INTERNATIONAL JOURNAL OF HEALTH & MEDICAL RESEARCH

ISSN(print): 2833-213X, ISSN(online): 2833-2148

Volume 03 Issue 12 December 2024

DOI : 10.58806/ijhmr.2024.v3i12n06

Page No. 868-872

Biochemical Characteristics and Clinical Significance of Il-35: A Review Article

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ABSTRACT: IL-35 belongs to the IL-12 family of cytokines that are involved in immune-regulation and homeostasis. It generally features as a heterodimeric cytokine composed of IL-12p35 and EBV-induced gene 3, mainly secreted by regulatory T cells and B cells within the human body. Therefore, IL-35 is known to have enormous immune-suppressive abilities. This paper thus provides the existing insights over the biochemistry and pathophysiology of IL-35 concerning inflammation, microbial infections, carcinogenesis, as well as autoimmune disorders, meanwhile intending to identify lacunae and suggest prospective lines of research.

INTRODUCTION

IL-35, an interleukin of the IL-12 family, has been found to be very important in immune regulation and inflammation in any given biological context. Specifically, interleukin-35 is unique in control of immunity self-homeostasis. IL-35 is a heterodimeric cytokine mostly synthesized by regulatory T cells (Tregs) and B cells and is known for its immunosuppressive activity (Li et al., 2012).

Although the biochemistry and physiological roles of IL-35 are fairly well understood, quite a few gaps are present in this knowledge. For instance, the actual mechanisms by which IL-35 regulates NK cell responses and its influence in tumor microenvironments have not been clearly defined so far. Also, although IL-35 is known as an immunosuppressor, it would be interesting to see whether it has any pro-inflammatory roles in certain cases too. Quite a few gaps still exist in the literature to make definite conclusions about IL-35's clinical significance. Although the direction has generally been set by disease-specific studies, conclusive proof via comprehensive investigations of the mechanisms of this cytokine inside different tissue microenvironments is still missing. Thus, further studies should be focused on the mechanism of action of this cytokine in the different tissue microenvironments towards clarifying its role in autoimmune diseases and cancer and indicating other ways of intervention. Moreover, the prognostic significance of IL-35 in disorders like primary myelofibrosis (PMF) is yet to be fully looked into. Hence, studying IL-35 in the context of disease severity and treatment response in PMF as a possible biomarker would offer great insight into its clinical applications (Tefferi et al., 2011).

BIOCHEMICAL CHARACTERISTICS OF IL-35

IL-35 is a dimeric cytokine, composed of two distinct chains, EBI3, and p35 that are partnered into a functional heterodimer. It explants an entirely unique signaling setting as compared to other cytokines from the IL-12 family in view of the fact that it uses an unusual receptor complex 'Collison' which includes receptors that are not commonly associated with other IL-12 family cytokines (Collison et al. 2012). IL-35 is unlike other usual anti-inflammatory cytokines such as IL-10 and TGF-β in that it does not constitutively express. IL-35 is sensitive to its surroundings and hence expressed only when stimulated with inflammatory stimuli. Such sensitivity implies that probably IL-35 works more on arresting existing inflammation rather than barring its onset, turning it an important therapeutic target in chronic inflammatory situations (Yeung et al., 2018).

MECHANISMS OF IL-17 PRODUCTION

Complementation of IL-17 by Vgamma5+ epidermal γδ T cells has been strongly implied, with Komatsu et al. (2013) stressing this particular aspect, clarifying unambiguously that the production of this cytokine is not the preserve of the classical CD4+ T cells subset members only. Furthermore, as Gaffen et al. (2014) have stressed, "Infecting a mouse with M. tuberculosis increases its susceptibility to other infections." Indeed, as observed for infections such as EAE, other chronic inflammatory conditions could benefit from having a pathological role for Th17 cells. Late induction and differentiation of these cells produce the final IL-17; this further underscore the significance of the IL-23–IL-17 axis concerning all initiation and development aspects of autoimmune disease pathogenesis. It was underlined by Komatsu et al. in 2013 the necessity of epidermal Vgamma5+ γδ T cells for IL-17 production

and hence their contribution to host defense, indicating that this production is not strictly dependent only on classical CD4+ T cells but also on other innate immune cells doing so in a rapid way responsive to infections.

ROLE IN INFLAMMATION AND IMMUNE REGULATION

The immunosuppressive actions of IL-35 have been well documented in various studies. IL-35-producing B cells were demonstrated to be critically involved in controlling immunity in the course of autoimmune diseases and infections (Shen et al., 2014). Such production is not only important for maintaining immune tolerance but also for controlling the activities of other immune cells, including NK cells. Currently, there are suggestions that IL-35 might influence NK cell maturation and the actual mode of action, something that could be of particularly high relevance in tumor microenvironments since NK cells are highly relevant in anti-tumor immunity.

Recently, IL-35 has been implicated in the control of pro-inflammatory cytokines, and its role as the pivot in balancing inflammatory and anti-inflammatory signals in immunity cannot be ignored (Li et al., 2012). Such complex signaling pathways that are correlated with the functioning of IL-35, especially the JAK/STAT, PI3K/AKT, etc., underscore further the complexity and hence importance with respect to immune modulation (Zhang et al., 2017; Zegeye et al., 2018).

IL-35 has been an interesting player regarding such conditions as atherosclerosis due to its immunosuppressive features. IL-35 has potential for inflammatory modulation through undisputed mechanisms, reflecting its significance in immune homeostasis maintenance. This infers that up-regulating IL-35 activity may be beneficial when managing chronic inflammatory diseases for further new therapeutic strategies targeting inflammation to improve patient outcomes (Mirlekar, 2022).

IL-17 IN TUMOR PROGRESSION

Research has also suggested that IL-35 may be assigned dual roles in tumor biology, i.e., that of an immune host against tumor suppression as well as a potential host for tumor induction. ‘Interaction of IL-35 with TAMs and IL35-induced PD-L1 expression would represent a possible mechanism by which tumors take advantage of IL-35 to escape from immune surveillance’. It underlines the necessity to acquire more detailed knowledge about molecular pathways on which IL-35 action relies with context to tumor microenvironment (Zhao et al., 2021).

Of especial note in cancer immunology is the involvement of IL-35 since this contributes to the immune-suppressive tumor microenvironment. The immune-suppressive role of IL-35 in promoting tumor progression and metastasis has recently been reviewed by Mirlekar (2022), who recommended that targeting IL-35 might enhance antitumor immunity. Such association brings a new look at a possible mode of therapeutic intervention by modulating IL-35 to bring about an effective immune response against tumorigenesis. Additionally, such collaboration of IL-35 with other immune-suppressive cytokines forms a complicated network that might be used for advanced anti-cancer therapy. Broader insight into these interactions might be instrumental in coming up with better treatment protocols that boost the immune response against tumor growth (Behzadi et al., 2016).

IMPLICATIONS FOR AUTOIMMUNE DISEASES

The relationship between IL-35 and autoimmune diseases is very complex. Being an anti-inflammatory cytokine, it is suggested that IL-35 may be having a pro-inflammatory balance with other members of IL-12 family states IL-12, IL-23 that are linked to different autoimmune conditions (Jiang et al., 2018). The recent addition of new members into this family like IL-39 adds more complexity to the already complicated network of cytokine interactions and their related roles in the pathogenesis of diseases. Thus, the only way to come up with rational and plausible targeted therapy is through a clear understanding of how IL-35 interacts with these cytokines. This has been extensively investigated in autoimmune diseases, and the molecule has indeed emerged as a promising novel therapeutic target. Even though it was first reported as an immune suppressive cytokine, IL-35 was able to inhibit T cell proliferation and reduce significantly the autoimmune response in diabetes, thus benefiting the protection of pancreatic β-cells in type 1 diabetes (Bettini et al., 2012). Indeed, Dambuza et al. (2017) have reported that IL-12p35 drives the expansion of IL-35-producing regulatory B cells, dampening autoimmune diseases, underscoring IL-35’s importance in immune regulation in autoimmune contexts. Choi et al. (2015) have provided additional evidence supporting the relevance of IL-35 in autoimmunity, thereby implying that its control over immune responses could shed light on possible therapeutic avenues for immune-mediated conditions. The study has stressed the exceptional nature of IL-35 as an anti-inflammatory cytokine that functions in a manner distinct from IL-10 and TGF-β, supporting its specific application in clinical therapies.

CONCLUSION

IL-35 is indeed an interesting cytokine, on account not only of its unusual biochemistry but also heavy impact concerning immune regulation and pathophysiology. With further discoveries regarding its complexities, it could turn out to be one major target concerning therapeutic interventions against autoimmune diseases and cancers. There is a need to address the knowledge gaps that exist for the full harnessing of IL-35’s potential in clinical settings. New therapeutic application targets should certainly include

immune dysregulation-associated disease in vitro and in vivo IL-35 research, its interaction, and application process for improving the patient outcome particularly in autoimmune diseases, cancers, and chronic inflammatory conditions.

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