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Letter to the Editor

IL-1 AND TNF SECRETION BY MICROGLIA AND DOWN-REGULATION SIGNALS

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INTRODUCTION

Microglia are macrophage-type innate immune cells resident in the brain that perform various functions such as maintaining neuronal health, repairing neuronal damage caused by injuries, and brain regulation and development. In addition, microglia eliminate infectious agents, dead cells, and harmful antigens. The excessive activation of these cells causes a high production of cytokines mediating inflammation which can even lead to the death of the individual. Here, we discuss the current understanding of the potential signaling mechanisms and the secretion of cytokines by microglia.

DISCUSSION

Microglia are macrophage-like cells that reside in the central nervous system (CNS) and when activated with appropriate antigens, or by pathological states such as necrotic and apoptotic cells, they produce pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and chemokines. These cytokines are produced in defense of the organism, but when they are activated, they produce highly inflammatory products with effects that are deleterious for neurons and for the life of the individual. Excessive production of cytokines and chemokines by microglia activation can lead to neurological diseases including Alzheimer's disease and Parkinson's disease, amongst others.

IL-1 and TNF are polypeptide cytokine soluble products released by activated monocytes/macrophages with a broad range of biological activities, most importantly of which is that they have potent regulatory effects on the immune system (1). These two monokines are generated by a variety of cell types but are predominantly secreted by monocyte-macrophage cells and other cells, which play an important role in different phases of the immune response to both foreign and certain self-antigens. However, many aspects of the production and actions of IL-1 and TNF remain largely unknown (2,3). It has been reported by many authors that the roles of microglia and other antigen-activated macrophage cells in monokine production and T-cell activation are very critical for orchestrating the immune response by the host (4). Antigens are known to stimulate macrophages (and microglia in the brain) to generate IL-1 and TNF, two important initial signals for activating quiescent T cells to become antigen-specific T cells. Indeed, T cells recognize antigens displayed on the surface of macrophages in association with major histocompatibility complex II (MHCII). Naïve T cells respond to IL-1 and TNF to become activated T cells capable of expressing the IL-2 receptor, producing soluble IL-2, and secreting other cytokines such as IL-4, IL-6, and gamma interferon (IFN-γ) (5).

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In recent years, there has been substantial progress in the understanding of cytokine production and regulation pathways by macrophages, even though the exact mechanisms are still an enigma. However, results reported in the immunological literature tell us that IL-4, a growth and regulatory factor for activated B cells and T cells, and IL-6, downregulate the production of IL-1 and TNF by human monocytes (6,7).

Moreover, immunosuppressive products of cyclooxygenase, such as inflammatory prostaglandin E2 and thromboxane A2 cellular aggregation, are produced by macrophages after stimulation with antigen and/or some cytokines such as IL-1 and TNF. It has been hypothesized that some cyclooxygenase products are also negative feedback signals for the downregulation of IL-1 and TNF production by macrophages. For example, IL-4 produced by T helper cells appears to downregulate and inhibit the generation of fever *in vivo* induced by IL-1 and TNF (8). The means by which IL-4 and IL-6 downregulate the generation of IL-1 and TNF may involve the regulation of other protein syntheses, such as IL-10, IL-1 receptor antagonist (IL-1Ra), IL-37, IL-38, and the soluble TNF receptor, molecules that are all released during immune activation.

In addition, it is possible that IL-4 and IL-6 may mediate their downregulatory effects on IL-1 and TNF production at the level of DNA transcriptional control. For example, IL-4 and IL-6 can influence cytokines and the cytokine receptor gene that assist immunoregulatory molecules, such as specific enhancers and promoters of DNA binding proteins at AP-1 and NF-κB sites. Interestingly, many side effects observed in cytokine immunotherapy appear to be mediated by IL-1 and TNF, in part through the production of arachidonic acid metabolites that can cause fever, cell aggregation, release of cytoplasmic granules, hypotension, capillary leak, edema, and other side effects (9).

Therefore, the inhibitory effects of IL-4, IL-6, IL-10, and other cytokines on the production and activity of IL-1 and TNF could play an extremely important role in controlling the delicate immunoregulatory balance in the brain during the immunological response and inflammation.

CONCLUSIONS

Here we report that the IL-1 family members secreted by microglia can have dual effects as pro or anti-inflammatory cytokines. Taken together, recent findings suggest that microglial activation with the release of pro-inflammatory cytokines deserves interest as the target of treatment for neurodegenerative disorders.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Dinarello CA. Proinflammatory Cytokines. *Chest*. 2000;118(2):503-508. doi:https://doi.org/10.1378/chest.118.2.503
2. Malik A, Kanneganti TD. Function and regulation of IL-1α in inflammatory diseases and cancer. *Immunological Reviews*. 2017;281(1):124-137. doi:https://doi.org/10.1111/imr.12615
3. Croft M. The TNF family in T cell differentiation and function – Unanswered questions and future directions. *Seminars in Immunology*. 2014;26(3):183-190. doi:https://doi.org/10.1016/j.smim.2014.02.005
4. Yin J, Valin KL, Dixon ML, Leavenworth JW. The Role of Microglia and Macrophages in CNS Homeostasis, Autoimmunity, and Cancer. *Journal of Immunology Research*. 2017;2017:1-12. doi:https://doi.org/10.1155/2017/5150678
5. Gemmell E, Seymour GJ. Cytokines and T Cell Switching. *Critical Reviews in Oral Biology & Medicine*. 1994;5(3):249-279. doi:https://doi.org/10.1177/10454411940050030301
6. te Velde A, Huijbens R, Heije K, de Vries J, Figdor C. Interleukin-4 (IL-4) inhibits secretion of IL-1 beta, tumor necrosis factor alpha, and IL-6 by human monocytes. *Blood*. 1990;76(7):1392-1397. doi:https://doi.org/10.1182/blood.v76.7.1392.1392
7. Tanaka T, Narazaki M, Kishimoto T. IL-6 in Inflammation, Immunity, and Disease. *Cold Spring Harbor Perspectives in Biology*. 2014;6(10):a016295-a016295. doi:https://doi.org/10.1101/cshperspect.a016295
8. Dinarello C. Interleukin-1 and interleukin-1 antagonism. *Blood*. 1991;77(8):1627-1652. doi:https://doi.org/10.1182/blood.v77.8.1627.1627

9. Boersma B, Jiskoot W, Lowe P, Bourquin C. The interleukin-1 cytokine family members: Role in cancer pathogenesis and potential therapeutic applications in cancer immunotherapy. *Cytokine & Growth Factor Reviews*. 2021;62. doi:https://doi.org/10.1016/j.cytogfr.2021.09.004