Biosight 2023; 04(01): 99-103

Role of Interleukin-8 with Special Progress of Atopic Dermatitis

Muhammad Noman Khan[1, 2]

[1] *Henan Provincial people's Hospital, Zhengzhou, Henan, P.R.China.*
[2]*Unani Medicine Research Laboratory, Faculty of Eastern Medicine, Hamdard University, Karachi, Pakistan*

Abstract: Atopic dermatitis (AD) is a recurrent pruritic chronic inflammatory skin disease, also known as atopic eczema and neurodermatitis sown. Its actual cause is still unknown, but association of disease progression may be related to immune system abnormalities. Many studies reported that AD lesions are linked with mainly increased no. of T lymphocytes with other inflammatory cells including monocytes, eosinophils and macrophages. T Lymphpocytes mediate inflammation and local immune response by secondary antibody production which are involved in cell-mediated immunity and delayed type hypersensitivity inflammatory reactions. IL-8 which is a proinflammatory cytokine and have high chemotactic activity on neutrophils, T lymphocytes and basophils along with activation of proinflammatory cells to perform immune functions. High expression of IL-8 was also reported in AD lesions which can cause chemotaxis, aggregation and activation of inflammatory cells. It also promotes IL-4 and IL-3 overexpression resulting in the proliferation and differentiation of mast cells which further aggravates AD. Here, in this manuscript IL-8 and related cytokines involved in atopic dermatitis pathogenesis and progression are reviewed more than spring season in dogs.

Keywords: Interleukin-8, atopic dermatitis, cytokines, T lymphocytes.

Received: June 22, 2022
Accepted: September 22, 2022
DOI: 10.46568/bios.v4i1.68

***Correspondence:** Muhammad Noman Khan, Henan Provincial people's Hospital, Zhengzhou, Henan, P. R. China, Tel: +8613130483361 Email: nomankhan007@hotmail.com

INTRODUCTION

Atopic dermatitis (AD) begins due to many non-specific inflammatory cells and mediators involved in multiple factors like genetic and immunological state of the host. The pathogenesis of AD depends on environmental condition of the country thatswhy its epidemiology is more common in developing countries because of urbanization, pollution and malnutrition [1]. . Its immunological mechanism is very complex. A number of immune cells such as cytokines, chemokines and pro-inflammatory molecules are involved in the pathogenesis [2, 3]. Most researchers believed that immune-mediated inflammatory T cells including Th1/Th2 cells immune imbalance are involved [4, 5]. When mast cells sensitized to allergens, it degranulates or releases inflammatory cytokines such as histamine, IL-8 and IL-13. These inflammatory cytokines stimulate eosinophils to release IL-4 and the synergies which induced Th2 cells migrate to the skin lesion, promotes the proliferation and differentiation of mast cells and increasing the inflammation process [6]. The relationship between Th1/Th2 differentiation imbalance with atopic dermatitis has been reported, but the effects of the innate immune response on other cytokines involved in atopic dermatitis inflammation in atopic dermatitis is rarely reported. In parallel with the important role of Th2/Th22 cells, the upregulation of chemokines and chemokines receptors is also an integral component of atopic inflammation like CCL1, CCL4,

CCL13, CCL17, CCL18, CXCL, CXCL2, CXCL3, CXCL8, CXCL9 and CXCL10 [7]. This review focuses on the involvement of IL-8 in the progression of atopic dermatitis.

IL-8 is an inflammatory chemokines that attracts circulating neutrophils, macrophages and T lymphocytes into the tissue. From the injured tissue, lysosomal enzyme are released which generate oxidative reactive oxygen species, damage to the surrounding tissue to produce a series of immune response including the release of proinflammatory cytokines. Studies have shown that patients with atopic dermatitis have increased expression of IL-8 which causes recruitment and activation of inflammatory cells to promote overexpression of IL-4 [8, 4].

Atopic Dermatitis

In recent years, AD prevalence has increased, as a result of many factors like the environmental contact of allergens and abnormal immune interactions, still its pathogenesis is not clear [9].It prevalence is more common in children with 10 to 16% and generally consider to be increasing worldwide and also the occurrence of AD in elderly patients is also currently an important issue [10].

At present, many scientists believe that the incidence of atopic dermatitis is mainly related to the imbalance of Th1/Th2 differentiation, and have demonstrated that the Th1, Th2 and Th17 inflammatory cells are involved in progression of different stages of atopic dermatitis. In healthy individuals, Th1 and Th2 cells maintain body homeostasis, when differentiated imbalance , like one subsets of cells differentiated more than another subsets of cells, occurs it can cause abnormal secretion of cytokines which causes in the progression of the disease [11].

Patients with AD have damaged skin epidermis with the accumulation of large number of T lymphocytes and other inflammatory cells mainly $CD4^+$ Th cells and Th2 cells in the inflamed dermis. Activated Th2 cells induce B cells to produce IgE, which binds to its receptors present on mast cells, prompting the release of chemokines to activate and recruit eosinophils at the site of inflammation. Upon activation, eosinophils release an array of inflammatory mediators including major basic protein (MBP) eosinophil peroxidase (EPO) and eosinophil cationic protein (ECP), which are important to defence against extracellular parasitic infections but can also cause excessive tissue damage in atopic dermatitis [12]. Furthermore, Th17 cells produce IL-17 and IL-22 chemokines which activate keratinocytes to produce pro-inflammatory cytokines, antimicrobial proteins and Vascular Endothelial Growth Factor (VEGF) which affect the proliferation and differentiation of keratinocytes, so as to further promote skin cells function and structural changes and affect the process of repairing of skin tissue.

IL-8 and its receptors

Interleukin-8 (IL-8) is an important activator and chemoattractant cytokine for neutrophils that is implicated in variety of inflammatory diseases. IL-8 was first isolated in 1987 by Yashimma from the supernatant of Lipopolysaccharide (LPS) and Phytohemeagglutinin stimulated human monocytes in a conditioned media. This has shown strong chemotactic activity for neutrophils, which is why it was named Monocyte Derived Neutrophil Chemotactic Factor (MDNCF) which was later changed to Interleukin-8 (IL-8). It belongs to the CXC-α subfamily (also known as CXCL-8) and its gene is located on chromosome no. 4, having relative molecular mass of 8×10^3-14×10^3, and maintained at a pH of 2.4-2.9 [10]. IL-8 precursor proteins have 99 amino acids, the amino terminal-specific proteolytic formed six different forms of the mature IL-8. In response to the stress, the mononuclear cells, immune cells, epithelial cells and other similar cells secrete IL-8. Various *invivo* experiments demonstrate that monocytes, macrophages and neutrophils which secrete IL-8 contain 72 amino acids; whereas non-immune cells such as the endothelial cells produce IL-8 contains 77 amino acids [13, 14]. Contemporary studies show that biological activities of IL-8 involve inflammation and other immune responses, along with angiogenesis (the formation of new blood vessels). Chemotactic activity for inflammatory cells including

neutrophils, macrophages and basophils and also involve in immune defence against many infections.

IL-8 receptors are mainly of three kinds namely; CXCR1, CXCR2 and Duffy antigen chemokine receptors [15, 16]. The biological effects of IL-8 are mediated through the binding of IL-8 to two cell surface G-protein coupled receptors, termed as CXCR1 and CXCR2 which contains a peptide chain by two 59 kDa and 67 kDa subunits of dimeric glycoprotein respectively. Both amino acid sequences have a high degree of homology, having similar structure and biological areas. IL-8 and other CXC chemokines subfamily are mainly dependent on the amino acid sequence of the receptor tail end (glutamic acid - leucine - arginine). After receptor binding, structural changes caused by receptor epitope exposure, promote functional G protein-coupled, and start biological effect. The biological effects of both receptors, after activation, include chemotaxis, intracellular calcium flow and phagocytosis [17].

Role of IL-8 in Inflammatory Diseases

IL-8 is a small soluble peptide (8 -10 kDa) and chemokine subfamily member which is identified as a chemotactic factor secreted by activated monocytes and machrophages that promotes the directional migration of neutrophils and T lymphocytes towards foci of infection or tissue injury site from the blood. These inflammatory cells produce superoxide anion degranulation, stimulate lysosomal activity and promote phagocytosis resulting in a non-specific immune response targeted at infected or damage tissue [18, 19]. During inflammation, the IL-8 and inflammatory cell membrane proteins together form a chemotactic gradient which induce monocyte and macrophage recruitment to the sites of inflammation and activate body's immune defence response [20]. IL-8 may also facilitate to move basophils and T lymphocytes, which further promote and increase the inflammatory process. Under normal circumstances, IL-8 mainly binds through its receptors CXCR1, CXCR2 which activates and promotes chemotaxis of neutrophils to produce inflammation. But excessive leukocyte recruitment can also cause tissue damage, increased inflammation, slowing tissue repair and even cause further damage to tissue fibrosis. Furthermore, IL-8 does not get hydrolyzed easily, due to which it can withstand the microenvironment at sites of inflammation and cannot be inactivated, which is why in early inflammation, IL-8 can last for days or even a few weeks play a role in the local inflammation or tissue damage[21]. In summary IL-8 is closely related to the occurrence and development of a variety of inflammatory diseases. There are many studies which show that IL-8 with other chemokines like TNF, IL-6 and other inflammatory mediators can induce inflammation [22].

Role of IL-8 in Atopic Dermatitis

Patients with atopic dermatitis are mainly with T-cell (Th1 / Th2) differentiation imbalance, with a predominant expression of Th2 cells. Activation of these Th2 cells may promote B cell activation and differentiation, producing IgE antibodies, which in-turn can promote increase eosinophils in blood. There are various factors which activate eosinophils to release inflammatory cytokines, and other basic protein that lead to the inflammation of skin. Activation of T cells produce cytokines including IL-4, IL-8, etc. which stimulate epidermal keratinocytes proliferation to release inflammatory cytokines further enhance T cell activity and thus creating a vicious cycle. IL-8 can specifically activate neutrophils, T lymphocytes and eosinophils by chemotaxis and gets attracted towards infected skin from blood. Activation of neutrophils degranulates anionic superoxide, stimulate lysosomal activity and promote phagocytosis. Furthermore, it also promotes the synthesis of acute phase proteins that are involved in atopic dermatitis exacerbation in inflammatory response. When skin is affected by exogenous allergens, it stimulates keratinocytes to produce inflammatory factors in atopic dermatitis and other inflammatory skin diseases which further elevate disease progress [5]. Furthermore, high expression of IL-8 causes chemotaxis, aggregation and activation of inflammatory cells. It also promotes IL-4

overexpression further aggravates atopic dermatitis. IL-8, IL-4 and IL-3 jointly promote mast cell proliferation and differentiation [23]. Studies have shown that skin lesions in atopic dermatitis patients have high IL-8 mRNA expression level than normal skin tissue [8, 24]. Regulation of the IL-8 overexpression may be one of the effective treatment methods against AD.

CONCLUSION

Physiological and pathological effects of IL-8 are very extensive and closely related to the occurrence and development of a variety of inflammatory response from small skin infections to tumor development Therefore, further studies are needed to prove its role in atopic dermatitis, which will provide new ideas for its treatment.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

Declare None.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declare None.

REFERENCES

1. Nutten S. Atopic dermatitis: Global epidemiology and risk factors. Ann Nutr Metab 2015; 66(Suppl 1): 8-16.
2. Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis-part: Clinical and pathologic concepts. J Allergy Clin Immunol 2011; 127(5):1110-18.
3. Leung DY. New insights into atopic dermatitis: Role of skin barrier and immune dysregulation. Allergol Int 2013; 62(2): 51-61.
4. Hanifin JM, Chan S. Biochemical and immunologic emerging therapies. J Am Acad Dermatol 1999; 41(1): 72-7.
5. Schmidt E, Reimer S, Kruse N, *et al.* Auto-antibodies to BP180 associated with bullous pemphigoid release IL-6 and IL-8 from cultured human keratinocytes. J Invest Dermatol 2000; 115: 842-8.
6. Mc Pherson T. Current understanding in pathogenesis of atopic dermatitis. Indian J Dermatol 2016; 61(6): 649-55.
7. Esaki H, Ewald DA, Ungar B, *et al*. Identification of novel immune and barrier genes in atopic dermatitis by means of laser capture microdissection. J Allergy Clin Immunol 2015; 135: 153-63.
8. Murata S, Kaneko S, Morita E. Interleukin-8 levels in the stratum corneum as a biomarker for monitoring therapeutic effect in atopic dermatitis patients. Int Arch Allergy Immunol 2021; 182: 592-606.
9. Kim KH. Overview of atopic dermatitis. Asia Pac Allergy 2013; 3(2): 79-87.
10. Tanei R, Katsuoka K. Clinical analyses of atopic dermatitis in the aged. J Dermatol 2008; 35: 562-9.
11. Howell MD, Kim BE, Gao P, *et al*. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol 2009; 124(3 Suppl 2): 7-12.

12. Hu Y, Liu S, Liu P, Mu Z, Zhang J. Clinical relevance of eosinophils, basophils, serum total IgE level, allergen-specific IgE, and clinical features in atopic dermatitis. J Clin Lab Anal 2020; 34(6): e23214.
13. Remick GD. Interleukin-8. Crit Care Med 2005; 33(12 Suppl): 5646-47.
14. Waugh DJ, Wilson C. The interleukin-8 pathway in cancer. Clin Cancer Res 2008; 14(21): 6735-41.
15. Standiford TJ, Kunkel SL, Basha MA, *et al*. Interleukin-8 gene expression by a pulmonary epithelial cell line.A model for cytokine networks in the lung. J Clin Invest 1990; 86(6): 1945-53.
16. Holmes WE, Lee J, Kuang WJ, *et al*. Structure and functional expression of a human interleukin-8 receptor. Science 1991; 253(5025): 1278-80.
17. Xiong X, Liao X, Qiu S, *et al*. CXCL8 in tumor biology and its implications for clinical translation. Front Mol Biosci 2022; 9: 723846.
18. Rose MS, Shukkur MF, John RG, *et al*. The functional significance behind expressing two IL-8 receptor types in PMN. J Leukoc Biol 2009; 86(3): 529-43.
19. Jinzhou Z, Jiannan H, Daopeng D, *et al*. Recombinant human interleukin-1 receptor antagonist treatment protects rats from myocardial ischemia reperfusion injury. Biomed Pharmacother 2019; 111: 1-5.
20. Patti G, A. D'Ambrosio, Mega S, Giorgi G, *et al*. Early interleukin-1 receptor antagonist elevation in patients with acute myocardial infarction. J Am Coll Cardiol 2004; 43: 35-8.
21. Li L, Khan MN, Li Q, Chen X, *et al*. G31P, CXCR1/2 inhibitor, with cisplatin inhibits the growth of mice hepatocellular carcinoma and mitigates high-dose cisplatin-induced nephrotoxicity. Oncol Rep 2015; 33(2):751-7.
22. Gimbrone MA Jr, Obin MS, Brick AF, *et al*. Endothelial interleukin-8: a novel inhibitor of leukocyte-endothelial interactions. Science 1989; 246(4937):1601-3.
23. Khan MN, Wang B, Wei J, *et al*. CXCR1/2 antagonism with CXCL8/Interleukin-8 analogue CXCL8(3-72)K11R/G31P restricts lung cancer growth by inhibiting tumor cell proliferation and suppressing angiogenesis. Oncotarget 2015; 28(25): 21315-27.
24. Hanifin JM, Chan S. Biochemical and immunologic mechanisms in atopic dermatitis:new targets for emerging therapies. J Am Acad Dermatol 1999; 41(1):72-7.