it promotes different pathways. The nuclear form of IL-1α is responsible for the regulation of the inflammatory response in the cell, while the membrane form promotes inflammation and interacts with interferon (IFN)-γ, allowing and promoting many of its functions. One of the key regulators of the expression of IL-1α is IL-1β, which also plays a role in determining inflammation, particularly in response to lipopolysaccharide (LPS) and IL-1α.

IL-1 is a well recognized innate immunity driver: its activity is driven by damage or pathogen-associated molecular patterns (DAMPs and PAMPs), both natural and artificial. Indeed, it has been demonstrated that the aspecific beneficial effects of vaccines are IL-1 mediated. The role of IL-1 on adaptive immunity is more complex, as it partly depends on the enhancement of innate immunity (6), but there are also other mechanisms through which it activates the adaptive system. One of the suggested mechanisms is the so called "metabolic pathway": IL-1 appears to stimulate hypoxia inducible factor 1 (HIF1), which promotes the shift from oxidative phosphorylation to aerobic glycolysis, a key factor in adaptive immunity. IL-1 can also directly stimulate the enhancement of glycolysis *vs* oxidative phosphorylation (14).

The role of IL-1 in human pathology is of great interest, particularly in the case of cancer. It has been demonstrated that IL-1 is present in tumor microenviroment, where it promotes growth and development of different tumor forms. IL-1 is fundamental in angiogenesis and it appears to act as a promoter of both colorectal and ovarian cancer. On the other hand, higher levels of IL-1 at the tumor site increase immune response to the tumor itself, with a higher number of $CD8^+$ T cells, NK cells and M1-differentiated macrophages. Nonetheless, most studies point towards the hypothesis that

IL-1 has mostly a pro-tumor activity, but local and concentrated stimulation with IL-1 at the site of tumor may have some beneficial effect (2).

IL-33 is another dual-function IL, presenting both a nuclear and a membrane form. In its nuclear form, IL-33 has been linked to an anti-inflammatory role, but as it appears to favor inflammation in rheumatoid arthritis, it is argued that its membrane form has instead inflammatory activity (15). Also in hypersensitivity diseases, such as allergies, IL-33 has an ambiguous role: indeed, it appears that its blockage, in association with the blockage of IL-17, can induce an improvement in this group of diseases (16). The different roles which IL-33 appears to play are probably secondary to the different receptors it interacts with. The bond between IL-33 and the IL-1 family orphan receptor, suppression of tumorigenicity 2 (ST2), is one of the most studied and activates a complex cascade of different events. Myeloid differentiation response protein (MyD88), IL-1R-associated kinase, TNF receptor-associated factor 6, mitogen-activated protein kinases (including JNK, p38, and ERK), and nuclear factor-kappa B (NF-κB) are only some of the different proteins and kinases which are activated and which are pivotal to different cell processes, such as the secretion of other cytokines, cell replication and survival. IL-33 can also directly interact with NF-κB, promoting among others wound healing (17).

IL-33 is capable of stimulating a Th2 type of response, especially in the gut, which is particularly rich in ST2 receptors. When it binds to ST2 on antigen presenting cells (APCs), there is an important increase in the production of type 2 immune response cytokines (IL-4, IL-5, and IL-13), which, in turn, enhance IL-33-induced type 2 innate lymphoid cell (ILC2) activation (17-18).

On the other hand, IL-33 is capable of inducing CD4+Foxp3+ regulatory T lymphocytes (TREGs), which is one of the ways through which it determines its anti-inflammatory effects. This activity is particularly evident in the gut, where IL-33 appears to be extremely active. While the activation of the Th2 pathway via IL-33 is quite straightforward, the regulatory activity of IL-33 in the gut is also influenced by the resident microbiota, which, on the other hand, is influenced by IL-33 signaling: Malik et al. have demonstrated, for instance, that IL-33-deficient mice have a different microbiota compared to wild type mice (19).

Given its intense activity in the gut, IL-33 has been studied in relation to inflammatory bowel disease (IBD) and it seems that IL-33 is linked specifically to ulcerative colitis (UC): patients with active disease have a higher level of IL-33 w compared to patients in remission, but a clear causative relationship between UC and IL-33 has not yet been established (17).

IL-37 is another member of the IL-1 family and is responsible for the modulation of IL-18 (also known as the IFN-γ inducing factor). Even though it is an inflammatory interleukin, IL-37 is responsible for an anti-inflammatory effect when it acts on the IL-18 pathway: when it binds to the IL-18R, STAT3 is activated and an inhibitory signal is started (20). Another pathway through which IL-37 exerts its immune-modulating capacity is through binding with small mother against decapentaplegic (SMAD)3, forming a complex with important nuclear regulatory capacity. Proof of the importance of this interaction has been demonstrated through inhibition of SMAD3, which resulted in IL-37's loss of immune-modulating function (21).

The modulating effects of IL-37 are particularly interesting in the context of joint and skin inflammatory conditions: in skin lesion biopsies of patients suffering from psoriasis, IL-37 levels were lower than expected. Low levels of this interleukin have been linked to an incorrect modulation of key mediators involved in murine psoriasis (e.g. IL-8, IL-6 and S100 calcium-binding protein A7-S100A7) (22).

While low levels of IL-37 have clearly been linked to an incomplete immune-modulation capacity, it seems that also very high levels of IL-37 can lead to an increase of overall inflammation. In patients suffering from rheumathoid arthritis (RA), for example, levels of IL-37 are normal in the synovium and over the normal range in peripheral blood. Such mechanism could be explained by the negative feedback mechanisms through which IL-37 appears to be regulated: when present in high concentrations IL-37 forms homodimers, which are

less effective in the blockade of the IL-18 signaling pathway. Also, it is noteworthy that IL-37 can inhibit osteoclastogenesis, resulting even more interesting in the field of future RA therapies (23).

Interestingly, both IL-33 and IL-37 have anti-inflammatory and pro-angiogenic functions, suggesting that there might be similar underlying pathways. IL-37 angiogenic efficacy has been reported to be as strong as that of VEGF (24-25).

IL-6 AND ADAPTIVE IMMUNITY

IL-6 is prevalently involved in immune reactions to infections. Its activity is deeply tied to the IL-1 family, as similar stimuli can induce their synthesis and IL-1β can also induce IL-6 production. There are different signaling pathways activated by IL-6: in the "classic" pathway IL-6 bonds with its receptor, IL-6R, which activates glycoprotein 130 (gp130) in its membrane form. This kind of signaling is typical of hepatocytes, neutrophils, monocytes, activated B cells and CD4 T cells. IL-6 can also activate gp130 through trans-signaling, activated by the bond between IL-6 and the soluble form of IL-6R (sIL-6R). This form of signaling is extremely interesting, as it allows IL-6 signaling in all those cells which do not present a membrane IL-6R.

gp130 is involved in many different signaling pathways and is activated by different factors, such as leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), IL-11, cardiotrophin-like cytokine factor 1 (CLCF1), IL-27 and IL-35, partly accounting for the redundancy in the functions of IL-6.

IL-6 plays a complex role in modulating immunityas it stimulates the first innate responses to a stressor, such as leukocytosis, increased blood vessel permeability and liver synthesis of acute phase proteins. As a matter of fact, the liver is extremely sensitive to the action of IL-6, as hepatocytes are among the cellular types that actually respond to classic IL-6 and they mediate the response of other organs to IL-6 signaling pathway. For example, anemia following chronic inflammation is caused by hepdicin, which is produced by the liver after IL-6 stimulation, allowing IL-6 to control indirectly erythropoiesis.

Besides its role in innate immune response, IL-6 also shapes adaptive immunity, stimulating B-lymphocytes to differentiate in plasma-cells. Also T-lymphocytes are influenced by IL-6 signaling, as they are induced to shift towards a Th17 phenotype, while TREG production is inhibited. Il-6 interferes with TGF-β, which promotes TREG differentiation, increasing the activity of its SMAD protein pathway. SMAD-I in particular can silence TGF-β. It is worth noting that IL-6, like IL-33, is extremely important in regulating immunity of the gut, but it seems to be a protective factor against IBDs. On the other hand, IL-6 may promote the development of colorectal cancer in a similar fashion to IL-1. The roles of IL-1 and IL-6 are similar also in the context of autoinflammatory diseases, but IL-6 is associated to a much vaster array of diseases, ranging from adult onset Still's disease, to depression, to myocardial infarction; different studies and case reports have reported encouraging results after blockade of IL-6 (26).

TARGETING INTERLEUKINS IN ADAPTIVE IMMUNITY DISORDERS

Blockade of ILs has worked as a therapy in different diseases. IL-6 blockade, for instance, has given positive results in different conditions, but the underlying immunologic mechanisms are not completely clear. Depression is one of the diseases in which IL-6 blockade has given encouraging results that are not yet fully understood: even though many authors report an altered inflammatory status in patients experiencing depression, the actual role of immunity is still under scrutiny. Also in heart failure and cardiovascular disease, in general, IL-6 is an interesting and apparently effective target.

Targeting ILs belonging to the IL-1 family and IL-6 began in the context of autoinflammatory diseases, but is particularly interesting and promising in the context of cancer therapy. As previously stated, IL-1 is extremely important in promoting tumor progression and growth. The use of drugs such as Anakinra, which inhibit IL-1 signaling pathway, reduce the inflammatory status induced by the tumor and correct the metabolic

alterations, possibly reducing associated symptoms such as neoplastic cachexia. Such effects are due not only to the inhibition of IL-1 expressed by the tumor, but also through the inhibition of CD14+ and CD16+ monocytes present at the tumor site. The effects on angiogenesis are also important and are enhanced by the effects of platelet blockade of IL-1 signaling. The sensitivity of platelets towards IL-1 signaling accounts for the importance of anti-IL-1 therapy, specifically IL-1β through Canakinumab, in atherosclerosis: studies conducted on patients who were at high risk of developing such condition showed that not only treated patients had a better cardiovascular health profile, but also lung cancer incidence and mortality dropped.

In the rheumatologic field, inhibition of ILs has been tested also on diseases that are not autoinflammatory, but also autoimmune, such as rheumatoid arthritis. In particular, juvenile forms benefit from blockade both of IL-1 family and IL-6. Overall, many diseases with an important inflammatory component, e.g. heart failure, diabetes, have been treated in experimental settings through IL-1 family or IL-6 blockade with interesting results. The positive effects of similar therapies obtained in such a broad spectrum of diseases is a sign of how ILs act on different aspects and components of the immune system.

CONCLUSIONS

ILs are key components of the innate immune system and determine the first stages of all immune and inflammatory reactions. However, ILs have a much broader spectrum of action, as they can interact directly and indirectly with the adaptive immune system and even with tissues and cells not belonging to the immune system. These results do not only improve our understanding of the importance of ILs specifically and the immune system in general, but also offer interesting therapeutic perspectives for a vast array of diseases.

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