A REVIEW ON- INTERLEUKIN-1

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***Abstract*: Interleukins (ILs) are a group of cytokines (secreted proteins and signal molecules) that were first seen to be expressed by white blood cells (leukocytes). ILs can be divided into four major groups based on distinguishing structural features. However, their amino acid sequence similarity is rather weak (typically 15–25% identity). The human genome encodes more than 50 interleukins and related proteins.**

The function of the immune system depends in a large part on interleukins, and rare deficiencies of a number of them have been described, all featuring autoimmune diseases or immune deficiency. The majority of interleukins are synthesized by helper CD4 T lymphocytes, as well as through monocytes, macrophages, and endothelial cells. They promote the development and differentiation of T and B lymphocytes, and hematopoietic cells.

***Keywords*: human genome , lymphocytes, B lymphocytes, hematopoietic cells**

Discovery-

Discovery of these cytokines began with studies on the pathogenesis of fever. The studies were performed by Eli Menkin and Paul beeson in 1943–1948 on the fever-producing properties of proteins released from rabbit peritoneal exudatecells. These studies were followed by contributions of several investigators, who were primarily interested in the link between fever and infection/inflammation. The basis for the term "interleukin" was to streamline the growing number of biological properties attributed to soluble factors from macrophages and lymphocytes. IL-1 was the name given to the macrophage product, whereas IL-2 was used to define the lymphocyte product.

In 1985 two distinct, but distantly related complementary DNAs encoding proteins sharing human IL-1 activity were reported to be isolated from a macrophage cDNA library, thus defining two individual members of the IL-1 family – IL-1α and IL-1β.

Introduction-

IL-1 family is a group of 11 cytokines, which induces a complex network of proinflammatory cytokines and via expression of integrins on leukocytes and endothelial cells, regulates and initiates inflammatory responses.

IL-1α and IL-1β are the most studied members, because they were discovered first and because they possess strongly proinflammatory effect. They have a natural antagonist IL-1Ra (IL-1 receptor antagonist). All three of them include a beta trefoil fold and bind IL-1 receptor (IL-1R) and activate signaling via MyD88 adaptor, which is described in the Signaling section of this page. IL-1Ra regulates IL-1α and IL-1β proinflammatory activity by competing with them for binding sites of the receptor. Nine IL-1 superfamily members occur in a single cluster on human chromosome two; sequence and chromosomal anatomy evidence suggest these formed through a series of gene duplications of a proto-IL-1β ligand. In this way, IL-1β, IL-1α, IL-36α, IL-36β, IL-36γ, IL-36RA, IL-37, IL-38, and IL-1RA are very likely ancestral family members sharing a common lineage.However, IL-18 and IL-33 are on different chromosomes and there is insufficient sequence or chromosomal anatomy evidence to suggest they share common ancestry with the other IL-1 superfamily members. IL-33 and IL-18 have been included into the IL-1 superfamily due to structural similarities, overlap in function and the receptors involved in their signalling.

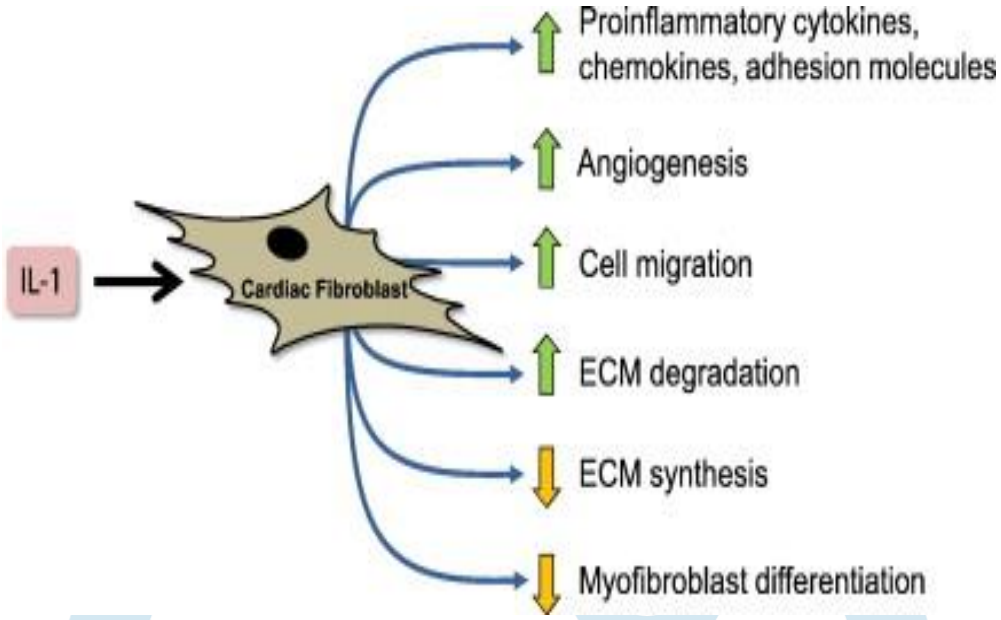
Synthesis-

All of the members of IL-1 family, except IL-1Ra, are first synthesized as a precursor protein, which means it is synthesized as a long form of a protein which has to be proteolytically cleaved to a shorter, active molecule, which is generally called a mature protein. IL-1 family precursors do not have a clear signal peptide for processing and secretion and none of them are found in the Golgi; they belong to so-called leaderless secretory protein group. The similar feature of IL-1α and IL-33 is that their precursor forms can bind to their respective receptor and can activate signal transduction. But this is not a common feature for all IL-1 family members, since IL-1β and IL-18 precursor forms do not bind their receptors and require proteolytic cleavage by either intracellular caspase-1 or extracellular neutrophilic proteases.

Functions-

IL-1 is a master regulator of inflammation via controlling a variety of innate immune processes . From a historical point of view, IL-1 has a wide range of biological functions, which include acting as a leukocytic pyrogen, a mediator of fever and a leukocytic endogenous mediator, and an inducer of several components of the acute-phase response and lymphocyte-activating factor (LAF) . LAF was later shown to be a macrophage-derived immune mediator acting on T- and B- lymphocytes and was designated as IL-1 in the Second International Lymphokine Workshop held in Switzerland in 1979 . In addition, serum blocking factors in breast cancer patients identified by the leukocyte adherence inhibition test were reported. The serum adherence-promoting factors were regulated by IL-1 . To date, the tumor microenvironment has been characterized by dominant immunosuppression, being infiltrated

by tumor immunosuppressive myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor-associated macrophages (TAMs).



Signaling

IL-1α and IL-1β bind to the same receptor molecule, which is called type I IL-1 receptor (IL-1RI). There is a third ligand of this receptor – the Interleukin 1 receptor antagonist (IL-1Ra), which does not activate downstream signaling, so it acts as an inhibitor of IL-1α and IL-1β signaling by competing with them for binding sites of the receptor.

IL-1α or IL-1β bind first to the first extracellular chain of IL-1RI, that recruits the IL-1 receptor accessory protein (IL-1RAcP), which serves as a coreceptor and is necessary for signal transduction and it is also needed for activation of IL-1RI by IL-18 and IL-33.

Biological activity

IL-1 is intensely produced by tissue macrophages, monocytes, fibroblasts, and dendritic cells, but is also expressed by B lymphocytes, NK cells, microglia, and epithelial cells. They form an important part of the inflammatory response of the body against infection. These cytokines increase the expression of adhesion factors on endothelial cells to enable transmigration (also called diapedesis) of immunocompetent cells, such as phagocytes, lymphocytes and others, to sites of infection. They also affect the activity of the hypothalamus, the thermoregulatory center, which leads to a rise in body temperature (fever) . That is why IL-1 is called an endogenous pyrogen. Besides fever, IL-1 also causes hyperalgesia (increased pain sensitivity), vasodilation and hypotension

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