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REVIEW ARTICLE

Tuberculosis and scavenger receptors: Exploring their relationship

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A B S T R A C T

Tuberculosis (TB) remains a significant global health concern, particularly in low- and middle-income countries. Several risk factors are associated with TB infection and its progression from infection to disease onset, including host factors, microbial factors, environmental factors, and socio-economic status. Host genetic factors play a significant role in determining susceptibility to acquiring infection, progression to active disease, and the severity of the disease. Innate immunity is essential in the initial defense, advancement, and long-term control of mycobacterial infection. Among various cell surface and intracellular receptors mediating mycobacteria uptake, scavenger receptors play a crucial role in innate immunity. Scavenger receptors are classified into 12 classes, with class B comprising SR-B1 (SCARB-1), SR-B2 (LIMP2), and SR-B3 (CD36). SR-B1 and CD36 are involved in the uptake and phagocytosis of Mycobacterium tuberculosis (Mtb). Scavenger receptors promote cytokine production and modulate cytokine production during antimycobacterial responses. The SR-B1 and CD36 genes contain various single nucleotide polymorphisms in their intronic and exonic regions. These polymorphisms may influence the expression of the genes, leading to changes in Mtb uptake and antimycobacterial response. In this current review, we have explored the importance of scavenger receptors in TB pathogenesis. Additionally, we have summarized SNPs in SR-B1 and CD36 genes and their effect on protein expression.

Keywords: *Tuberculosis, Scavenger receptors, SR-B1, CD36, Single nucleotide polymorphisms*

Introduction

Tuberculosis (TB), caused by a single infectious agent, is the leading cause of death worldwide, surpassing HIV/AIDS. TB remains a significant global health concern, particularly in low-income and middle-income countries. TB can be of different forms, depending on a range of factors, including the site of infection, the immune response of the individual, and the presence of drug resistance. In 2021, there were an estimated 1.4 million deaths among HIV-negative people and 0.19 million deaths among HIV-positive people, for a combined total of 1.6 million.[1] According to the WHO TB Report 2022, 08 countries accounted for two-thirds of the global TB cases in 2021. Mycobacterium tuberculosis (Mtb) is the primary culprit responsible for human TB infections. Mtb is a slow-growing small bacillus, acid-fast, non-motile, rod-shaped, aerobic bacterium that divides every 18-20 hours and possesses a

unique cell wall composition, which includes mycolic acids and lipids. Mtb, also known as Koch's Bacillus, was first identified by Robert Koch in 1882. Mtb can exist in metabolically inactive latent and metabolically active disease states. The bacterium stays dormant and does not actively multiply in the latent form. In contrast, in an active disease state, it actively multiplies and causes clinical manifestations of TB.[2] Approximately 5% of the individuals infected with Mtb rapidly progress to active disease and can transmit the condition.[3] The remaining individuals develop a latent infection and carry a lifetime risk of Mtb reactivation and active TB.

Innate and Adaptive Immunity in TB Pathogenesis

When an individual inhales air contaminated with Mtb, the bacteria can reach the lungs and begin to multiply. The consequences of Mtb deposition in the lungs include the prompt removal of Mtb from the body, the individual's direct commencement of active disease, latent TB infection, disease reactivation, and the emergence of an active disease several years after dormant infection. The pathogenesis of TB can be divided into several stages. The pathogenesis of TB involves a complex interaction between Mtb and the host immune system. When a person inhales aerosols containing Mtb, bacteria reach the lungs and invade the respiratory epithelium. The survival and progression of Mtb depend on its capacity to interact with the host immune system.

To induce infection, Mtb fights and neutralizes both neutrophils and macrophages in the lungs, compromising different lysosomal trafficking pathways. First, alveolar macrophages are infected with Mtb, triggering an innate immune reaction.[4] Various immune cells, including dendritic cells and neutrophils, get involved as the infection progresses. These infected alveolar macrophages travel to the pulmonary interstitium and infect additional macrophages, dendritic cells (DCs), and neutrophils.[5,6]

Infected dendritic cells travel to nearby lymph nodes and initiate the priming of T-cells, activating an adaptive immune response that consequently travels to the location of infection to restrict infection establishment and spread.[7] Mycobacteria use various mechanisms to evade the host immune response and start to multiply, initiating active TB infection. If the immune system cannot keep bacteria under control, Mtb can reproduce quickly, leading to active TB. Unfortunately, 5-10% of infected individuals develop active TB infection and show clinical symptoms of TB.[8]

During the pathogenesis of TB, the bacteria can also trigger an immune response, leading to the formation of granulomas, which can contain both infected macrophages and other immune cells.[9] When an efficient cell-mediated immunological response is established, T lymphocytes, B lymphocytes, and stimulated alveolar macrophages develop a specific granuloma. This protective shell retains Mtb confined and under control, which leads to latent TB infection in approximately 90% of cases.[10] Most of the time, the multiplication of bacteria is stopped, and the inflammatory response diminishes. Patients with latent TB have an adaptive immunological response to Mtb; however, there are no clinical signs of TB.[7] An effective adaptive immune response results in various outcomes, from successful containment of the disease (sterilized infection) to asymptomatic or mild disease (subclinical disease).

Reactivation occurs when the immune mechanism is disrupted, and the control of infection is compromised due to factors such as AIDS, advanced age, inadequate nutrition, and high levels of stress.[11] Reinfection can occur in individuals who have previously had TB, either in the form of LTBI or have been successfully treated with TB.

Role of Host genetics in TB pathogenesis

Several risk factors are associated with TB infection and its progression from infection to disease, including host factors, microbial factors, environmental factors, and socio-economic status. The variability in the clinical outcome of disease among individuals is attributed to the variation in human genes involved in host defence mechanisms.[12] An increasing body of evidence suggests that host genetic factors play a significant role in both susceptibility to acquiring infection and the likelihood of developing severe complications.[13]

Experiments involving transgenic mice demonstrated that overexpression of chemokines made them more susceptible to TB.[14] In another mouse model study, the macrophage-mediated intracellular pathogen resistance gene was identified as a genetic factor crucial in providing innate immunity to Mtb infection.[15] A murine model study

identified the importance of immunoregulatory genes in modulating the inflammatory environment, subsequently facilitating protection against TB infection.[16]

A significant demonstration of the impact of host factors on varying responses to infection was observed in Lübeck when a virulent strain of Mtb was mistakenly administered through the contamination of a locally produced BCG vaccine.[17] More excellent concordance for TB in monozygotic and dizygotic twin pairs suggests that genetic predisposition plays a significant role as a risk factor for tuberculosis susceptibility in humans.[18]

Studies of TB in several ethnic groups have shown that this disease is linked to host genetic mutations. Multiple research groups have reported a significant association between the genes involved in TB immunopathogenesis and TB susceptibility. Some recent studies are quoted here. In the Ethiopian population, polymorphisms in inflammatory cytokines have been identified as significant host genetic risk factors for TB infection.[19] Genetic variations in Th17 pathway genes are crucial for the clinical manifestations of PTB in the Chinese population.[20] Data from different studies suggest a significant association between nuclear receptor polymorphisms and TB susceptibility in Asian populations.[21-23] A comprehensive meta-analysis provided strong evidence supporting the association of polymorphisms in one of the subgroups of PRRs with TB infection across diverse ethnicities, including Asians, Caucasians, and Africans.[24]

Scavenger receptors

Scavenger receptors (SRs) are a family of cell surface proteins (Figure 1) that bind and internalize various ligands. In 1979, Brown and Goldstein first described SRs.[25] SRs as pattern recognition receptors (PRRs) are capable of recognizing damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). They can bind various pathogens, i.e., cell-wall components found in Gram-positive and Gram-negative bacteria, including lipoteichoic acid (LTA), lipopolysaccharide (LPS), and β-glucan present in fungal cell walls.[26] Endocytosis, phagocytosis through adhesion and activation of downstream signalling, is commonly used by SRs to remove degraded or harmful substances.[27]

Classification of SRs

SRs comprise a structurally diverse superfamily of various classes with minimal structural similarity. The primary distinguishing feature among different courses is their ability to bind shared ligands [28] (**Error! Reference source not found.**2). The classification of SRs is based on sequence alignment of their nucleotide and analyzing their protein structures. According to the proposed nomenclature, there are 12 known classes (A-L) of mammalian scavenger receptors.[29] Class B of scavenger receptors is explained in detail in succeeding paragraphs.

Class B scavenger receptors: SR-B

Class B scavenger receptors comprise the conserved CD36 domain, and its members include SR-B1 (SCARB-1), SR-B2 (LIMP2) and SR-B3 (CD36). This class can bind diverse ligands, including viruses, bacteria, and HDL particles.[28] Three members of this class feature two

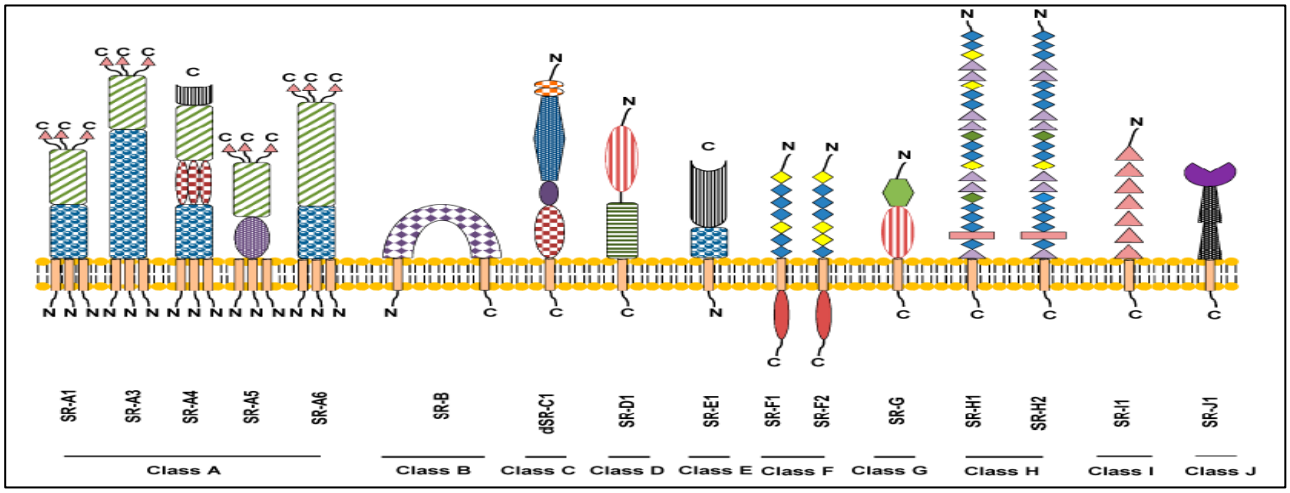

Figure 1: Classification of scavenger receptors [30]

transmembrane regions positioned near the N- and C-termini, enclosing a central domain of 400-450 residues. This glycosylated main domain is crucial in ligand recognition.[30]

aspects of macrophage biology, including migration, signalling, and inflammatory processes such as foam cell formation.[33] It is also involved in the host's immune response to bacteria and fungi.

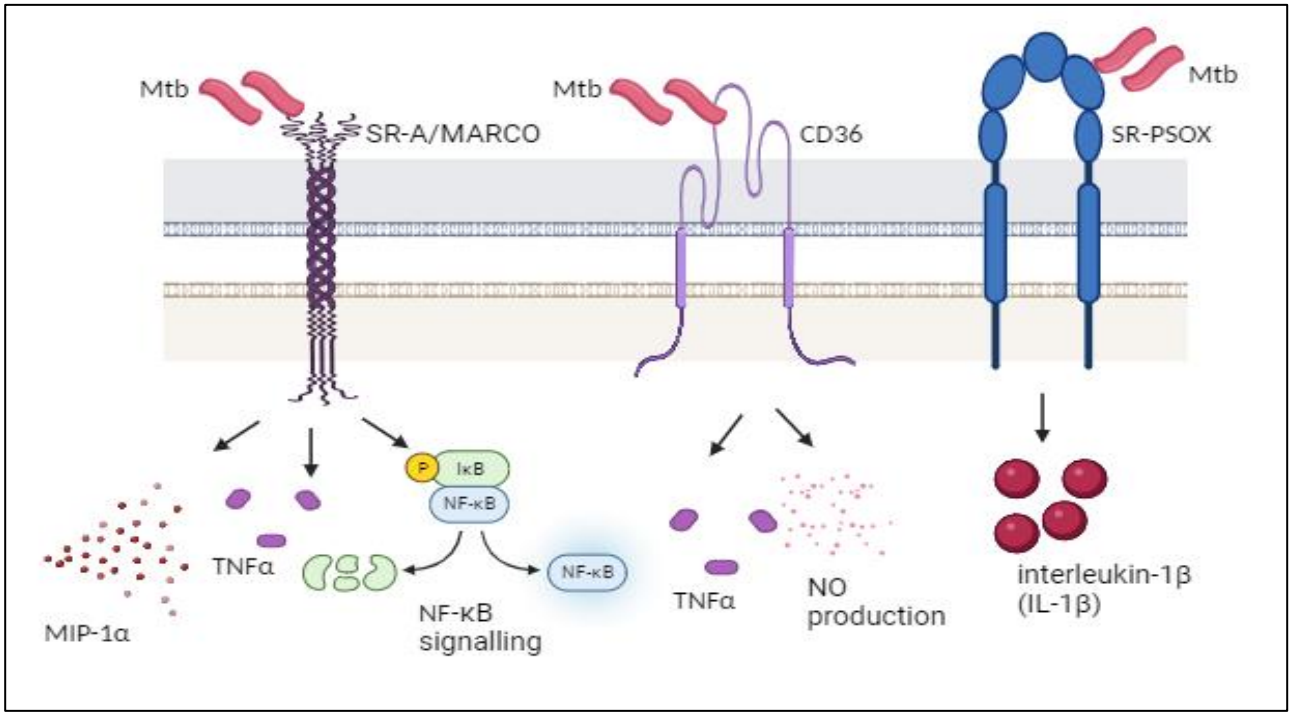

Figure2: Proposed mechanism of the role of scavenger receptors in cytokine production and modulation

SR-B1

This gene, located on human chromosome 12, is the first discovered high-density lipid (HDL) and anionic phospholipid receptor. It facilitates the selective transport of lipids, including cholesteryl esters, from HDL and other lipoproteins to cells.[31] Hepatocytes and steroidogenic cells show the highest expression levels of SR-B1 (Figure 3). It is also present in cells within the arterial wall and macrophages, including those in human and mouse atherosclerotic lesions.[27]

CD36

CD36, located on human chromosome 7, is the most widely studied scavenger receptor. It is expressed in various cell types, including hematopoietic and specialized epithelial cells.[27] Different ligands bind CD36 (Figure 3), including thrombospondin-1, OxLDL, long-chain fatty acids, modified lipid particles, apoptotic cells, and bacterial and fungal pathogens.[32] CD36 is essential in various

Scavenger receptors and innate immunity

SRs play a crucial role in innate immunity because of their ability to specifically bind various ligands and function as PRRs. The identification and characterization of SR genes suggest their role in the host defence mechanisms against foreign and endogenous molecules.[34] They can recognize, engulf, and eliminate various PAMPs on microbial surfaces, such as LPS and LTA. Additionally, SRs can function as co-receptors for other PRRs, primarily Toll-like receptors (TLRs), to detect and phagocytose PAMPs and DAMPs. This cooperation extends to cytokine production, enabling an effective immune response against different pathogens and during inflammatory processes.[26] Non-opsonic phagocytosis of pathogenic microorganisms by macrophages and dendritic cells is the most common function of SRs.[35] Different studies show pathogens often exploit SRs to enter host cells.[36, 37] Genetic screening disclosed that endothelial SRs play role in physiological and pathological processes in innate immunity and infection.[38]

Role of Scavenger Receptors in TB

Innate immunity plays a significant role in antimycobacterial response, the progression and long-term control of Mtb infection. The genes encoding PRRs serve as the primary components of the innate immune system that facilitate the direct molecular interaction between the host and Mtb. Scavenger receptors are one of the various cell surface and intracellular receptors mediating bacteria uptake.[39] This close interaction suggests the possibility of co-evolution between the host immune system and the pathogen over time.

MSCs phagocytose Mtb through SR-B1 and MARCO and exhibit innate control of mycobacterial replication through autophagy. MSCs are found in both human and mouse Mtb granulomas and play a role in TB pathogenesis. They are also involved in mediating macrophage into M1 and M2 phenotypes.[43] The SR-B1 on M cells interact with Mtb EsxA, enabling it to cross airway mucosa and initiate infection. Mtb binding and translocation across M cells reduce if SR-B1 genes are disrupted.[44]

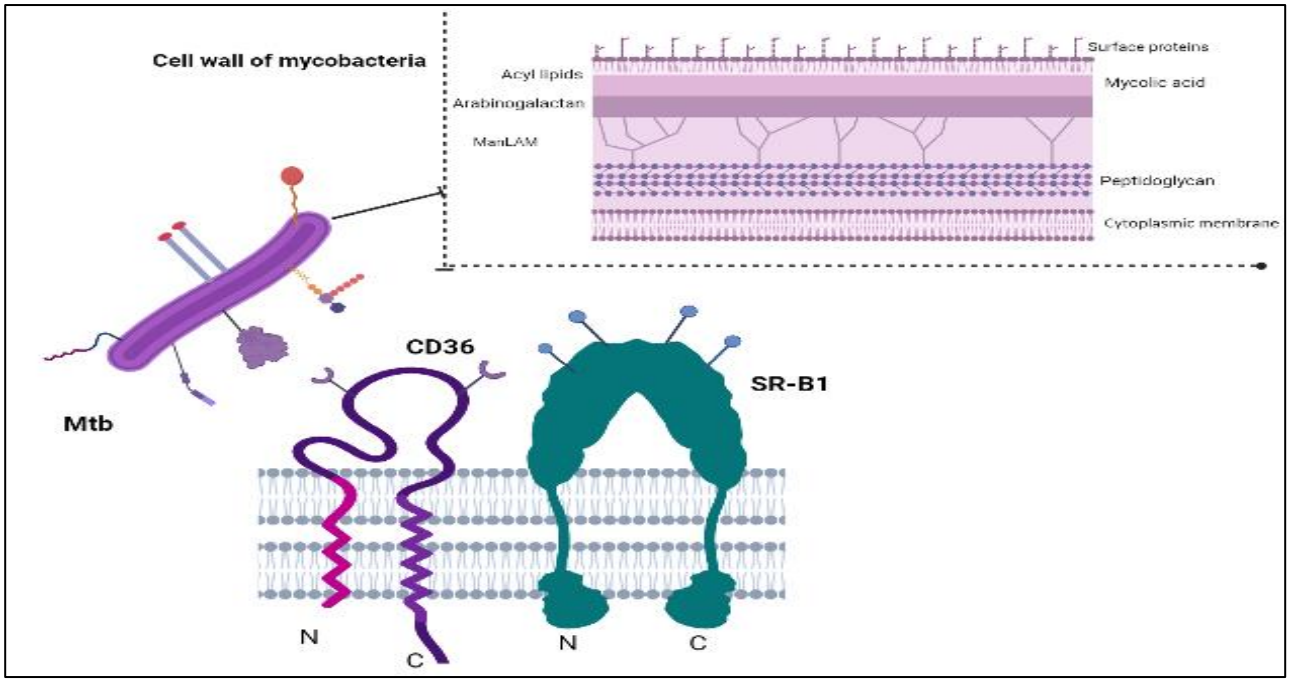

Figure 3: Specific lipoprotein components and lipoglycans in cell-wall of Mtb are recognized by SR-B1 and CD36

Effect on phagocytosis

Scavenger receptors promote the phagocytosis of Mtb through macrophages, dendritic cells, mesenchymal stem cells (MSCs), and airway microfold cells (M cells). CD36 mediates the uptake of surfactant lipids by macrophages, which promotes the growth of Mtb within macrophages.[40] SR-B1, as a receptor on macrophages, is also involved in recognizing BCG. [41] Mtb and BCG binding increases when SR-B1 is overexpressed in macrophages, whereas BCG binding is unaffected by comparable knockout in murine macrophages.[42]

Mice deficient of the ATG7 gene in macrophages express enhanced MARCO and macrophage scavenger receptor-1 (MSR-1), resulting in the increased phagocytic capability of macrophages.[45] In BCG-infected mice, CD36 becomes more abundant in multinuclear phagocytes (MP) during periods of Mtb persistence.[46] A study by Liu et al. indicates higher expression levels of scavenger receptor CD163 on CD16+ monocytes and a higher serum CD163 (sCD163) level in pleural TB patients.[47]

Cytokine production and modulation

Scavenger receptors play a crucial role in TDM-induced MAPK activation and TNF-α production. A study indicates that the expression of MARCO or SR-A enables TDM-induced NF-kB signalling in TLR-transfected HEK293 cells. Furthermore, macrophages lacking MARCO demonstrate

an impaired inflammatory response to Mtb, indicating the significance of SR in an effective macrophage cytokine response against this pathogen.[48] MARCO and CD36 are known to interact with Mtb LAM (lipoarabinomannan) and play a role in its recognition by immune cells. Experimental analysis suggests that CD36 is responsible for mediating the effects of ManLAM (mannose-capped lipoarabinomannan), leading to the release of TNF-α in peritoneal murine macrophages.

Ligands of SRs have similar effects on TNF-α and NO production as observed with ManLAM. Recently, SR-PSOX/CXCL16 has been found to facilitate the production of interleukin-1β (IL-1β) in response to dextran sulfate stimulation in murine peritoneal macrophages infected with Mtb.[49] During Mtb infection, macrophage SR-A (MSR-A) control excessive production of proinflammatory cytokines (TNF-α and MIP-1α/CCL3) by activated macrophages.[50]

Impact on adaptive immune response

During the chronic phase of Mtb infection, SR-A acts as a modulator that inhibits the adaptive immune response. SR-A deficiency in mice led to delayed progression of TB to severe terminal phase, and their prolonged survival was linked to significantly elevated quantities of CD4+ lymphocytes and antigen-presenting cells.[51] CD36 plays a role in the granuloma turnover process and is involved in the expansion of the intracellular reservoir of mycobacteria.[52]

SR-B1 gene polymorphisms

Different genetic polymorphisms can occur within a population, from a single nucleotide change to more significant structural changes in the DNA sequence. Single nucleotide polymorphisms (SNPs) can alter a disease's outcome, influence how individuals respond to an illness and affect the gene expression, function and structure, leading to phenotypic differences. Several SNPs have been reported in SR-B1 genes associated with different diseases and have also been reported to affect the expression levels of the gene. The effect of other SNPs of SR-B1 on its expression levels is summarized in

Table **2: Effect of various SNPs in CD36 gene on its expression levels**

SNP	Location	Nucleotide change	Amino acid change	Effect on expression levels
rs1761667	Exon 1A	18436G>A	None	
rs3211870	Intron 4	60706C>T	None	
rs3211909	Intron 7	67612T>C	None	Decrease [57]
rs3211913	Intron 7	68101A>G	None	
rs3211938	Exon 10	73946T>G	Tyr325Ter	
rs9784998	Exon 1F	36498C>T	None	Increase

A study by Love-Gregory et al. revealed that SNPs in the CD36 gene influence the levels of CD36 protein expression in African Americans. The study investigated the association of SNPs with CD36 expression on the surface of monocytes and platelets. Variants in the gene's coding and non-coding regions impacted the expression levels. The variations in exon 1A and exon 10 were associated with a reduction in monocyte CD36 expression, whereas mutations in intron 7 reduced CD36 expression in both monocytes and platelets. The exon 1F variant was linked to increased platelet CD36 expression, while the intron 4 variant was associated with decreased platelet CD36 expression.

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Mutations at both exonic and intronic regions can alter the SR-B1 expression levels. The mutation at exon 8, which changes the RNA secondary structure and affects protein translation, results in reduced expression and impaired function of SR-B1.[53] At exon 1 and intron 3, mutations were significantly associated with reduced SR-B1 protein translation and expression levels. [54] Similarly, mutations in intronic regions, specifically at intron 7 and intron 11, lowered hepatic SR-B1 expression.[55, 56]

Table 1: Effect of various SNPs in SR-B1 gene on its expression levels

SNP	Location	Nucleotide change	Amino acid change	Effect on expression levels
rs5888	Exon 8	68772T>C	Ala350Ala	Decrease [53]
rs2278986	Intron 3	54151T>C	None	Decrease [54]

rs4238001	Exon 1	5275G>A	Gly2Ser	Decrease [54]
rs3782287	Intron 7	64255G>C	None	Decrease
rs838896	Intron 11	83721G>C	None	Decrease

CD36 gene polymorphisms

Genetic mutations in the CD36 gene give us insight into its impact on health and disease. Several CD36 gene polymorphisms have been identified and extensively studied, representing their ability to influence disease outcomes and induce modifications in the gene. Different studies have demonstrated the impact of genetic variations on expression levels of the CD36 gene **Error! Reference source not found.**.

Table 2: Effect of various SNPs in CD36 gene on its expression levels

SNP	Location	Nucleotide change	Amino acid change	Effect on expression levels
rs1761667	Exon 1A	18436G>A	None	
rs3211870	Intron 4	60706C>T	None	
rs3211909	Intron 7	67612T>C	None	Decrease [57]
rs3211913	Intron 7	68101A>G	None	
rs3211938	Exon 10	73946T>G	Tyr325Ter	
rs9784998	Exon 1F	36498C>T	None	Increase

A study by Love-Gregory et al. revealed that SNPs in the CD36 gene influence the levels of CD36 protein expression in African Americans. The study investigated the association of SNPs with CD36 expression on the surface of monocytes and platelets. Variants in the gene's coding and non-coding regions impacted the expression levels. The variations in exon 1A and exon 10 were associated with a reduction in monocyte CD36 expression, whereas mutations in intron 7 reduced CD36 expression in both monocytes and platelets. The exon 1F variant was linked to increased platelet CD36 expression, while the intron 4 variant was associated with decreased platelet CD36 expression.

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