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Pathophysiology and Potential Clinical Significance of Il-5: A Review Article

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ABSTRACT: Interleukins belong to the group of cytokines that play a key role in immune system cell signaling. Among them, Interleukin-5 (IL-5) gains paramount significance in the regulation of eosinophils, which are thinly scattered in most allergic as well as inflammatory conditions, especially asthma. A biochemical characterization of IL-5 is a prerequisite for understanding the basic aspects of its function and finding a precise treatment. Interleukin-5 (IL-5) is a critical cytokine that primarily drives the development and differentiation of eosinophils and B cells, playing a key role in the allergic response and the pathogenesis of asthma. Therefore, the knowledge of its biochemical structure is a prerequisite for any plan to develop targeted therapies for resides in their regulatory capabilities of immune eosinophilia-related diseases. The clinical relevance of interleukins responses, with an ever-growing recognition in diverse pathologies such as allergic manifestations, autoimmune diseases, or neoplastic processes. Interleukins in clinical application should be the focus of research, specifically IL-5, synthesizing observable from the latest related studies and knowledge deficits that should entice future research in the same line. This paper, therefore, gives a review based on already existing research findings concerning the biochemical structure of IL-5.

KEYWORDS: Biochemistry, Pathophysiology, Clinical Importance, IL-5

INTRODUCTION

IL-5 is constituted of two similar subunits associating noncovalently to a receptor designated the IL-5 receptor. The latter consists of two subunits: a specific α-chain and a common β-chain. Receptor engagement initiates a series of IL-5-dependent intracellular signaling events, predominantly involving the JAK-STAT pathway (Olin & Wechsler, 2014; Broughton et al., 2012). Among the structural features of IL-5 are receptor binding sites that are critical to the biological activity of the molecule in supporting the survival and activation of eosinophils (Moult et al., 2016; Takatsu, 2011).

Establishment of the IL-5 binary complex has revealed a great deal about how IL-5 engages its receptor to spur downstream signaling. This process is crucial to both eosinophil differentiation and activation—processes central to the pathogenesis of eosinophilic inflammation and asthma . The biochemical structure of IL-5 is therefore one of the most intensely studied in the context of immune modulation since its role is so essential in eosinophilic inflammation. Since the purpose of this study is to review recent literature regarding the structural characteristics of IL-5 and its receptor interactions, as well as their implications in therapeutic targeting, it is evident that the structural characterization of cytokines is a prerequisite to understanding the mechanisms of action of these proteins. Though reports specifically focused on the structure of IL-5 are scant, research on related cytokines and proteins provides invaluable insights. For example, the study by Lan et al. (2020) on the SARS-CoV-2 spike protein structure and interaction with ACE2 receptor protein may provide some basis for understanding details of protein-receptor interactions, something that might eventually be extended to IL-5's interaction with its receptor, IL-5R.

IL-5 is a member of the GM-CSF/IL-3/IL-5 cytokine family that holds a central role in hemopoietic cell differentiation and function. With the new breakthroughs in structural biology and the description of an IL-5 binary complex, valuable insights into the mechanisms of cytokine-receptor interactions have become available. Such findings are critical for the development of anti-IL-5 signaling therapies in the context of inflammatory diseases, for example, asthma and chronic rhinosinusitis (Broughton et al., 2012). IL-5 shares overall structural features with other family cytokines, IL-3 and GM-CSF and seems to share similar features involving receptor activation as well. The accessibility of such similarities allows for cross-family therapeutic approaches, thus widening the utility of interventions based on cytokine action (Broughton et al., 2012).

Despite all the above-mentioned achievements made in the structural understanding of cytokines, some particular structural vacuities still exist in the full characterization of IL-5. For example, the interface that takes place between IL-5 and its receptor at atomic detail remains to be established. Much more attention in reference to IRQ-5 has to be done on its rather unique conformational changes than that done for most cytokines, and their related implications for immune response control. Much more knowledge has to be accumulated despite the progress made in understanding the structure and function of IL-5. For instance, although the structural dynamics of IL-5 and its receptor have been worked out, the highly specific molecular basis for the dimerization of the receptor and how this leads to the triggering of a signal is not properly understood. Subsequent research will have to determine all the signaling

pathways that are triggered by IL-5 and how they contribute to the development of eosinophilic inflammation. More studies are also required in other immune responses that would enable additional therapeutic designs around an IL-5 that goes beyond the regulation of eosinophil biology. In addition to these, future studies should be directed to the structural determination of the IL-5:R complex under various physiological conditions to understand at atomic resolution how environmental factors may affect its activity. Such information may eventually lead to enhanced therapeutic strategies against asthma and other allergic conditions in which IL-5 holds a well-established central position.

POTENTIAL CLINICAL APPLICATIONS OF IL-4

IL-5 has gained considerable attention as a possible therapeutic target due to its importance in eosinophilic disorders. Monoclonal antibodies against IL-5 or its receptor are some of the most effective drugs in the clinic today, offering new hope for the treatment of severe asthma and other eosinophil-associated conditions (Molfino et al., 2012; Pelaia et al., 2019). Thus, knowledge of IL-5 at a biochemical level not only helps to understand its function but also leads to the design of biologic therapies that attempt to counterbalance eosinophil inflammation in damaging effects.

IL-5 is known to play a major role in eosinophilic inflammation predominantly in asthma and allergic diseases. It is necessary for the differentiation, survival, and activation of eosinophils, which have been termed key cells in the pathophysiology of type 2-driven asthma. Studies have shown that inhibition of IL-5 has significant therapeutic benefits in the treatment of asthma patients, particularly those severe phenotypes with elevated eosinophil numbers (Barnes, 2018; Robinson et al., 2017). An IL-5 inhibitor, mepolizumab, has been found to significantly reduce asthma exacerbations while improving lung function in patients resistant to standard therapies in clinical trials (Wynn, 2015). Moreover, the evidence linking IL-5 with other Type 2 cytokines such as IL-4 and IL-13 indicates a concerted response in allergic conditions (Gieseck et al., 2017; Licona-Limón et al., 2013). These findings provide new optimism for combination therapies targeting multiple interleukins.

In addition to its established role in asthma, IL-5 is increasingly found to be important in other clinical scenarios as well. For example, it has been identified to participate in nasal polyps. In a trial, IL-5 inhibition reduced polyp mass and improved symptom scores for patients who otherwise do not improve when given corticosteroids. This supports IL-5 as an important player in eosinophilic disease management outside of asthma, making the therapeutic horizon wider. Besides, revelation of the presence of IL-5 producing cells in anti-tumor surveillance introduces fresh avenues of research. The participation of IL-5 not only in these allergic responses but also in micro-environmental modulation of tumors might impinge upon metastasis explains the need for more studies into this intriguing protein and its application to tumor immunology.

The role of interleukins in neuroinflammation should also be a priority area of interest. IL-5 has not been associated with neurodegenerative conditions, such as Alzheimer's disease. However, its possible involvement in the inflammatory route indicates that it might take part in neuroinflammatory processes. Wang et al. (2015) posits that IL-5 must work hand-in-hand with other pro-inflammatory cytokines; hence, this prompts research on how it may regulate or participate in neurodegeneration and neuroprotection.

PATHOPHYSIOLOGY OF IL-5

IL-5R activation initiates the dimerization of receptors that is obligatory for launching further steps of multiple intracellular signaling pathways. Of particular note is the role of the JAK-STAT signaling pathway in providing information concerning the modes IL-5 effects on target cells. Upon binding to its ligand, the receptor again undergoes conformational changes that make possible phosphorylation of STAT proteins leading to transcription of target genes related to proliferation as well as survival functions of eosinophils. More than just regulation of eosinophils, IL-5 also has a direct impact on general immune competence by modulating activity. This fact, in turn, has further broadened its relevance and significance in both normal immune homeostasis and the pathogenesis of multiple diseases. IL-5 initiates activation and enhanced survival of eosinophils, thereby being associated with conditions like chronic rhinosinusitis with nasal polyps. Higher IL-5 levels have been associated with tissue eosinophilia and disease recurrence after surgery, therefore underscoring its potential as a useful biomarker and drug target (Gevaert et al., 2022). Monoclonal antibodies and other agents directed at IL-5 signaling pathways have their origin in structural information regarding IL-5 and its receptor. The strides taken in these therapeutics serve as an example of how structural studies can be relevant to the clinic in fighting diseases driven by dysregulated IL-5 expression.

Many gaps remain with evidence supporting the clinical significance of IL-5. For example, the interaction mechanisms of IL-5 with other interleukins in different disease contexts are not understood. Research on IL-5 signaling pathways and molecular mechanisms might provide more insight into its contribution to allergic as well as non-allergic conditions.

Moreover, IL-5 in cancer immunotherapy has not reached the daylight as of yet. Appropriate future studies should be designed to determine the effect of IL-5 on the biology of the tumor and immune responses within their microenvironment. Dynamics at play may one day bring about novel ways to make use of IL-5 for cancer treatment.

Lastly, further research is required into the interplay of IL-5 with other interleukins, particularly in complex disease states such as COVID-19, to which multiple cytokines participate in the inflammatory response. Exploring how IL-5 fits into the broader context

of cytokine networks in infectious diseases could inform treatment approaches and improve patient outcomes (Montazersaheb et al., 2022; Liu et al., 2020).

CONCLUSION

In conclusion, this structural work on IL-5 biochemical attribution is necessary for understanding the molecular basis of its action in the immune responses and pathologies regarding eosinophilia. While current studies have laid the foundation, there is much left to be known. Further research initiatives toward advanced structural determination and functional analysis are prerequisites for optimal application to therapy. Such application would be possible since knowledge about cytokine biology has been improved. Increased structural knowledge has allowed for new types of treatment through blocking IL-5 actions, especially in conditions related to eosinophilia. More advanced research will further improve our understanding of IL-5 receptor dynamics as we build on this to intervene more specifically in inflammation and immune conditions. IL-5 is a central cytokine of allergic diseases and eosinophilic inflammation and has been newly appreciated for its emerging involvement in other settings, such as cancer and neuroinflammation. Therapeutic targeting of IL-5 holds the potential to enhance clinical outcomes in a range of conditions manifesting abnormal immune responsiveness. Much more work needs to be done to understand fully the mechanisms of this interleukin, its cross-talk with other members of the family, and possible applications in different therapeutic settings for the discovery of IL-5's clinical relevance and to design effective interventions.

REFERENCES

1) Barnes, P... (2018). Targeting cytokines to treat asthma and chronic obstructive pulmonary disease. Nature Reviews Immunology, 18, 454 - 466. http://doi.org/10.1038/s41577-018-0006-6
2) Bartemes, K.., Iijima, K.., Kobayashi, Takao., Kephart, G.., McKenzie, A.., & Kita, H. (2012). IL-33–Responsive Lineage−CD25+CD44hi Lymphoid Cells Mediate Innate Type 2 Immunity and Allergic Inflammation in the Lungs. The Journal of Immunology, 188, 1503 - 1513. http://doi.org/10.4049/jimmunol.1102832
3) Broughton, S.., Dhagat, U.., Hercus, T.., Nero, T.., Grimbaldeston, M.., Bonder, C.., Lopez, Angel F.., & Parker, M. (2012). The GM–CSF/IL-3/IL-5 cytokine receptor family: from ligand recognition to initiation of signaling. Immunological Reviews, 250, 277 - 302. http://doi.org/10.1111/j.1600-065X.2012.01164.x
4) Gevaert, P., Van Bruaene, N., Tieu, D., Perez-Novo, C., Holtappels, G., Zhang, N., ... & Bachert, C. (2022). The roles of eosinophils and interleukin-5 in the pathophysiology of chronic rhinosinusitis with nasal polyps. International Forum of Allergy & Rhinology, 12(3), 345–356
5) Gieseck, Richard L.., Wilson, M.., & Wynn, T. (2017). Type 2 immunity in tissue repair and fibrosis. Nature Reviews Immunology, 18, 62-76. http://doi.org/10.1038/nri.2017.90
6) Hofer, N.., Zacharias, E.., Müller, W.., & Resch, B. (2012). An Update on the Use of C-Reactive Protein in Early-Onset Neonatal Sepsis: Current Insights and New Tasks. Neonatology, 102, 25 - 36. http://doi.org/10.1159/000336629
7) Kaplanski, G. (2017). Interleukin-18: Biological properties and role in disease pathogenesis. Immunological Reviews, 281, 138 - 153. http://doi.org/10.1111/imr.12616
8) Kastritis, P.., Moal, I.., Hwang, Howook., Weng, Z.., Bates, P.., Bonvin, A.., & Janin, J. (2011). A structure-based benchmark for protein–protein binding affinity. Protein Science, 20. http://doi.org/10.1002/pro.580
9) Licona-Limón, P.., Kim, L.., Palm, Noah W.., & Flavell, R. (2013). TH2, allergy and group 2 innate lymphoid cells. Nature Immunology, 14, 536-542. http://doi.org/10.1038/ni.2617
10) Liu, Tao., Zhang, Jieying., Yang, Yuhui., Ma, Hong., Li, Zhenyu., Zhang, Jiaoyue., Cheng, Ji., Zhang, Xiaoyun., Zhao, Yanxia., Xia, Zihan., Zhang, Liling., Wu, Gang., & Yi, Jianhua. (2020). The role of interleukin-6 in monitoring severe case of coronavirus disease 2019. EMBO Molecular Medicine, 12. http://doi.org/10.15252/emmm.202012421
11) Liu, Yulan., Chen, Feng., Odle, J.., Lin, Xi., Jacobi, S.., Zhu, Huiling., Wu, Zhifeng., & Hou, Yongqing. (2012). Fish oil enhances intestinal integrity and inhibits TLR4 and NOD2 signaling pathways in weaned pigs after LPS challenge. The Journal of nutrition, 142 11, 2017-24. http://doi.org/10.3945/jn.112.164947
12) McGonagle, D.., Sharif, K.., O'Regan, A.., & Bridgewood, C. (2020). The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmunity Reviews, 19 , 102537 - 102537 . http://doi.org/10.1016/j.autrev.2020.102537
13) Molfino, N.., Gossage, D.., Kolbeck, R.., Parker, J.., & Geba, G.. (2012). Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. Clinical & Experimental Allergy , 42 . http://doi.org/10.1111/j.1365-2222.2011.03854.x
14) Montazersaheb, S.., Khatibi, Seyed Mahdi Hosseiniyan., Hejazi, M.., Tarhriz, Vahideh., Farjami, Afsaneh., Sorbeni, Faramarz Ghasemian., Farahzadi, R.., & Ghasemnejad, T.. (2022). COVID-19 infection: an overview on cytokine storm and related interventions. Virology Journal , 19 . http://doi.org/10.1186/s12985-022-01814-1

15) Moult, J.., Fidelis, K.., Kryshtafovych, A.., Schwede, T.., & Tramontano, A.. (2016). Critical assessment of methods of protein structure prediction: Progress and new directions in round XI. Proteins: Structure , 84 . http://doi.org/10.1002/prot.25064
16) Ohne, Y.., Silver, J.., Thompson-Snipes, L.., Collet, Magalie A.., Blanck, J.., Cantarel, B.., Copenhaver, Alan M.., Humbles, A.., & Liu, Yong-jun. (2016). IL-1 is a critical regulator of group 2 innate lymphoid cell function and plasticity. Nature Immunology , 17 , 646-655 . http://doi.org/10.1038/ni.3447
17) Olin, J.., & Wechsler, M.. (2014). Asthma: pathogenesis and novel drugs for treatment. BMJ : British Medical Journal , 349 . http://doi.org/10.1136/bmj.g5517
18) Pelaia, C.., Paoletti, G.., Puggioni, F.., Racca, F.., Pelaia, G.., Canonica, G.., & Heffler, E.. (2019). Interleukin-5 in the Pathophysiology of Severe Asthma. Frontiers in Physiology , 10 . http://doi.org/10.3389/fphys.2019.01514
19) Ribeiro-Soares, J.., Oliveros, M.., Garín, C.., David, M.., Martins, L. G. P.., Almeida, C. A.., Martins-Ferreira, E.., Takai, K.., Enoki, T.., Magalhães-Paniago, R.., Malachias, Â.., Jorio, A.., Archanjo, B.., Achete, C.., F'isica, L. C. D. D.., Gerais, Universidade Federal de Minas., Horizonte, B.., Mg, ., Brazil, ., F'isica, D. D.., Lavras, Universidade Federal de., Lavras, ., Materiais-DIMAT, Divisao de Metrologia de., Metrologia, Instituto Nacional de., Tecnologia-INMETRO, Qualidade e., Science, Department of Materials., Technology, ., Bioscience, Faculty of., Chemistry, A.., University, H.., Kajino-chou, ., Koganei, ., Tokyo, ., Japan., ., Chemistry, D.., Thecnology, Tokyo Institute of., Ookayama, ., & Meguro-ku, . (2015). Structural analysis of polycrystalline graphene systems by Raman spectroscopy. Carbon , 95 , 646-652 . http://doi.org/10.1016/j.carbon.2015.08.020
20) Robinson, D.., Humbert, M.., Buhl, R.., Cruz, Á.., Inoue, H.., Korom, S.., Hanania, N.., & Nair, Parameswaran. (2017). Revisiting Type 2-high and Type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. Clinical & Experimental Allergy , 47 , 161 - 175 . http://doi.org/10.1111/cea.12880
21) Rutkowsky, J.., Knotts, T.., Ono-Moore, Kikumi D.., McCoin, Colin S.., Huang, Shurong., Schneider, Dina A.., Singh, Shamsher., Adams, S.., & Hwang, D.. (2014). Acylcarnitines activate proinflammatory signaling pathways.. American journal of physiology. Endocrinology and metabolism , 306 12 , E1378-87 . http://doi.org/10.1152/ajpendo.00656.2013
22) Su, H.., Lei, Chuntao., & Zhang, Chun. (2017). Interleukin-6 Signaling Pathway and Its Role in Kidney Disease: An Update. Frontiers in Immunology , 8 . http://doi.org/10.3389/fimmu.2017.00405
23) Takatsu, K.. (2011). Interleukin-5 and IL-5 receptor in health and diseases. Proceedings of the Japan Academy. Series B, Physical and Biological Sciences , 87 , 463 - 485 . http://doi.org/10.2183/pjab.87.463
24) Tamura, K.., Peterson, D.., Peterson, N.., Stecher, G.., Nei, M.., & Kumar, Sudhir. (2011). MEGA5: molecular evolutionary genetics analysis using maximum likelihood, evolutionary distance, and maximum parsimony methods.. Molecular biology and evolution , 28 10 , 2731-9 . http://doi.org/10.1093/molbev/msr121
25) Wang, Wen-Ying., Tan, M.., Yu, Jin-Tai., & Tan, L.. (2015). Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease.. Annals of translational medicine , 3 10 , 136 . http://doi.org/10.3978/j.issn.2305-5839.2015.03.49
26) Wynn, T.. (2015). Type 2 cytokines: mechanisms and therapeutic strategies. Nature Reviews Immunology , 15 , 271-282 . http://doi.org/10.1038/nri3831
27) Xia, X.. (2013). DAMBE5: A Comprehensive Software Package for Data Analysis in Molecular Biology and Evolution. Molecular Biology and Evolution , 30 , 1720 - 1728 . http://doi.org/10.1093/molbev/mst064
28) Zhang, Xiao-hui., Zeng, Yuanyuan., Qu, Qiu-Xia., Zhu, Jianjie., Liu, Zeyi., Ning, Weiwei., Zeng, Hui-chang., Zhang, Nan., Du, W.., Chen, Cheng., & Huang, Jian-an. (2017). PD-L1 induced by IFN-γ from tumor-associated macrophages via the JAK/STAT3 and PI3K/AKT signaling pathways promoted progression of lung cancer. International Journal of Clinical Oncology , 22 , 1026-1033 . http://doi.org/10.1007/s10147-017-1161-7
29) Zhao, T.., Su, Zhongping., Li, Yingchang., Zhang, Xiaoren., & You, Q.. (2020). Chitinase-3 like-protein-1 function and its role in diseases. Signal Transduction and Targeted Therapy , 5 . http://doi.org/10.1038/s41392-020-00303-7
30) Zhaolin, Z.., Li, Guohua., Wu, Shiyuan., & Zuo, W.. (2018). Role of pyroptosis in cardiovascular disease. Cell Proliferation , 52 . http://doi.org/10.1111/cpr.12563