International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X
P-ISSN: 2664-9411
www.dermatologypaper.com
Derma 2024; 7(2): 154-157
Received: 17-06-2024
Accepted: 23-07-2024

Eman Ibrahim El-Giar
Department of Dermatology and Venereology, Faculty of Medicine, Tanta University, Egypt

Esraa El-sayed El-Hawary
Department of Dermatology and Venereology, Faculty of Medicine, Tanta University, Egypt

Dina Magdy El-Gendy
Department of Pathology, Faculty of Medicine, Tanta University, Egypt.

Ghada Fawzy Rezk
Department of Dermatology and Venereology, Faculty of Medicine, Tanta University, Egypt

Corresponding Author:
Eman Ibrahim El-Giar
Department of Dermatology and Venereology, Faculty of Medicine, Tanta University, Egypt

Calprotectin in Dermatology

Eman Ibrahim El-Giar, Esraa El-sayed El-hawary, Dina Magdy El-gendy and Ghada Fawzy Rezk

DOI: https://doi.org/10.33545/26649411.2024.v7.i2c.215

Abstract
Calprotectin represents a potential biomarker of inflammation that may forecast a serological relapse prior to a clinical one in many inflammatory disorders. It is released by myeloid cells, including neutrophils, monocytes, as well as macrophages, but lymphocytes and basophils do not express calprotectin. Calprotectin is proposed as an inflammatory marker, a component of defensive mechanisms, and a regulator of the immune system's physiological processes. It is aberrantly expressed in the epidermis in some inflammatory hyperproliferative conditions and during wound healing, whereas increased serum calprotectin levels could be identified in inflammatory diseases as well as autoimmune responses.

Keywords: Calprotectin, inflammatory skin disease, psoriasis, atopic dermatitis, acne vulgaris, acne inversa, lichen planus

Introduction
Calprotectin represents a specific heterodimer composed of two S100 EF-hand calcium-binding proteins, S100A8 as well as S100A9. CP works within the host's innate immune response to pathogen infections, which exploits on their need for transition metals for growth and survival. CP impedes pathogen development by chelating certain transition metals with superior affinity, so depriving them of main nutrients, a process known as nutritional immunity. CP contributes to the host inflammatory response by serving as a ligand for pattern recognition receptors, involving the receptor for advanced glycation end products (RAGE), toll-like receptor 4 (TLR4), and cluster of differentiation 33 (CD33) [1].
These receptors are stimulated by various ligands and transmit signals via a MAPK-dependent kinase cascade, activating the NF-κB transcription factor. The resultant expression of inflammatory cytokines as well as chemokines, together with the creation of reactive oxygen species, stimulates inflammation. This signaling cascade results in heightened expression of ligands as well as receptors, supporting a pro-inflammatory environment; specifically, the secretion of CP from immune cells initiates a positive, pro-inflammatory feedback loop [2].
Numerous chronic inflammatory conditions, including rheumatoid arthritis, allograft rejection, inflammatory bowel disease, cancer, as well as pulmonary disorders, have been associated with elevated plasma levels of calprotectin. A favorable correlation has been shown between serum calprotectin and inflammatory skin disorders such as psoriasis, as well as between fecal calprotectin and children developing atopic dermatitis [3].

Calprotectin
Calprotectin was first identified as an antibacterial protein located within the cytoplasm of neutrophil granulocytes. It has now been identified as a potential inflammation marker, or rather a trace of the antagonism going on inside the organism. Moreover, the molecule shares in inflammatory cells' recruitment via interacting with endothelial cells. Additionally, its zinc-capturing activity could influence physiological balance. Calprotectin's pleiotropic effects are mostly linked to active inflammatory processes, including antibacterial defense mechanisms as well as Th1-mediated responses, like allograft rejection and autoimmune reactions [4].

The Membrane Calprotectin Role

Calprotectin's function in cellular adhesion has been shown, as the monoclonal antibody 27E10 obstructs the monocytes' binding to collagen as well as fibronectin. These extracellular matrix proteins stimulate calprotectin expression concurrently with the release of inflammatory cytokines tumor necrosis factor alpha (TNFα) and interleukin-6, as well as the creation of superoxide anions [5].

The correlation between CP expression and increased TNFα release capacity has also been reported in human alveolar macrophages derived by bronchoalveolar lavage [6].

Intracellular calprotectin

Calprotectin regulates intracellular pathways of innate immune cells while facilitating the inflammatory response coordination [7]. CP regulates cytoskeletal alterations, thus enabling leukocyte recruitment and promoting the transfer of arachidonic acid to inflammatory areas. Additionally, nuclear S100A9/CP acts as a coactivator while modulating transcription during inflammatory processes as well as malignant changes [8].

CP was recognized as a fatty acid-binding protein. Additionally, CP represents the primary arachidonic acid-binding protein in human neutrophils, exhibiting Ca2+ dependence. Additionally, it seems to be specific to this particular S100 protein. Arachidonic acid stands as a powerful inflammatory lipid mediator, crucial for leukotriene B4 production, thus promoting inflammation as well as tissue damage in inflammatory bowel disease (IBD) [9].

Furthermore, nuclear S100A9/CP has been shown to possess a potential transcription coactivator role. In sepsis, S100A9 has been seen to move from the cytosol to the nucleus in certain myeloid-derived suppressor cells, therefore increasing the immunosuppressive mediators' expression [8]. Nuclear S100A8/ A9 could initiate oncogenic pathways while amplifying breast cancer transformation [9].

Extracellular calprotectin

The S100A8/S100A9 complex is efficiently produced to facilitate extracellular CP TLR4 and RAGE mediated functions. Nonetheless, extracellular CP could create intricate protein structures with unique biological roles as well as equivalent receptors, which may not be elucidated by traditional signaling pathways. For instance, CP could engage with the cluster of differentiation (CD36) receptor during its interaction with polyunsaturated fatty acids [9].

Dysregulated primary bone marrow expansion could similarly be mediated by S100A9-induced CD33 signaling. Additionally, S100A9 modulates TLR2/3 pathways. The S100A8/A9 complex triggers innate immune responses while promoting inflammation, possibly via several receptors involvement within a cell type- and tissue-specific way. CP is reported to induce neutrophil chemotaxis as well as endothelial adhesion [10].

Extracellular CP complexes facilitate the chelation of several transition metal ions, essential for both invasive as well as commensal gut bacteria, since they support bacterial enzymatic activity, cellular homeostasis, as well as signaling pathways [11]. S100A9 could further interact with TLR4, thus enhancing MAPK signaling and the differentiation of monocytic cells. Furthermore, CP contributes to the differentiation of regulatory T-cells, which exert immunosuppressive effects while maintaining self-tolerance [12].

The Soluble Calprotectin Role

Calprotectin exhibits antibacterial as well as apoptosis-inducing properties, mitigated by the introduction of zinc. Calprotectin inhibits matrix metalloproteinases by zinc sequestration, affecting zinc-dependent enzymes crucial for embryonic development, angiogenesis, wound healing, inflammation, cancer, as well as tissue degradation. Calprotectin is efficient at controlling several vital functions within the body [13].

Additionally, calprotectin induces microbial growth inhibition when competing for zinc. Zinc chelation, mediated by histidine-rich regions of calprotectin, stands as an essential antimicrobial mechanism within host defense [14].

Calprotectin levels ranging from 50 to 250 µg/ml were seen to limit the growth of Escherichia coli, Staphylococcus aureus, as well as Staphylococcus epidermidis, whereas lower values of 4 to 32 µg/ml were enough to inhibit the development of Candida albicans. Cells with calprotectin expression could exhibit resistence to invasion by Listeria monocytogenes as well as Salmonella enterica serovar Typhimurium. Calprotectin presumably serves as a defensive mechanism, protecting neutrophils as well as other calprotectin-expressing cells against pathogens that infiltrate the host's cell cytoplasm [13].

Calprotectin functions within the skin

The genes for calprotectin are situated inside the epidermal differentiation complex on the chromosome 1 long arm, exhibiting coordinated local regulation among other S100 proteins as well as the cornified cell membrane components, involving involucrin, loricrin, along with filaggrin. Calprotectin promotes keratinocyte migration while inhibiting their proliferation *in vitro* under inflammatory stimuli [15].

Consequently, the CP overexpression limits the damaged cells' growth, promotes apoptosis while preventing UV-induced carcinogenesis. Additionally, such a mechanism shows effectiveness against viral pathogens [16].

Calprotectin shows a potent expression in nflammatory cells' infiltration. Additionally, it could exhibit a potential role in skin carcinogenesis. Calprotectin is present in almost all dermatoses characterized by epithelial cell hyperproliferation and throughout the wound healing process. Calprotectin is present in the suprabasal layers and throughout the epidermis of bullous skin following drug-induced epidermal necrolysis. The binding of calprotectin to the endothelium could also take place within the dermis. Calprotectin-positive macrophages were identified as being linked to urticaria contact dermatitis or the local melanoma progression [9].

In the latter late wound healing stages, namely the proliferative and remodeling phases, Calprotectin promotes the proliferation, migration, along with differentiation of keratinocytes as well as fibroblasts. Additionally, It supports proteases and growth factors' release. Calprotectin facilitates keratinocyte differentiation via activating the NF-κB pathway when stimulating epithelial nicotinamide adenine dinucleotide phosphate [15].

Furthermore, it establishes a positive feedback loop

promoting keratinocytes' proliferation involving cytokines: Interleukin (IL)1α, IL6, IL8, TNF-α, interferon (IFN)-α, IFN-γ, as well as chemokine ligand. Calprotectin overexpression hinders cellular differentiation as well as growth. The flagellin of Escherichia coli (E. coli) enhances Calprotectin expression within keratinocytes [17].

Calprotectin not only indirectly enhances innate immunity via stimulating cytokine production but also actively fights E. coli, Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella, as well as fungal infections as an antimicrobial peptide. Calprotectin unexpectedly exhibits an anti-inflammatory phenotype within dendritic cells [14].

Calprotectin Expression in inflammatory skin diseases

The calprotectin role has been examined in only a limited number of dermatoses:

In psoriasis, Calprotectin exhibits a significant overexpression in the lesions then controlled by oncostatin M via the STAT3 pathway. Calprotectin effectively inhibits keratinocyte proliferation while promoting differentiation; however, this mechanism is clearly inefficient in psoriasis, characterized by excessive keratinocyte hyperproliferation [18].

In atopic dermatitis, CP is untraceable. The pimecrolimus administration for atopic dermatitis significantly promotes Calprotectin expression while improving barrier function [15].

In acne vulgaris, serum calprotectin levels are elevated among cases relative to healthy controls and are positively connected with disease severity, perhaps aiding in acne severity assessment [19].

In hidradenitis suppurativa/ acne inversa

Calprotectin is strongly overexpressed in the affected skin as opposed to the same patient's healthy skin. Cases developing hidradenitis suppurativa have not addressed any association between condition severity and Calprotectin's serum levels. Nevertheless, functional pathways as well as Calprotectin interactions within hidradenitis suppurativa require more investigations [20].

As regards lichen planus patients, Calprotectin concentration exhibits a significant elevation as opposed to medically-free subjects. A significant positive association was documented between severity and calprotectin concentrations, with serum level being elevated in severe lichen planus [21].

Conflict of Interest

Not available

Financial Support

Not available

References

1. Wang S, Song R, Wang Z, Jing Z, Wang S, Ma J. S100A8/A9 in inflammation. Frontiers in Immunology. 2018;9:1298.
2. Garcia V, Perera YR, Chazin WJ. A structural perspective on calprotectin as a ligand of receptors mediating inflammation and potential drug target. Biomolecules. 2022;12:79.
3. Ali AA, El-refaei AM, Ahmed SH. Relation between serum and fecal calprotectin and atopic dermatitis. Benha Journal of Applied Sciences. 2022;7:47-53.
4. Premjeyanth V, Shipman AR, Shipman KE. Faecal calprotectin in dermatology practice. Clinical and Experimental Dermatology. 2020;45(6):831-835.
5. Muro P, Zhang L, Li S, Zhao Z, Jin T, Mao F, *et al*. The emerging role of oxidative stress in inflammatory bowel disease. Frontiers in Endocrinology. 2024;15:1390.
6. Kotsiou OS, Papagiannis D, Papadopoulou R, Gourgoulianis KI. Calprotectin in lung diseases. International Journal of Molecular Sciences. 2021;22(3):1706.
7. Donato R, Cannon BR, Sorci G, Riuzzi F, Hsu K, Weber DJ, *et al*. Functions of S100 proteins. Current Molecular Medicine. 2013;13(1):24-57.
8. Dai J, Kumbhare A, Youssef D, McCall CE, Gazzar ME. Intracellular S100A9 promotes myeloid-derived suppressor cells during late sepsis. Frontiers in Immunology. 2017;8:1565.
9. Jukic A, Bakiri L, Wagner EF, Tilg H, Adolph TE. Calprotectin: from biomarker to biological function. Gut. 2021;70(12):1978-1988.
10. Tsai SY, Segovia JA, Chang TH, Shil NK, Pokharel SM, Kannan TR, *et al*. Regulation of TLR3 activation by S100A9. Journal of Immunology. 2015;195(9):4426-4437.
11. Diaz-Ochoa VE, Lam D, Lee CS, Klaus S, Behnsen J, Liu JZ, *et al*. Salmonella mitigates oxidative stress and thrives in the inflamed gut by evading calprotectin-mediated manganese sequestration. Cell Host & Microbe. 2016;19(6):814-825.
12. Lin CR, Wei TYW, Tsai HY, Wu YT, Wu PY, Chen ST. Glycosylation-dependent interaction between CD69 and S100A8/S100A9 complex is required for regulatory T-cell differentiation. FASEB Journal. 2015;29(12):5006-5017.
13. Abtin A, Eckhart L, Gläser R, Gmeiner R, Mildner M, Tschachler E. The antimicrobial heterodimer S100A8/S100A9 (Calprotectin) is upregulated by bacterial flagellin in human epidermal keratinocytes. Journal of Investigative Dermatology. 2010;130(10):2423-2430.
14. Zygiel EM, Nolan EM. Transition metal sequestration by the host-defense protein calprotectin. Annual Review of Biochemistry. 2018;87:621-643.
15. Benedyk M, Sopalla C, Nacken W, Bode G, Melkonyan H, Banfi B, *et al*. HaCaT keratinocytes overexpressing the S100 proteins S100A8 and S100A9 show increased NADPH oxidase and NF-κB activities. Journal of Investigative Dermatology. 2007;127(8):2001-2011.
16. Kerkhoff C, Voss A, Scholzen TE, Averill MM, Zänker KS, Bornfeldt KE. Novel insights into the role of S100A8/A9 in skin biology. Experimental Dermatology. 2012;21(11):822-826.
17. Almansouri D, Zouboulis CC. Calprotectin functions in the skin: an overview. Hong Kong Journal of Dermatology and Venereology. 2017;25(3):115-121.
18. D'Amico F, Granata M, Skarmoutsou E, Trovato C, Lovero G, Gangemi P, *et al*. Biological therapy downregulates the heterodimer S100A8/A9 (Calprotectin) expression in psoriatic patients. Journal of Inflammation Research. 2018;67:609-616.
19. Fouda I, Obaid ZM, Hegazy SF, Abd Al-Samie HS, Nofal A. Calprotectin in acne vulgaris: A possible contributory role. Journal of Cosmetic Dermatology.

2021;20(5):621-625.
20. Wieland C, Vogl T, Ordelman A, Vloedgraven H, Verwoolde L, Rensen J, *et al*. Myeloid marker S100A8/A9 and lymphocyte marker, soluble interleukin 2 receptor: Biomarkers of hidradenitis suppurativa disease activity? British Journal of Dermatology. 2013;168(6):1252-1258.
21. Khattab FM, Ghonaim R, Samir MA. Estimation of neutrophil activation marker in lichen planus patients. Journal of Cosmetic Dermatology. 2022;21(3):1625-1628.

How to Cite This Article
El-Giar EI, El-sayed El-hawary E, El-gendy DM, Rezk GF. Calprotectin in Dermatology. International Journal of Dermatology, Venereology and Leprosy Sciences. 2024; 7(2): 154-157.