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Role of CD163 in dermatology

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Abstract
Scavenger receptor CD163 is specifically found on monocytes and macrophages, serving as a prominent marker for alternatively activated macrophages. The expression of CD163 is notably heightened in circulating monocytes of individuals experiencing systemic inflammation. Additionally, soluble CD163 molecules may impede the activation and proliferation of human T lymphocytes *in vitro*, thus contributing to the attenuation of the inflammatory response. Elevated levels of sCD163 have been observed during the wound healing process, suggesting a potential involvement of CD163 in the development of fibrotic diseases and the remodeling of connective tissue. In psoriatic lesional skin, CD163+ cells exhibit a threefold increase, returning to baseline levels in non-lesional skin following effective treatment. The infiltration of CD163-positive macrophages is indicative of systemic involvement in sarcoidosis. Furthermore, sCD163 and CD163+ tumor-associated macrophages serve as prognostic indicators for early-stage cutaneous melanoma, while CD163+ cells, which are markers of alternatively activated macrophages, are present in the lesional skin of atopic dermatitis.

Keywords: CD163, dermatology, systemic lupus erythematosus, psoriasis, Sarcoidosis, cutaneous melanoma, atopic dermatitis

Introduction
Macrophages serve as crucial sentinels within the innate immune system. Their primary function is thought to involve phagocytosis, contributing to tissue homeostasis, the clearance of erythrocytes, and the removal of cellular debris resulting from tissue remodeling. Historically, macrophages have been acknowledged as antigen-presenting cells, possessing the ability to activate T cells during the stimulation of the adaptive immune response [1-3]
In healthy skin, CD163 has been identified as the most reliable marker for macrophages. CD163 is a scavenger receptor that binds to the hemoglobin-haptoglobin complex and is predominantly expressed on mature tissue macrophages [4].
Additionally, CD163 is present on monocytes and macrophages, and it can be released into the bloodstream in a soluble form (sCD163) following stimulation by Toll-like receptors and oxidative stress. Elevated serum levels of sCD163 have been associated with inflammatory or infectious conditions [5, 6]
Furthermore, the soluble form of CD163 (sCD163) is known to inhibit the activation and proliferation of T lymphocytes, which suggests that sCD163may play a role in inflammatory disorders mediated by T-lymphocytes and monocyte-macrophage lineage cells. sCD163 has been clinically confirmed as a new macrophage-specific biomarker for cardiovascular disorders, infections, and collagen disease [7].

CD163
The CD163 gene in humans encodes the protein known as CD163 (Cluster of Differentiation 163). It was initially found in 1987 [8].
It is located on chromosome 12 in region p13. The scavenger receptor CD163 has a high affinity for the hemoglobin-haptoglobin complex and a decreased affinity for haemoglobin alone when haptoglobin is not present. It also serves as a marker for monocyte/macrophage-line cells. For both gram-positive and gram-negative bacteria, CD163 serves as an innate immune sensor [9].

Molecular structure of CD163

The 130-kDa membrane protein CD163 has a single transmembrane segment, a short cytoplasmic tail, and a sizable ectodomain made up of nine scavenger receptor cysteine-rich (SRCR) scavenger receptor class B domains. A variety of human CD163 isoforms have been identified, including three variations with varying cytoplasmic tail lengths. The most prevalent is the short tail type, which consists of 42 amino acids. Every variation has endocytic activity and shares internalisation motifs [6, 10].

Cellular expression of CD163

Human CD163 expression is primarily confined to the monocytic-macrophage lineage, exhibiting high levels in various macrophage populations, including those found in the red pulp of the spleen, bone marrow, liver (Kupffer cells), lungs, and several other tissues [11]. Monocytes display a moderate level of CD163 expression, which significantly increases when cultured, along with the acquisition of other macrophage characteristics. Discrepancies in previous studies regarding monocyte CD163 expression have been clarified through receptor-based investigations, which demonstrated that the sensitivity of cellular staining in flow cytometry is influenced by the specific antibodies and incubation conditions employed, thereby affecting the reproducibility of the findings [12].

In contrast, low or absent CD163 expression is observed in other monocyte-derived cells, such as dendritic cells, Langerhans cells, and white pulp macrophages in the spleen [11].

The most effective stimulators of CD163 expression include glucocorticoids, interleukin (IL)-6, IL-10, and heme/Hb. Conversely, factors such as IL-4, lipopolysaccharide (LPS), TNF-α, interferon γ, CXC-chemokine ligand 4 (CXCL4), and granulocyte-macrophage colony-stimulating factor are known to downregulate CD163 expression. The *in vitro* effects of glucocorticoids have been corroborated by in vivo studies involving human monocytes following glucocorticoid administration to volunteers [13].

The regulation of CD163 by glucocorticoids is further supported by the discovery of three glucocorticoid receptor-binding sites within the promoter region of the CD163 gene. Additionally, binding sites for various transcription factors critical for myeloid differentiation have been identified. Collectively, these findings indicate that CD163 is characteristic of macrophages that develop into "alternatively activated" macrophages, which stand in contrast to the classical M1-type macrophages [14].

Consequently, CD163-expressing macrophages have been found in inflammatory locations, including atherosclerotic plaques, chronically inflamed arthritic joints, and the area around tumour cells (tumor-associated macrophages) [15].

CD163 as a clinical biomarker in inflammation

CD163 has been identified as a key mediator in the management of systemic inflammation, playing a significant role in the resolution of both acute and chronic inflammatory processes during the late downregulatory phase [16].

his protein is present in elevated quantities within inflamed tissues, where it functions to modulate the inflammatory response of macrophages. Furthermore, CD163 expression is heightened in the circulating monocytes of individuals experiencing systemic inflammation. It is noteworthy that the expression of CD163 on monocytes is also subject to regulation during the initial stages of the innate immune response. Recent studies have indicated that CD163 is involved in the induction of tolerance and the regeneration of tissues. Additionally, some findings suggest that soluble forms of CD163 may inhibit the activation and proliferation of human T lymphocytes *in vitro*, thus contributing to the suppression of the inflammatory response [17].

CD163 and Systemic lupus erythematosus

Compared to healthy control participants, there is a substantial increase in CD163+ macrophages. The production of autoantibodies and complement activation are the main mechanisms that start the inflammatory response in systemic lupus erythematosus. However, cellular immune mechanisms mediated through infiltration are involved in the skin inflammation in SLE patients, where the number of CD163+ macrophages and the concentration of serum sCD163 are mononuclear cells, including macrophages, that play a significant role in the amplification and progression of SLE [18].

Immunohistochemical analyses of DLE skin revealed a subpopulation of CD163+ macrophages that express both M1 and M2 proteins linked to macrophages. Additionally, it has been discovered that sCD163 is elevated during wound healing, suggesting that CD163 may play a part in the development of fibrotic disorders and connective tissue remodelling [19].

CD163 and Psoriasis

T cells, dendritic cells (DCs), and keratinocytes interact intricately to cause psoriasis, a chronic inflammatory skin condition. T helper 17 (Th17) cells are a novel group of T cells that have recently been added to the pathophysiology of psoriasis, which was formerly a strictly classical type 1 (Th1) illness that was triggered by IFN-γ. It is still unclear how macrophages contribute to inflammatory skin conditions like psoriasis. By generating TNF-α, M1 macrophages are thought to have a role in the onset of psoriasis, particularly in its early stages. It was recently shown that CD163+ macrophages produce IL-23 [20].

Following successful etanercept therapy, CD163+ cells in psoriatic lesional skin grow threefold and recover to levels seen in non-lesional skin. Because they are not immunostimulatory, macrophages in psoriasis cannot polarise T cells to create IL-17. As the connection between psoriasis skin disease and the metabolic syndrome has come to light, there has been increased interest in the involvement of macrophages in psoriatic inflammation. Systemic inflammation may be triggered by TNF, and skin and adipose tissue macrophages may play a critical part in this process. Understanding the systemic symptoms of psoriasis requires characterisation of the markers, capacities, and roles of macrophages in the disease [21].

CD163 and Sarcoidosis

Sarcoidosis is a chronic systemic inflammatory condition characterized by the presence of noncaseating epithelioid granulomas in affected individuals. Cutaneous manifestations occur in approximately 9% to 35% of patients with sarcoidosis and encompass a range of clinical subtypes. The disease typically impacts multiple organs and exhibits a variable clinical trajectory, referred to as systemic sarcoidosis (SS). In some instances, however, it may be

confined solely to the skin, a condition known as cutaneous sarcoidosis (CS) [22].

Research by Isohisa T *et al*. indicated that serum levels of soluble CD163 are associated with immune cell activity in patients with sarcoidosis; nevertheless, the roles of M1 and M2 macrophages in the progression of the disease remain ambiguous. CD163-positive cells are predominantly located in the interstitial regions surrounding epithelioid granulomas in cases of systemic sarcoidosis, suggesting that the infiltration of CD163-positive macrophages may serve as a predictor of systemic involvement in the disease [23].

CD163 and cutaneous melanoma

The prognostic implications of CD163 and Programmed cell death protein-1 (PD-1) expression in cutaneous melanoma have been documented. Additionally, the prognostic relevance of LAG-3 in this type of melanoma has also been noted. It has been demonstrated that CD163 positive M2-Tumor-associated macrophages (TAMs) can promote the expression of Lymphocyte activating gene-3 (LAG-3), PD-1, and TIM-3 on CD8+ T cells *in vitro* [24].

CD163 and Atopic dermatitis

A recent investigation conducted by Sugaya *et al*. reveals that the quantity of CD163+ cells, which serve as a marker for alternatively activated macrophages, in the lesional skin of atopic dermatitis (AD) is significantly greater than that found in normal skin. Notably, the quantity and distribution of CD163+ cells closely resemble those of CD68+ cells, aligning with findings from an earlier report [25].

Conflict of Interest

Not available

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Not available

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