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Role of calprotectin in dermatology

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Abstract
Two proteins, S100A8 and S100A9, combine to form the heterodimer known as calprotectin. Activated monocytes and neutrophils in the bloodstream and in inflammatory tissues are the primary producers of this protein. Calprotectin may play a part in inflammatory situations because it was found to have a cytokine-like activity in addition to its bacteriostatic function. It plays a role in controlling how inflammatory cells adhere to the endothelium. While higher blood calprotectin levels can be found in inflammatory illnesses and autoimmune reactions, it is aberrantly produced in the epidermis in some inflammatory hyperproliferative situations and during wound healing.

Keywords: Calprotectin, psoriasis, atopic dermatitis, hidradenitis suppurativa, epidermal differentiation complex, lichen planus

Introduction
Calprotectin (CLP) is a soluble protein secreted by activated monocytes and neutrophils, playing key roles in inflammation and antimicrobial defense, and is a heterodimer composed of S100A8 and S100A9 from the S100 calcium-binding protein family, with α-helix motifs that bind calcium and other divalent metal ions like zinc [1].

The molecular configuration of S100A8/S100A9 demonstrates remarkable complexity, with the ability to form heterodimeric or heterotetrameric structures that are fundamental to both intracellular and extracellular biological functions. While these proteins can circulate independently, the heterodimeric form represents the most stable configuration and serves as the primary mediator of critical protein interactions. Notably, calprotectin can be quantitatively assessed through multiple biological specimens, including fecal and serum samples, with particular emphasis on its involvement in inflammatory pathological processes [2].

Physiological investigations have established normative serum concentrations of calprotectin ranging between 0.1 and 1.6 μg/ml. However, these levels can experience significant variations in response to diverse pathological conditions, including infectious states, inflammatory processes, and neoplastic developments [3].

The protein demonstrates substantial clinical relevance through its correlation with disease activity across multiple autoimmune and inflammatory conditions. Specifically, calprotectin has been associated with pathological manifestations in systemic lupus erythematosus (SLE), rheumatoid arthritis, Still's disease, and acute gouty arthritis, underscoring its potential as a critical biomarker [4].

Emerging research has furthermore elucidated calprotectin's intricate role in psoriasis pathogenesis. The protein exhibits direct chemotactic influences on immune cell populations, demonstrating capabilities to stimulate proinflammatory cytokine production by keratinocytes and induce proangiogenic mediator generation, thereby contributing to the complex immunological landscape of dermatological inflammatory conditions [5].

Calprotectin
Calprotectin, also known as S100A8/A9, is a complex protein comprising S100A8 and S100A9, members of the S100 protein family, and is referred to by various names, including MRP8/MRP14, calgranulin A/B, L1 protein, and cystic fibrosis antigen [6].

The S100A8/A9 protein complex, primarily found in neutrophils, monocytes, and early

macrophages, plays a significant role in immune and inflammatory processes. Inside the cell, it interacts with cytoskeletal elements like actin, vimentin, and microtubules, aiding phagocyte migration across endothelial barriers. Outside the cell, it exhibits antimicrobial properties, activates endothelial cells, disrupts endothelial integrity, induces endothelial apoptosis, and attracts neutrophils, all contributing to inflammation. Additionally, it regulates key cellular functions such as proliferation, differentiation, calcium balance, and migration. When released extracellularly, S100A8/A9 acts as an alarmin by binding to receptors such as RAGE and TLR4, activating NF-κB signaling pathways and stimulating the production of proinflammatory cytokines, thereby amplifying the inflammatory response. This complex is central to both local and systemic inflammation [7].

The protein complex facilitates the release of pivotal inflammatory mediators, including tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which promote chemotaxis and leukocyte recruitment. Notably, S100A8/A9 demonstrates a nuanced inflammatory profile, exhibiting both pro-inflammatory and potential anti-inflammatory functionalities. In specific physiological contexts characterized by intensive inflammatory responses threatening tissue integrity, the protein complex can modulate inflammatory processes, thereby maintaining critical biological homeostasis [6].

An additional significant function of S100A8/A9 involves pathogen resistance, specifically through mechanisms that attenuate bacterial adhesion and invasion. Diverse inflammatory stimuli—including infection, trauma, thermal stress, and psychological stress—substantially elevate S100A8/A9 cellular levels. The protein's upregulation occurs across various inflammatory conditions, encompassing not only immune system-related pathologies such as autoimmune diseases and hypersensitivity reactions but also metabolic inflammatory states like gout, diabetes, obesity, and degenerative inflammatory processes such as osteoarthritis [8].

Structure

The S100 protein superfamily represents a significant calcium-binding protein group characterized by the EF-hand motif, encompassing over 20 members in the human genome localized on chromosome 1q21[9].

Notably, calprotectin, composed of S100A8 and S100A9 subunits, exemplifies the molecular complexity of this protein family. Predominantly expressed in myeloid cellular lineages, including neutrophils and monocytes, these proteins-alternatively termed myeloid-related proteins (MRP-8 and MRP-14) or calgranulins-demonstrate substantial calcium-binding capabilities [10].

Intracellular functions of CLP

Within polymorphonucleate neutrophils (PMNs), calprotectin plays a crucial role in cytoskeletal dynamics and cellular migration. The protein facilitates rapid cytoskeletal rearrangement through tubulin-dependent mechanisms. Specifically, calcium-induced heterotetrameric formations of S100A8 and S100A9 enable membrane translocation, promoting tubulin polymerization. Experimental evidence from S100A9-knockout murine models substantiates the protein's significance in granulocyte motility [11].

CLP is instrumental in triggering the respiratory burst mechanism. Upon calcium activation, S100A9 interacts with arachidonic acid in the cytosolic environment, subsequently transporting it to the neutrophil plasma membrane's nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex through a protein kinase C-mediated pathway. The protein complex demonstrates multifaceted interactions with oxidase subunits, including gp91phox, p67phox, and rac-2, ultimately stimulating reactive oxygen species production essential for PMN functionality [12].

Secretion of CLP occurs through diverse mechanisms following danger signal recognition. Primary release mechanisms include non-Golgi-associated pathways involving active non-classical secretion and PKC activation. Additionally, recent investigations have revealed alternative release strategies, such as chromatin-bound release within neutrophil extracellular traps (NETs) and passive secretion from necrotic cellular environments [13].

Extracellular functions of CLP

The protein demonstrates receptor-binding capabilities contingent upon specific conformational states. CLP heterodimers interact with various cell-surface molecules, including heparan sulphate proteoglycan, carboxylated N-glycan, and critical inflammatory receptors like TLR4 and receptor for advanced glycated end products (RAGE) [14].

TLR4 serves as the primary receptor, with signal transduction mediated through MyD88 and NF-κB activation. This process triggers pro-inflammatory cytokine expression, including TNF-α, interleukin-1β, and various chemokines. RAGE engagement similarly activates inflammatory signaling pathways, generating a positive feedback mechanism that amplifies inflammatory responses [15].

A fundamental function of CLP involves regulating leukocyte chemotaxis and tissue infiltration. The protein enhances integrin receptor expression, facilitating increased cellular adhesion to critical extracellular matrix components and endothelial surfaces [11].

The protein's inflammatory potential extends to endothelial interactions, inducing cellular activation through glycan and receptor-mediated mechanisms. This activation leads to chemokine expression, compromised endothelial integrity, and ultimately contributes to vascular and tissue modifications through inflammatory and apoptotic processes [16].

Role of calprotectin in inflammatory skin diseases

Epidermal Differentiation Complex

The Epidermal Differentiation Complex (EDC) on chromosome 1q21 encompasses S100 genes critical to keratinocyte differentiation [17]. Notably, S100 proteins including S100A7, S100A8, S100A9, and S100A12 demonstrate significant upregulation in skin disorders characterized by aberrant keratinocyte proliferation and differentiation [18].

Strategically positioned within the EDC locus, S100A8/A9 genes exhibit coordinated expression. Under inflammatory conditions, calprotectin demonstrates complex regulatory mechanisms: stimulating cell migration while simultaneously restraining proliferation. This intricate process enables the protein to inhibit damaged cell replication, trigger apoptosis, and provide protection against

ultraviolet-induced carcinogenesis and viral infections [19].

Psoriasis

In psoriasis, S100A8/A9 experiences substantial overexpression within lesional tissues, regulated through the oncostatin M-STAT3 pathway. Despite its potential as a differentiation inducer and proliferation inhibitor, the protein's mechanism proves ineffective against the extreme keratinocyte hyperproliferation characteristic of psoriatic conditions [20].

Atopic dermatitis

Interestingly, atopic dermatitis presents a contrasting scenario, where S100A8/A9 remains undetected. Remarkably, pimecrolimus therapy can promote S100A8/A9 expression and enhance barrier function [21].

Hidradenitis suppurativa

Hidradenitis suppurativa patients demonstrate marked S100A8/A9 overexpression compared to individuals with healthy skin. Contrary to psoriasis, a 29-patient investigation revealed no correlation between disease severity and serum S100A9/A8 levels [22, 23].

Wound healing

During wound healing, S100A8/A9 demonstrates a dynamic role. In the initial inflammatory phase, it stimulates inflammatory cell migration and mediator release. Subsequent proliferative and remodeling phases witness its activation of nuclear factor kappa-B, promoting keratinocyte and fibroblast proliferation, migration, and differentiation [24, 25].

The protein's antimicrobial capabilities extend to fighting various pathogens. Upon exposure to bacterial lipopolysaccharides, S100A8/A9 upregulates in keratinocytes, directly combating microorganisms including E. coli, S. aureus, and various fungal species [26].

Lichen planus

In lichen planus (LP), S100A8 and S100A9 expressions reveal potential pathogenic implications. Recent research indicates significantly elevated calprotectin serum levels in LP patients compared to control groups, suggesting its potential as a diagnostic and prognostic marker [27].

Conflict of Interest

Not available

Financial Support

Not available

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