International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X
P-ISSN: 2664-9411
www.dermatologypaper.com
Derma 2023; 6(1): 141-144
Received: 13-05-2023
Accepted: 24-06-2023

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Role of YKL-40 in cutaneous and systemic diseases

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DOI: https://doi.org/10.33545/26649411.2023.v6.i1b.144

Abstract
YKL-40 is a glycoprotein that is formed by several types of cells that include immune, tumor, and stromal cells, and has growth factors and cytokines properties. Its exact function is not yet completely clear. It had been found markedly increased in the serum of individuals with various cutaneous and systemic inflammatory diseases suggesting a possible role in their development. Additionally, the degree of severity of the disease coincided with the blood levels of this protein. It may thus be regarded as one of the most useful indicators to assess the level and severity of inflammation in different disorders. Additionally, YKL-40 was found to be expressed by tumor-associated macrophages and several cancer cell types. Several study's findings indicated a substantial connection between YKL-40 and the development and propagation of cancer. As a result, it was thought that YKL-40 might be useful as a marker for the development of cancer and the patient's reaction to the applied drugs.

Keywords: YKL-40, cutaneous, systemic diseases

Introduction
YKL-40 belongs to the mammalian chitinase-like proteins but lacks chitinase activity [1, 2]. The protein is known as YKL-40 because it contains 3 N-terminal amino acids leucine (L), lysine (K), and tyrosine (Y) with a molecular weight of (40 kDa) in the secreted form [3]. It include both growth factor and cytokines qualities, and it is composed by a various types of cell, that include tumor, stromal, and immune cells [4].
The differentiation, proliferation, and survival of several cells are all influenced by YKL-40, which leads to inflammatory alterations and tissue changes. Its unusual expression is related to the pathophysiology of many types of inflammatory skin conditions, such as papulosquamous disorders [5] as well as asthma, sepsis, diabetes, and rheumatoid arthritis [6, 7]. Additionally, glioblastoma, adenocarcinoma, and squamous carcinoma patients have been reported to have higher amounts of it [8-10].

Expression of YKL-40 in cutaneous and systemic diseases
1. Expression of YKL-40 in cutaneous diseases
a. Inflammatory skin diseases
YKL-40 in psoriasis
Findings from prior studies [11, 12] determined that YKL-40 contributed to psoriasis pathogenesis and that people with psoriasis who did not have any associated conditions had elevated levels of this variable [11]. It may be utilized as an indicator of inflammation in psoriasis, having a greater sensitivity than white blood cells (WBC) or C-reactive protein (CRPs), according to Salomon *et al*. [12] Increasing YKL-40 may thus suggest that psoriatic people have a greater level of systemic inflammatory conditions, which could affect treatment choices and prognosis [12].

YKL-40 in lichen planus
According to a previous research [13]. YKL-40 has an effect in the pathogenesis of lichen planus. The main symptoms of lichen planus, pruritus, has been found to be correlated with the higher blood YKL-40 level in lichen planus individuals.
It is thought that over the duration of the disease, inflammatory cells that are triggered produce this protein. However, the cause of increasing amounts is yet undetermined. Additionally, levels were observed to be substantially higher among those with oral type

compared to cutaneous type people without oral [13].

YKL-40 in hidradenitis suppurativa

Patients with hidradenitis suppurativa had blood levels of YKL-40 that were substantially higher [14]. Additionally, the Hurley grading system-assessed blood levels of this protein indicated the level of severity of the condition. Additionally, the cells responsible for inflammation in the hidradenitis suppurativa lesioned skin indicated a significant expression of YKL-40. These results support the possibility that YKL-40 is produced locally in inflammatory infiltrates, which may explain why patients with hidradenitis suppurativa have higher blood levels of this protein. YKL-40 can be assumed as one of the most important biomarkers for determining the grade of inflammatory condition and severity of hidradenitis suppurativa [15].

YKL-40 in atopic dermatitis

A prior study (16) found higher serum levels of YKL-40 in atopic dermatitis individuals, although the precise processes causing these higher levels are unknown. It is yet unknown if this protein is exclusively connected to inflammation or whether it is also secreted as a consequence of certain atopy-related biochemical activities. These results could add to the body of data supporting YKL-40's association with atopic allergies, but further research is necessary. If Indicators of prognosis that may be utilized before flare-ups of atopic dermatitis include YKL-40, more study is also required [16].

b. Malignant skin diseases

YKL-40 expression in squamous cell carcinoma

In cutaneous squamous cell carcinoma (SCC), YKL-40 is found in both tumor cells and infiltrates of inflammation in the stroma of the tumor, according to a previous study. The blood level of YKL-40 in these people may be affected by this phenomenon [9].

In cervix, head, neck, and anal SCC, expression of YKL-40 protein increases significantly in comparison to normal tissue [9, 17]. No research has been done on the expression of the YKL-40 protein in cervix SCC and it was not related to prognosis in head and neck SCC (18). In keratinizing cancer in anal SCC, YKL-40 expression was the greatest, and increased expression was associated with short survival [17].

YKL-40 in melanoma

Both tumor-associated macrophages and melanoma cells express the YKL-40 protein. Plasma YKL-40 is elevated in 13% of those with stage 1 melanoma and 45% of those with metastatic melanoma [19, 20]. Pre-treatment serum YKL-40 is a reliable predictor of response for individuals with stage 1, stage 2, and stage 4 melanoma [19, 20]. High serum YKL-40 among individuals following surgeries for stages 2B-3 melanoma is associated with poor survival in those who avoid receiving adjunct interferon therapy [21].

YKL-40 in mycosis fungoides

Based on the finding that YKL-40 higher in the serum and skin lesions of MF individuals as comparison to normal control persons in 2020 [22], Suzuki *et al*. recommended that a part of the pathogenesis of MF may be mediated by YKL-40. By using immunohistochemistry, they determined that tumor cells and epidermal keratinocytes in the skin lesions of CTCL expressed YKL-40.

HH cells and Hut78 cells proliferated rapidly *in vitro* than CTCL cell lines, despite YKL-40 having no effect on the formation of cytokines from CTCL cell lines [22]. In addition, Neinaa *et al*. recommended YKL-40 as a predictive indicator of mycosis fungoides severity in a recent immunohistochemistry study in 2023 [23].

2. YKL-40 expression in systemic diseases

Inflammatory illnesses

Ykl-40 is a protein that is produced during the acute stage due to, when exposed to an inflammatory stimulation, its plasma concentration elevates by over 25%. According to some studies, plasma YKI-40 may serve as an indicator for both acute & chronic inflammation [1, 24, 25], as well as systemic low-grade inflammatory condition [26]. When contrasting with serum CRP, which is generated locally by neutrophils and macrophages in inflammatory tissues, YKL-40 is formed via hepatocytes within the liver in responses to increased levels of Il-6 [27, 28]. Plasma YKL-40 and CRP have no or weak associations, indicating that these biomarkers represent distinct components of the inflammation and that inflammation data are independently provided by plasma YKL-40 [29].

Infectious Diseases

YKL-40 is produced by macrophages and is found in the particular granules of neutrophils [30]. According to various studies (32-34) Serum levels of YKL-40 in those suffering from bacteremia, streptococcus pneumoniae, and sepsis are 10 times higher than those in normal people [32-34]. Plasma YKL-40 levels rise in human endotoxemia, which is characterized by elevated levels of plasma TNF and IL-6 [35]. A significant amount of YKL40 were found in the cerebral fluid of purulent meningitis patients, proving that stimulated macrophages in the CNS are another source of YKL40 [36].

Diabetes Mellitus

Individuals with Diabetes type 2 have greater serum levels of YKL-40 than those with normal tolerance to glucose [37, 38], and serum YKL-40 is linked to resistance to insulin [37], plasma fasting glucose, and serum IL-6 [38] but not to obesity [38], plasma CRP [37], or both. Individuals with diabetes type 1 have greater serum levels of YKL-40 than healthy individuals, and rising serum levels of YKL-40 are associated with rising albuminuria levels [39]. serum YKL-40 may be an evolving biomarker in people with diabetes and cardiovascular disease [39].

Rheumatic Diseases

When compared to normal people and those with inactive rheumatoid arthritis, individuals with highly active rheumatoid arthritis had higher serum YKL-40 levels [40, 41] serum YKL-40 have been correlated with serum CRP, clinical indicators of activity of the disease, as well as the progression of joint degeneration, have been studied in a few investigations [41, 42].

In contrast to serum CRP, plasma YKL-40 didn't provide rheumatoid arthritis patients with any more clinical knowledge into the course of the disease or its prognosis.

Rarely, and only when significant synovitis of major joints, such as the knee joint, is present, few people who have osteoarthritis have increased serum levels of YKL-40 [43].

In arteritic vessels, macrophages and giant cells express

YKL-40 [44]. At the diagnosis time, serum YKL-40 increased in individuals with giant cell arteritis, but throughout treatment with glucocorticoid drugs, serum YKL-40 was independent to serum CRP and the activity of the disease [44].

YKL-40 Expression in Cancer

Numerous cancer cell types, including those of the colon, breast, uterus, ovary, kidney, prostate, lung, glioblastoma, oligodendroglioma, and germ cell cancers, express YKL-40. YKL-40 has been determined to be the gene with the highest level of variation in expression in extracellular myxoid chondrosarcoma, papillary thyroid cancer, and glioblastoma multiforme. The YKL-40 protein is proposed to serve as a growth factor for cancer cells or prevent them from going through apoptosis [4].

YKL-40 in hematological malignancies

Some individuals with multiple myeloma [46-49], acute myeloid leukemia [45], and Hodgkin lymphoma have higher serum YKL-40, and increased pre-treatment serum YKL-40 is linked to poor prognosis [45-48]. Higher bone resorption activity and earlier development of myeloma-related bone disease were seen in individuals with myeloma and increased plasma YKL-40 levels [48].

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Elsayed HTI, El-Hamd Neinaa YM, Alshenawy HA, Gamei MM. Role of YKL-40 in cutaneous and systemic diseases. International Journal of Dermatology, Venereology and Leprosy Sciences. 2023; 6(1): 141-144.