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INTERLEUKIN 1 RECEPTOR ANTAGONIST

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INTRODUCTION

Interleukins are a group of cytokines that were first seen to be expressed by white blood cells.[1] 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 disorder. The majority of interleukins are synthesised 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 haematopoetic cells. Interleukin receptors on astrocytes in the hippocampus are also known to be involved in the development of spatial memories in mice.[2]

CYTOKINES

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities) and interleukin (cytokines made by one leukocyte and acting on other leukocytes).

Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both pro-inflammatory cytokines and anti-inflammatory cytokines. There is significant evidence showing that certain cytokines/chemokines are involved in not only the initiation but also the persistence of pathologic pain by directly activating nociceptive sensory neurons.[3]

Interleukin 1

The Interleukin-1 family (IL-1 family) is a group of 11 cytokines, which plays a central role in the regulation of immune and inflammatory responses to infections or sterile insults. IL-1

is intensely produced by tissue macrophages, monocytes and fibroblasts and dendritic cellsbut is also expressed by B lymphocytes, NK cells and epithelial cells(4). They form an important part of the inflammatory response of the body against infection. These cytokines increase the expression of adhesion factor 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.[5] [6]

EFFECT OF INTERLEUKIN 1 ON THE PERIODONTIUM

IL-1 plays an important role in the pathogenesis of periodontitis, through its involvement in the regulation of the host's inflammatory response and bone resorption. Therefore, the genes that encode for IL-1 production have recently received most attention as potential predictors of periodontal disease progression. Hence, the relationship between IL-1 genotype and periodontal disease has been investigated by a number of studies.[7]

ROLE OF IL IN DISEASE

IL-1 has a major role in inflammation.[8] During inflammation, there are increased levels of TNF and IL-1 in the brain,[9] and their presence may cause the breakdown of the blood-brain barrier.[9] Polymorphism in IL-1 genes have been found to contribute to genetic susceptibility to some cancers,[10] ankylosing spondylitis[11] and Grave's disease.[12]

In terms of clinical use, because of its characterisation as a hematopoetic factor, IL-1 was given to patients after bone marrow transplantation to improve the engraftment. But soon it was discovered that the patients were experiencing symptoms of systemic inflammation. Pharmacological blockade of these receptors was then sought in order to relieve symptoms. The endogenous IL-1 receptor antagonist (IL-1Ra), also known as anakinra, was tried in clinical trials to lessen systemic inflammation, but did not demonstrate a statistically significant difference from placebo.[13]

Nowadays, the blockade of IL-1 activity (especially IL-1β) is a standard therapy for patients with autoimmune diseases or lymphomas. Anakinra (IL-1Ra) is FDA-approved as a therapy for patients with rheumatoid arthritis,[14] because it reduces symptoms and slows joint destruction of this inflammatory disease. It has also been prescribed to patients with indolent

or smoldering myeloma with a high risk of progression to multiple myeloma. In combination with other medication, IL-1Ra provides a significant increase in the number of years of progression-free disease in its recipients. The benefits of this treatment are the natural structure and no toxicity or gastrointestinal disturbances.[15]

Clinical trials on IL-1α have been carried out that are specifically designed to mimic the protective studies in animals. IL-1α has been administered to patients during receiving autologous bone marrow transplantation.[9] The treatment with 50 mg/kg IL-1α from day zero of autologous bone marrow or stem cells transfer resulted in an earlier recovery of thrombocytopenia compared with historical controls. IL-1α is currently being evaluated in clinical trials as a potential therapeutic in oncology indications.

An anti-IL-1α therapeutic antibody, MABp1, is being tested in clinical trials for anti-neoplastic activity in solid tumours. Blocking the activity of IL-1α has the potential to treat skin diseases such as acne.

RATIONALE OF ANTI-CYTOKINE THERAPY

Periodontal destruction is initiated by bacteria that stimulate host responses leading to excess production of cytokines. Anticytokine therapy for periodontal diseases especially targets pro inflammatory cytokines, that is, TNF-α, IL-1, and IL-6, because these are essential for the initiation of the inflammatory immune reaction and are produced for prolonged periods in periodontitis(10-12). This therapy aims to bind the cytokines with the receptors present on target cells such as the fibroblasts. The three basic treatment strategies are.

(1) neutralisation of cytokines

(2) blockage of cytokine receptors

(3) activation of anti-inflammatory pathways, such as, immune-suppressive pathways.

This new therapy can act as a host response modulator in the control of inflammatory diseases of gums and may provide the basis for new molecular therapeutic approaches to the treatment of periodontitis.

ANTI CYTOKINE AGENTS

- **Infliximab** - Infliximab is a chimeric IgG monoclonal antibody. The term chimeric refers to the use of both mouse (murine) and human components of the drug.

- **Etanercept**- Etanercept is a fusion protein. It links human soluble TNF receptor to the Fc component of human IgG1.
- **Anakinra**- It is an interleukin-1 (IL-1) receptor antagonist. It competitively inhibits the binding of IL-1 to the Interleukin-1 type receptor.Anakinra blocks the biological activity of naturally occurring IL-1, including inflammation and cartilage degradation.

EXOGENOUS DRUGS

Anakinra.

Imaxicab.

PREVIOUS STUDIES

Previous studies show that IL-1a, IL-1B and TNF-a stimulate one resorptionand inhibit bone formation. Researches show that IL-1B levels to be increased in the gingival crevicular fluid in sites of new bone loss and periodontitis. It has also been proves that IL1 antagonist prevents or reduces the intensity of bone loss, reduction in inflammation induced by the periodontal pathogens.

CONCLUSION

In this era of molecular biology where research has been focused on the genetic level of analysis, treatment should be focused on eliminating the root cause.Strategies for preventing cell activation seek to inhibit the intracellular transduction of signals produced when ligands bind to their membrane receptors.

Signal transduction pathways are activated not only by cytokines, but also by other factors, such as bacterial proteins, lipopolysaccharide, or environmental stress. Inhibition of signal transduction pathways by cytokine-suppressive anti-inflammatory drugs (CSAIDs) would be expected to abolish both cell activation by cytokines or other stimuli and the production of pro-inflammatory cytokines. Various cell signalling pathways which are closely involved in the inflammation and can be blocked include following pathways.

Periodontal advancement should be diverted toward the use of anti-cytokine therapy in the near future.

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