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IL-4, IL-1 RECEPTOR ANTAGONIST, IL-37, AND IL-38 INHIBIT IL-1 AND TNF GENERATED BY MICROGLIA

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ABSTRACT

Microglia are innate immune cells resident in the brain with phagocytic activity similar to macrophages. Microglia are protagonists in inflammatory brain diseases and are large producers of interleukin (IL)-1. IL-4 is a growth factor for hematopoietic cells, helps B cells to produce immunoglobulins, and has the ability to down-regulate and inhibit the production of IL-1 generated by both macrophages and microglia. Here, we report that the anti-inflammatory cytokines, IL-1 receptor antagonist (IL1-Ra), IL-4, IL-37, and IL-38 can inhibit the generation of IL-1 produced by microglia in inflammatory brain diseases.

KEYWORDS: *IL-4, IL-1, IL-1-Ra, microglia, inflammation*

INTRODUCTION

Interleukin (IL)-4 is a 20-KDa cytokine glycoprotein product produced by T helper cells that has interesting biological effects. It is involved in the generation of the immunoglobulins IgG1 and IgE in mice, it has growth factor activity for T cells, mast cells (MCs), and thymocytes, and can activate T and B cells (1). IL-4 is also a growth factor for hemopoietic cells as well as an activation factor for macrophages (2,3). However, we believe the most interesting biological effect discovered so far for IL-4 is its capacity to down-regulate and inhibit IL-1 and tumor necrosis factor (TNF) produced by macrophages (4). In relation to the clinical sphere, it appears that IL-4 may suppress the generation of fever *in vivo*, and more surprisingly, in cancer patients, there seems to be a return of appetite and of weight gain after treatment with IL-4, thus reversing undesired symptoms generally mediated by IL-1 and TNF (5). Cytokine therapies for cancer patients have been shown to produce unwanted side-effects due to potent inflammation. Hypotension, thrombocytopenia, capillary leak syndrome, leukopenia, fever, and arachidonic acid product formation, are all involved in the toxic shock-like syndrome and are among the many undesired effects produced by IL-2, IL-1, TNF, IL-6, GM-CSF, and other cytokines. This cytokine release syndrome may even lead to death by inducing toxic shock syndrome (6).

DISCUSSION

The interleukin-1 receptor antagonist (IL-1Ra), IL-37, and IL-38 have been seen to inhibit IL-1 (7), the master of inflammation which induces other inflammatory cytokines. These anti-inflammatory proteins are monokines secreted by

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human monocytes and are structurally similar to IL-1β, but with no IL-1-like activity. They dump IL-1 by binding to its cell surface receptor and exert their biological effects.

It has been found that IL-1Ra is not only an IL-1 inhibitor, but that this protein can also potentiate IL-2 to activate natural killer (NK) cells and down-regulate DNA synthesis in mitogen stimulated lymphocytes (8); this latter phenomenon is most probably due to the IL-1 inhibition. However, the reason for these biological effects is not yet totally understood.

The inhibitory effects of IL-4 and IL-1Ra on IL-1 and TNF production plays an extremely important role in controlling the delicate immunoregulatory balance during immunity and inflammation following cytokine immunotherapy.

Microglia are macrophage-like cells that are part of the innate immune system of the central nervous system (CNS). Microglia can exhibit pro- or anti-inflammatory behavior in response to Th1 cytokines and Th2 cytokines, respectively (9). In fact, when these cells are activated, they can produce both pro-inflammatory IL-1, TNF, and IL-6 (M1 polarization) and anti-inflammatory IL-4 and IL-13 (M2 polarized phenotype) which reduce inflammation (10). The activation of microglia occurs with the consumption of mitochondrial energy which allows for cell survival, which is important for the intervention of microglia in neurodegenerative processes. Therefore, polarization of M1 microglia leads to the release of pro-inflammatory cytokines; while M2 polarization leads to the secretion of anti-inflammatory cytokines, including IL-4 (10) (Fig. 1).

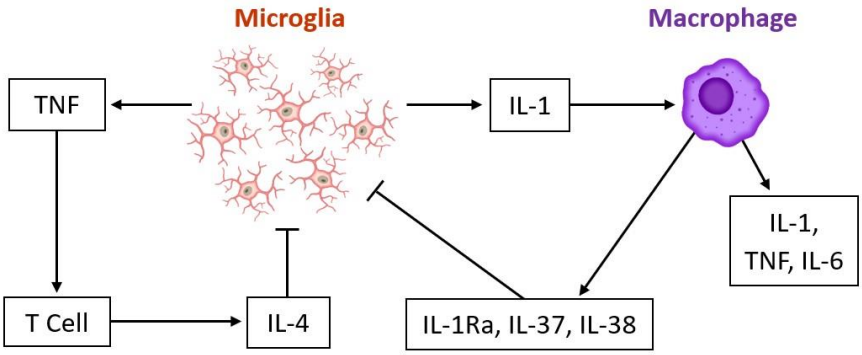

Fig.1. *Activated microglia secrete IL-1 and TNF which stimulate macrophages and T cells, respectively. Upon activation, macrophages release autocrine IL-1, pro-inflammatory TNF, and IL-6; while TNF secreted by microglia activates T cells to release IL-4. Activated macrophages can also secrete anti-inflammatory cytokines that inhibit microglia; while T cells release anti-inflammatory IL-4 which inhibits microglia.*

IL-4 has its gene located on the Th2 cytokine locus and is an epigenetic regulatory cytokine that is produced by various cells, including CD4+ cells, MCs, NK cells, basophils, eosinophils, and ILC2 cells. In the CNS, IL-4 is released by both microglia and neurons (11). IL-4 has many similarities with IL-13, of which it shares approximately 30% of the amino acid sequence, and the two cytokines also share the same receptor (12). The receptor for IL-13 is located on the Th2 cytokine locus.

The anti-inflammatory process can also be regulated by IL-37 which suppresses the activation of IL-1β and stimulates the generation of IL-10, another anti-inflammatory cytokine, and T regulatory (Treg) cells (13). IL-37 is generated by activated macrophages. Five isoforms (a, b, c, d, e) of this cytokine have been discovered, of which the most active and studied form appears to be "b" (14). IL-37 may inhibit IL-1 released by microglia and may relieve inflammation in neurological diseases (15).

IL-38 is also a macrophage product that can inhibit IL-1 produced by microglia and dump inflammation (16). IL-38 is one of the most recently discovered cytokines and is part of the IL-1 family. Since IL-38 is related to IL-36, its function is to block the IL-36 receptor, an effect reminiscent of that of IL-1Ra (17). IL-38 is expressed by various cells such as those located in the tonsils, heart, placenta, and brain. This cytokine has anti-inflammatory properties and has been implicated in several autoimmune and CNS diseases including autism spectrum disorder (16), Alzheimer's disease (18), ischemic stroke (19), systemic lupus erythematosus (20), and psoriasis (21) . In addition, IL-38 is produced by B

cells. Since IL-1-producing microglial cells play a fundamental role in inflammatory brain diseases, inhibition of IL-1 with IL-38 may have a significant therapeutic effect.

CONCLUSIONS

In addition to the previously discovered anti-inflammatory cytokines such as IL-4, IL-13, and IL-10, new anti-inflammatory compounds such as IL-Ra, IL-37, and IL-38 have now appeared on the scene (7,22). These cytokines may inhibit cerebral inflammation and could be an additional tool to utilize in therapies for inflammatory diseases that are mediated by IL-1.

Conflict of interest

The authors declare that they have no conflict of interest.

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