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Biochemistry, Pathophysiology and Clinical Importance of IL-4: A Review Article

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ABSTRACT: Interleukin-4 (IL-4) is one of the most important immunomodulatory cytokines. Although it is thought of purely as acting on the differentiation of T helper cells, IL-4 can polarize macrophages. That is why knowledge of the biochemical pathways and molecular mechanisms of IL-4 action is needed. Various biological activities have been ascribed to IL-4, including immune responses, inflammation, and tissue homeostasis. This wide range of activities is likely to be based on defined pathophysiological features in diseases within the nervous system and allergic disorders. Hence, this review attempts to compile the most recent findings regarding the pathophysiological functions of IL-4, focusing primarily on its contribution to neuroinflammation, macrophage polarization, and allergic responses. In conclusion, IL-4 is a multifaceted cytokine that plays crucial roles in immune responses, influencing macrophage polarization, tissue repair, and inflammation across various biological systems. Continued research into its biochemical pathways and interactions with other cytokines will be essential for harnessing its therapeutic potential in treating inflammatory and autoimmune diseases. The pathophysiology of IL-4 is multifaceted, influencing both immune responses and neural health. Its roles in microglial polarization, neuroinflammation, and allergic diseases highlight its significance as a therapeutic target. Despite the progress made in understanding IL-4's functions, further research is necessary to unravel its complex signaling mechanisms and to explore its potential in clinical applications across various pathological conditions.

KEYWORDS: Biochemistry, Pathophysiology, Clinical Importance, IL-4.

INTRODUCTION

Interleukin-4 (IL-4) is one of the key cytokines of the immune system and perhaps better known as central in many aspects of T-cell biology and the functional malleability of macrophages. Biochemical pathways and molecular mechanisms through which IL-4 acts are prerequisite steps toward any attempt to design rational treatment strategies for conditions reflective of inflammation and immune dysregulation. Although the evidence found propounding the effect of IL-4 in multiple physical and pathological conditions, several aspects remain unknown. For example, how exactly at the molecular level IL-4 affects the different types of cells by changing their metabolism is not quite clear. Wide parallelism between IL-4 and other cytokines in different inflammatory contexts also indicates a need for more research. Regarding these and related pathways, more attention should be directed in studies on chronic diseases, neurodegeneration, and aging. Future research should focus on the detailed pathways and molecular cross-talk during IL-4 signaling in neuroinflammation and related cognition. Such a dual study, pertaining to both the allergen-induced IL-4 signaling and neurodegenerative diseases, may fill some important gaps concerning the pathophysiological relevance of this cytokine. More studies are needed in this fragment area to give a full picture of IL-4 regarding its role in health and disease concerning crosstalk with other cytokines and other signaling pathways.

Clinical Significance of IL-4

Macrophage plasticity involves critical immune machinery, especially associated with inflammation and wound healing. The classic activation pathway of macrophages results from IL-4 exposure and is known to represent M2 functions in relation to repair of tissues and resolution of inflammation (Sica & Mantovani, 2012). The signaling pathways and transcriptional networks that bring upon this polarization are quite complicated and require further investigations. For instance, within this domain, c-MYC has emerged as an important transcription factor for M2 polarization elicited by IL-4 (Junttila, 2018). This implies that the targeting of c-MYC could be a new strategic avenue to design therapeutics against pathologies characterized by macrophage dysregulation, such as cancer and chronic inflammatory conditions. The function of IL-4 also exists in the central nervous system, more exactly in polarizing

microglia. IL-4 induces M2 expression and therefore phenotype in microglia that is associated with anti-inflammatory reactions and eventually tissue repair. The aforementioned metabolic shift from oxidative phosphorylation to aerobic glycolysis during activation of microglia is substantially dependent on IL-4. Such redirection bears some potential implications on therapeutic approaches to neurodegenerative diseases since inflammation is one of the basic characteristics involved.

IL-4 is an anti-inflammatory cytokine in the context of osteoarthritis. It therefore acts to counter the pro-inflammatory signals at the joint environment. Wojdasiewicz et al. (2014) described the balance between inflammatory and anti-inflammatory cytokines, where IL-4 belongs, as of much importance in understanding the pathogenesis of OA. Future studies might concentrate on how IL-4 signaling can be boosted to alleviate joint destruction and enhance therapeutic outcomes with OA. IL-4 belongs to optimal lung function and is one of the factors that stimulate epithelial cell migration and repair following lung injuries (Crosby & Waters, 2010). This provides reason for in-depth development of the interactions between it and other signaling pathways in the treatment of chronic lung diseases. Inhibition of IL-4 signaling might thus be used therapeutically for promoting faster recovery from lung injuries.

In post-traumatic brain injury, IL-4 acts as a potent anti-inflammatory cytokine that can naturally regulate the immune response and reduce secondary damage. Specific interactions with other cytokines are needed for treatment strategies aimed at optimizing recovery outcomes in brain injuries. A study, for instance, found that JAK inhibitors can block IL-4-induced Th2 differentiation, likely highly relevant to conditions such as rheumatoid arthritis (Ghoreschi et al., 2011). At the same time, manipulation of IL-4 signaling speaks to the dual nature of this factor in promoting inflammation and repair; therefore, further exploration of the therapeutic implications of altering IL-4 signaling could lead to greater insights into autoimmune diseases.

Interleukin-4 in Allergic Inflammation: IL-4 has a special contribution to allergic inflammation especially in the regulation of IgE production and immune response. As allergic diseases are increasing, studying the mechanism of IL-4 signaling might be a target that leads to new therapeutic strategies directed toward these pathways. Changes in MSC Function under Polarized Macrophage Influence— An Advance in Cardiac Repair Therapy following Myocardial Infarction: changes in MSC function under the influence of polarized macrophages, specifically M2 macrophages correlated with IL-4 and IL-13, bear significance relevance in the context of myocardial infarction. Survival signals by M2 cytokines for MSCs would be critical for cardiac repair (Olin & Wechsler, 2014). Hence, this relationship is crucial for the need of the inflammatory microenvironment for cardiac injury recovery. A study of aged mice found increased IL-4 in the choroid plexus of the brain in association with cognitive changes (Chen et al., 2011). This may indicate that IL-4 influences neuro-inflammation and thus also influences cognitive health, likely to open avenues for research as a potential area in which to target therapeutics to age-related cognitive decline.

PATHOPHYSIOLOGY OF IL-4

The polarization of microglia into M1 and M2 phenotypes, pro-inflammatory and anti-inflammatory, respectively, is significantly assigned to cytokines. For example, IL-4 is most known to show M2 phenotypic stimulation effects. Such polarization is crucial concerning neural homeostasis support and tissue repair in cases of injury. Therefore, IL-4 capability to alter the function and metabolic states of microglia suggests that it may not only mediate inflammatory responses but also support neuronal health, thus making its pathophysiological effects through neurodegenerative conditions.

Moreover, in the context of traumatic brain injury (TBI), IL-4 is considered through its anti-inflammatory functions in balancing and therefore ameliorating the effects of pro-inflammatory cytokines. Such dual role of IL-4 brings attention to its potential as a therapeutic target in the equilibrium between inflammation and promotion of neurorepair. Further research into the specific signaling pathways and receptors that are involved, especially in post-TBI, would increment knowledge on how to bring the use of this observation to its maximum effect.

Overexpression of IL-4 in T cells results in elevated levels of allergic inflammation as an effect on T cell differentiation and B cell immunoglobulin class switching to drive Th2 responses central to allergic inflammation. The facts through which IL-4 acts on the immune system, especially its receptor interactions and the signaling pathways opening ways to the treatment and management of allergic diseases. That is the treatment of allergic diseases in promoting and restoring homeostasis that can block pro-inflammatory signaling cascades by anti-IL-4 activities of Dupilumab relied on inhibition of signaling by IL-4. These are IL-4 further highlights the importance of these cytokines in the regulation of immune responses together with IL-13. This was the approach considering the identical signaling pathways shared by IL-4 and IL-13 in atopic disease that could extend to other therapeutic avenues against Th2-mediated diseases. The transcription factor c-MYC has been recognized as an important IL-4-induced macrophage polarization regulator (Bendinelli et al., 2010). Thus, this can explorate details further regarding the molecular mechanisms of IL-4 signaling and impact on changes in gene expression promoting anti-inflammatory responses. Further insight into the role c-MYC and other transcription factors play in the signaling of IL-4 could offer up possible disease-specific therapeutic targets for the treatment of dysregulated macrophage activation. Although these last studies have revealed fine views, lacunae still mar the picture of the complete rainbow of actions of IL-4, particularly within the central nervous system. Relationship with the cognitive processes has been suggested for it. Therefore, the mechanism through which this molecule influences, specifically probably in neuroprotection and also in cognitive functions, would have to be worked out (Junttila, 2018).

CONCLUSION

In conclusion, IL-4 is, therefore, a pleiotropic cytokine that plays roles in immune responses regarding macrophage polarization and influencing various biological systems related to tissue repair and inflammation. More studies in its biochemical pathways, especially the interactions with other cytokines, are required to exploit IL-4 therapy towards treating inflammatory and autoimmune diseases. The pathophysiological role of IL-4 is complex, impacting immuno-responses alongside the health of neurons. The functions in microglial polarization, neuroinflammation, and allergic diseases reflect the potential importance of this cytokine as a therapeutic target. More studies are still imperative to understand better how IL-4 works.

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