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Role of Interleukin 33 in Immune Response Process of Vitiligo Disease

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ABSTRACT

Background: When melanocytes cease to operate, vitiligo develops. It is a skin and mucosa depigmentation condition. Any area of the body can develop well-circumscribed white macules or patches in this disease. Approximately 1-2 percent of the population is affected by Vitiligo. Suppression of tumorigenicity 2 (ST2), a newly discovered member of the interleukin-1 (IL-1) family, acts as a receptor for the IL-1 receptor-like 1 protein (also known as IL-1RL1) while also acting as a ligand for the interleukin-1 receptor-like 1 protein (also known as IL-1RL1) and suppressing tumorigenicity 2.

Objective: To study Interleukin 33 (IL-33) in generalized and localized vitiligo patients and to assess their relationship with disease activity.

Conclusion: Vitiligo could be associated with increased serum levels of IL-33, which could help as predictor marker of disease activity in vitiligo.

Key words: Vitiligo, Interleukin 33 (IL-33).

INTRODUCTION

Skin depigmenting disorder (Vitiligo) is caused by a loss of functioning epidermal melanocytes in the affected area, resulting in milky-white macules on the skin. It is an acquired, common, and complex illness [(1)].

Epidemiology:

Only 0.5 percent of the world's people are stricken by this disease. There are no evident differences in incidence rates based on phototype or race for either sex. A study has shown that women are more inclined to seek therapy [(2)].

Quality of life:

Vitiligo is a debilitating autoimmune disease, not merely a skin problem. Psychological damage can result when this disfiguring disease affects the face or other visible parts of the body [(3)].

Clinical presentation:

Vitiligo is characterized by lightening of the skin and hair follicles. As a result, the number and size of white symmetrical macules and patches grow with time. Vitiligo first appears in sun-exposed areas in fair-skinned patients as a result of untouched skin darkening. Disease can start for a variety of reasons, such as severe sunburn or pregnancy. It can also start for reasons including traumatic cutaneous injury or high levels of psychological stress. Patients may experience the Koebner phenomenon, which is characterized by the appearance of new vitiligo lesions in places that have been subjected to injury or trauma [(4)].

Classification of vitiligo:

The clinical manifestations of vitiligo can be characterized as segmental or non-segmental based on the morphology of the clinical involvement. It can also be defined as either progressive or stable depending on how active the disease is at any given time. The extent of involvement might range from small (localized disease) to extensive (systemic disease) (generalized disease) [(3)].

Non-segmental vitiligo (NSV) and segmental vitiligo (SV) are the two primary kinds of vitiligo, according to the Vitiligo Global Issues Consensus Conference (VGICC), which was convened in Bordeaux in 2011 and described them as follows [(3)]:

Table (1): Classification of vitiligo [(3)]

Type	Subtype
Non-segmental Vitiligo	Generalized Acrofacial Mucosal(>1 mucosal site), Universal Mixed (associated with segmental vitiligo) Rare varient
Segmental vitiligo	Unisegmental and multisegmental
Undetermined /unclassified	

1. **Non-segmental vitiligo (NSV):**

They range in size from a few millimeters in diameter to several centimeters in diameter, and they affect both sides of the body, with a propensity to be evenly distributed. It might be all-encompassing, acrofacial, universal, mucosal, or a combination of these types of treatments (associated with SV). Hypochromic vitiligo/vitiligo minor is a rare form of NSV, as is vitiligo punctate [(3)].

- ***Generalized common vitiligo*:** There are many other types of vitiligo, but this is by far the most

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prevalent. It's characterized by milky-white macules that appear in symmetrical patterns on different areas of the body [5].

- ***Acrofacial vitiligo*:** There are just four body parts affected with acrofacial vitiligo: face, hands, and feet [3].
- ***Universal vitiligo* (Vitiligo Universalis):** Vitiligo that affects the entire body is known as universal vitiligo. It is the most severe type of the disease, and it frequently involves the hair [3].
- ***Mucosal vitiligo*:** Oral and/or genital mucosal vitiligo is a type of mucosal vitiligo [6].
- ***Mixed vtiligo:*** Mixed vitiligo is a condition in which SV was followed by NSV at least six months after the first occurrence of SV. Treatment-resistant "segmental" vitiligo is common in patients with mixed vitiligo [3].

2. Segmental Vitiligo:

Unilaterally, vitiligo lesions appear in a cluster on a single area of the skin. The tumors are symmetrical in relation to each other. SV most commonly manifests as mono-SV. One or both sides of the body have many segmental lesions [7].

Interleukin – 33:

IL-1 family member IL-33 is an interleukin. It contributes to tissue homeostasis and responses to environmental stimuli by playing an important role in innate and adaptive immunity. By binding to its receptor ST2, it induces a Th2 immune response. A wide range of immune and non-immune cells, including macrophages and dendritic cells, express IL-33, including fibroblasts and endothelial cells. When interleukin-33 was first discovered, it was thought to be a nuclear repressor factor [8].

In contrast to other members of the family, Interleukin-33 is not expressed by hematopoietic cells but in endothelial cells along the vascular tree, in tissues' epithelial cells (skin, lung, digestive tract and vaginal), in fibroblastic cells, lymphoid cells of the spleen and lymph node and in nerve cells [9].

Interleukin -33/ST2 axis:

An infectious, inflammatory, or allergic illness induces an innate immune response when IL-33 binds to ST2L via the C terminal (the IL-1-like domain). When IL-33 binds to ST2L, it activates MyD88, which then triggers the production of inflammatory mediators. Receptor-associated MyD88 promotes the activation of IL-1 receptor-associated kinase (IRAK) 1 and 4, resulting in the phosphorylation and degradation of the inhibitor of nuclear factor kinase B. MyD88 is found in a variety of tissues and organs (NF-kB) -α, the nuclear translocation of NF-kB and the activation of many signaling molecules that modulate IL-33's biological effects [10].

Processing and extracellular release:

In the aftermath of tissue injury, trauma, or necrosis, epithelial and endothelial cells may release interleukin-33 into the environment. When pro-inflammatory conditions exist, the production of several members of the IL-1 family, such as IL-1 and IL-18, is triggered by caspase-1 cleavage, which results in the production of physiologically active precursors. However, IL-33 is biologically active in its full-length form despite the fact that it is cleaved by caspase-1 in its commercially mature form. Although IL-33 is cleaved by caspase-1, it is thought to undergo a similar mechanism. It has been proven that caspase-1, -3, and -7 do not activate IL-33, but rather cleave the protein inside the C terminal domain, resulting in the cytokine's inactivation during apoptosis, according to the findings [11].

That IL-33 was produced by necrotic cells in an uncleaved but biologically active state whereas apoptotic ones had it in an unleashed but functional form raises the possibility that IL-33 acts as an endogenous danger signal. If this is indeed true, it means many types of inflamed cells produce proteases that can cleave the IL-33 protein rather than just one form of the protein. Neutrophil elastase, cathepsin G, and proteinase 3 release active versions of interleukin 33 (IL-33). The potency of these mature IL-33 variants compared to the full-length protein is ten times stronger. According to this, IL-33 activity may be regulated by innate immune cells in the inflammatory environment after tissue damage [12].

Interleukin-33 in skin diseases:

Healthy skin produces the cytokine interleukin-33. UVB light and pathogenic organisms like Staphylococcus aureus, as well as inflammatory cytokines, cause large quantities of IL-33 mRNA to be produced in the skin cells. Administration of recombinant IL-33, transgenic overexpression, neutralizing antibodies, or lack of the IL-33 receptor can alter skin inflammation as evidenced by the function of IL-33 in inflammatory skin disorders [13].

IL-33 is a pro-inflammatory cytokine found in the skin's outermost layer. Psoriasis, allergy-induced contact dermatitis, the chronic phase of atopic dermatitis and vitiligo are all examples of skin conditions in which interferon-γ is overexpressed [14].

When it comes to the development and progression of atopic dermatitis, the interplay of immune cells, keratinocytes, endothelium cells, and activated "hypersensitive" peripheral sensory neurons is critical. The skin lesions and blood of patients with atopic dermatitis reveal an increased IgE level and eosinophilia, indicating a Th2 response to allergens. Atopic dermatitis patients had significantly greater serum IL-33 levels than healthy controls, and these levels were linked to the severity of the condition. The mRNA for interleukin-33 and the protein ST2 are both increased in lesional skin [15].

When comparing psoriatic skin with healthy skin, interleukin-33 levels are higher in the latter. It was discovered in the nucleus and cytoplasm of psoriatic keratinocytes, as well as at the junctions between the cells, indicating that it was secreted. Mast cell and neutrophil interaction with IL-33 resulted in psoriasis-like plaque inflammation [(16)].

Serum IL-33 levels were observed to be elevated in vitiligo patients. There is increased expression of IL-33 and ST2 in the lesional skin of vitiligo patients, with IL-33 located only in the cytoplasmic fraction and not in the nucleus. However, it was found to be located within normal skin's nucleus implying that it may cause melanocyte death by controlling the cytokines in the cell's microenvironment. Vitiligo patients had an altered IL-33/ST2 system [(17)].

Vitiligo's process of melanocyte loss is linked to cytokines released from skin cells, such as basic fibroblast growth factor (bFGF) and stem cell factor (SCF), which can promote melanocytes or inhibit them (IL-6 and TNF-). The survival of melanocytes is dependent on stem cell factor. When it comes to ST2 signaling, melanocytes don't make any SCF but do express the receptor c-Kit for it, which is what controls it in mast cells [(18)].

The paracrine inhibitors of melanocytes that cytokines like IL-1, IFN-γ, or TNF- α are capable of causing include. A key cytokine implicated in the development of vitiligo is tumor necrosis factor- α. Melanocyte differentiation from stem cells is inhibited, as is melanocyte function, and melanocytes are destroyed by numerous apoptotic pathways that are induced [(19)].

TNF- α protein and transcript levels were found to be higher in vitiligo patients, indicating that melanocytes were dying early in the disease. Moreover, TNF- α triggers the creation of IL-1, which promotes B-cell proliferation, immune globulin synthesis, and dendritic cell maturation, leading to the emergence of autoimmunity. TNF- α promoter polymorphisms and increased TNF- α expression are linked to disease development [(19)].

Apoptosis occurs in vitiligo's keratinocytes. This interleukin inhibits the activity of surrounding keratinocytes by reducing the expression of SCF and bFGF, while simultaneously raising the expression of TNF- α and IL-6. Neuropeptides such as corticotropin-releasing hormone and neurotensin are released by peripheral nerve endings and work in conjunction with IL-33 [(20)].

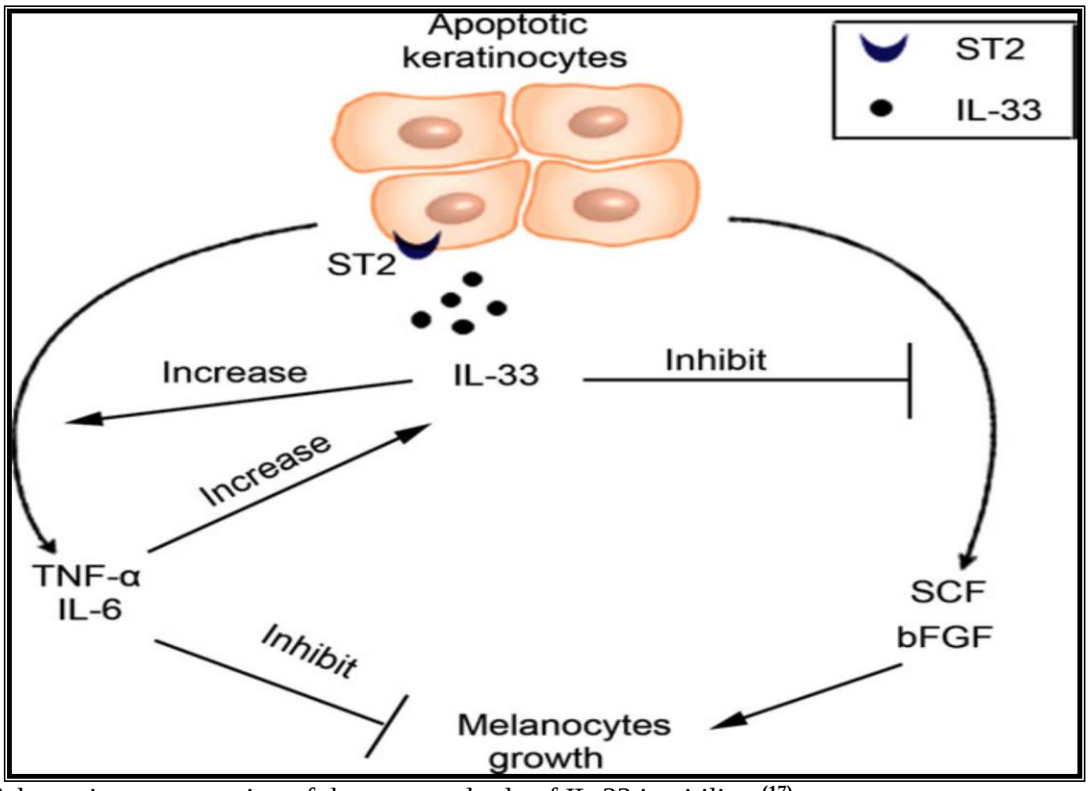

Figure (1): Schematic representation of the proposed role of IL-33 in vitiligo [(17)]

CONCLUSION

Vitiligo could be associated with increased serum levels of IL-33, which could help as predictor marker of disease activity in vitiligo.

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