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# The Role of the Mast Cell in Skin Aging

*Yang-lin Hua[1], Wei Gao[2], Hong-ying Li[2] and Jian Tang[1]**

[1]Research & Development Center, Infinitus (China) Company Ltd, China
[2]Healthy Star Bio-Tech R&D Ltd, Shanghai, China

**Corresponding author:** Jian Tang, Research & Development Center, Infinitus (China) Company Ltd, 1st Floor in Building1, Hong Tai Wisdom Valley, 19 Sicheng Road, Tianhe District, Guangzhou, China, E-mail: Tom.Tang@infinitus-int.com

## Abstract

Skin is the external organ of human body that provides protection against environmental stress. Direct and indirect damage causes skin aging. Scientists have been struggling to explore the mechanisms of skin aging and to think of ways to delay this course. The role of mast cell in regulating skin aging has attracted much attention recently. The granules of mast cell contain a great diversity of highly toxic compounds and active mediators. Degranulation of mast cell in papillary dermis may lead to extra cellular matrix reconstruction, inflammation and angiogenesis which result in accelerated skin aging. Essential factors implicated in aging and tissue damage in skin are possibly related to mast cells. Mast cell is becoming an important target for anti-aging therapy. Many natural products capable of inhibiting mast cell activation are considered functional ingredients for anti-skin aging.

## Keywords

Mast cell, Skin aging, Skin tissue reconstruction, Inflammation, Angiogenesis, Mast cell stabilizer

## Abbreviations

UV: Ultraviolet, TNF-α: Tumor Necrosis Factor-α, MMP: Matrix Metalloproteinase, ECM: Extracellular Matrix, SCF: Stem Cell Factor, PGD2: Prostaglandin 2, AP-1: Activating Protein-1, NF-κB: Nuclear Factor kappa B, FGF: Fibroblast Growth Factor, TGF: Transforming Growth Factor, VEGF: Vascular Endothelial Growth Factor, IL: Interleukin, ERK: Extra-signal Response Kinase, HMC-1: Human Mast Cell-1, JNK: Jun N-terminal Kinase, COX: Cyclooxygenase

## Introduction

Everyone hopes to look younger. A lot of women spare no efforts and spend a lot of money to prevent skin aging. Skin aging gradually becomes a medical and social problem in modern world [1,2]. The pathological process of skin aging and the sustainable solutions of anti-skin aging are investigated by medical and biological scientists through ages. No solution has been explored to completely reverse or prevent aged skin appearance up to now. But the comforting thing is that some key mechanisms of skin aging are uncovered [3,4].

Skin aging is a complex physiological and pathological changing process, including a series of continuous changes, which finally leads to structural damage and dysfunction of skin tissue. Skin aging can be divided into intrinsic and extrinsic aging. Extrinsic aging is also called photoaging because the major extrinsic factors is sun exposure, especially the ultraviolet (UV) radiation. Smoking is the second most common cause of extrinsic aging [5]. Chronic sun exposure profoundly impacts on the epidermis and dermis leading to signs of skin aging, including wrinkle, sagging, and laxity [6,7].

Recently, investigators have paid close attention to the role of mast cell in regulating skin aging. Mast cells mostly reside in tissues directly exposed to the environment, such as skin, airways and gastrointestinal tract [8]. In skin tissue, mast cells are prevalent in the papillary dermis around blood vessels, rarely observed in deep dermis and almost absent in epidermis. Once activated, mast cell will discharge particles i.e. degranulation of mast cell occurs. The granules of mast cell contain a great diversity of highly toxic compounds and active mediators, including chymase, tryptase, tumor necrosis factor-α (TNF-α), and histamine. These mediators are involved in inflammation from early phage of vessel reaction and extracellular matrix damage to later skin tissue reconstruction [9]. In vitro models demonstrated that cigarette smoke medium stimulated the production of chemokines [10] and induced phosphorylation of extra-signal response kinase (ERK) ½ in mast cells [11].

Ketotifen, one kind of mast cell stabilizers, has been proved to significantly prevent UV-induced wrinkle formation, skin thickening, and an increasing amount of mast cell and degranulation ratio. The underlying mechanism may relate to the inhibition of matrix metalloproteinase (MMP) -13 and MMP-9 expression, as well as inflammatory cell infiltration by Ketotifen dose dependently [12].

Thus it can be seen that the essential factors implicated in aging and tissue damage in skin may possibly relate to mast cells. The anti-aging therapy should aim at mast cell as an important target. Divers natural products are available and able to stabilize mast cell membrane thereby inhibiting skin damage induced by mast cell activation.

## Mast Cell and Extracellular Matrix (ECM) Reconstruction

Mast cells that exist in papillary dermis are concentrated around epithelia, nerves and blood vessels. Mast cells are derivatives

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of hematopoietic progenitor cells in the bone marrow. When progenitors move through the blood stream to peripheral tissues, they differentiate completely into mature mast cells with the action of micro environmental factors and stem cell factor (SCF) [13]. It is reported in a murine study that epidermal SCF production is upregulated by chronic UV irradiation. A considerable amount of SCF leads to mast cell increase in dermis after then [14].

Mast cells reside in dermis where UVB rays cannot reach that far. However, overwhelming evidences over the past decades revealed intensified dermal mast cell degranulation in response to sunlight [15]. Sensory nerve endings are rich in skin dermis. Neuropeptides from activated nerve endings often stimulate mast cell degranulation while releasing preformed mediators. Mediators released from UVB-irradiated keratinocytes have been identified to stimulate sensory nerves to release neuropeptides that could in turn trigger mast cell degranulation.

Investigators found an increase in elastin in papillary dermis of skin from the dorsum of the hand but not from the buttock. The deep cause of this observation was identified due to varying amounts of sun exposure to different areas of skin. They also noticed that extensive elastosis in sun-exposed hand skin was correlated with increased mast cell prevalence and with older age [16].

Typtase, the most abundant seine proteinase in granules of mast cells, differs from other trypsin like proteinases in its ability to evoke various processes leading to tissue remodeling [17]. Mast cell tryptase is a new potential enzyme discovered to contribute to trigger the matrix degradation process in dermis. Tryptase can activate MMPs which are recognized as the major enzymes in the ECM degradation process to cause direct damage on ECM proteins [9], especially on type I and type III collagen which are the vital components in dermal ECM (Figure 1).

It has been reported that tryptase is able to weaken the adhesive force of keratinocytes in epidermis and cleave fibronectinin the pericellular matrix of dermal fibroblasts. Fibronectin is an important adhesive protein in the dermal ECM. Therefore, tryptase is supposed to involve in dermal-epidermal separation which is another sign of skin aging [18,19]. However, literature also reported that UV-induced mast cell increasing and activation contribute to the tissue remodeling of photodamaged skin. Mast cells play an important role in maintaining the skin structural balance and help skin tissue restore itself from damage [20].

Activated mast cells are capable of evoking degranulation of adjacent mast cell through paracrine. Tryptase released from activated mast cells is proved to induce histamine release from non-activated mast cells [21]. Histamine is another predominant component in granules of mast cells and it is able to stimulate keratinocytes to produce MMP-9, to promote immune cell migration and to accelerate type IV collagen degradation [22].

## Mast Cell and Inflammation

Fibroblast, the major type of cells in dermis, can synthesize almost all kinds of extracellular matrix as collagen fibers, elastin fibers, and proteoglycans [23,24]. It was reported that fibroblasts in dermis may decrease in number during age [25]. Hence, if the number of fibroblasts is lowered with age, renewal potency of aged skin is diminished. Interestingly, the number of mast cells observed in skin was increasing along with the decrease of fibroblasts.

Phenomenon that quantity of mast cell increases with ages is likely to be bound with inflammatory processes in dermis developed along the life. External and internal factors like UV irradiation, air humidity and temperature changes always induce repeatedly occurred dermal

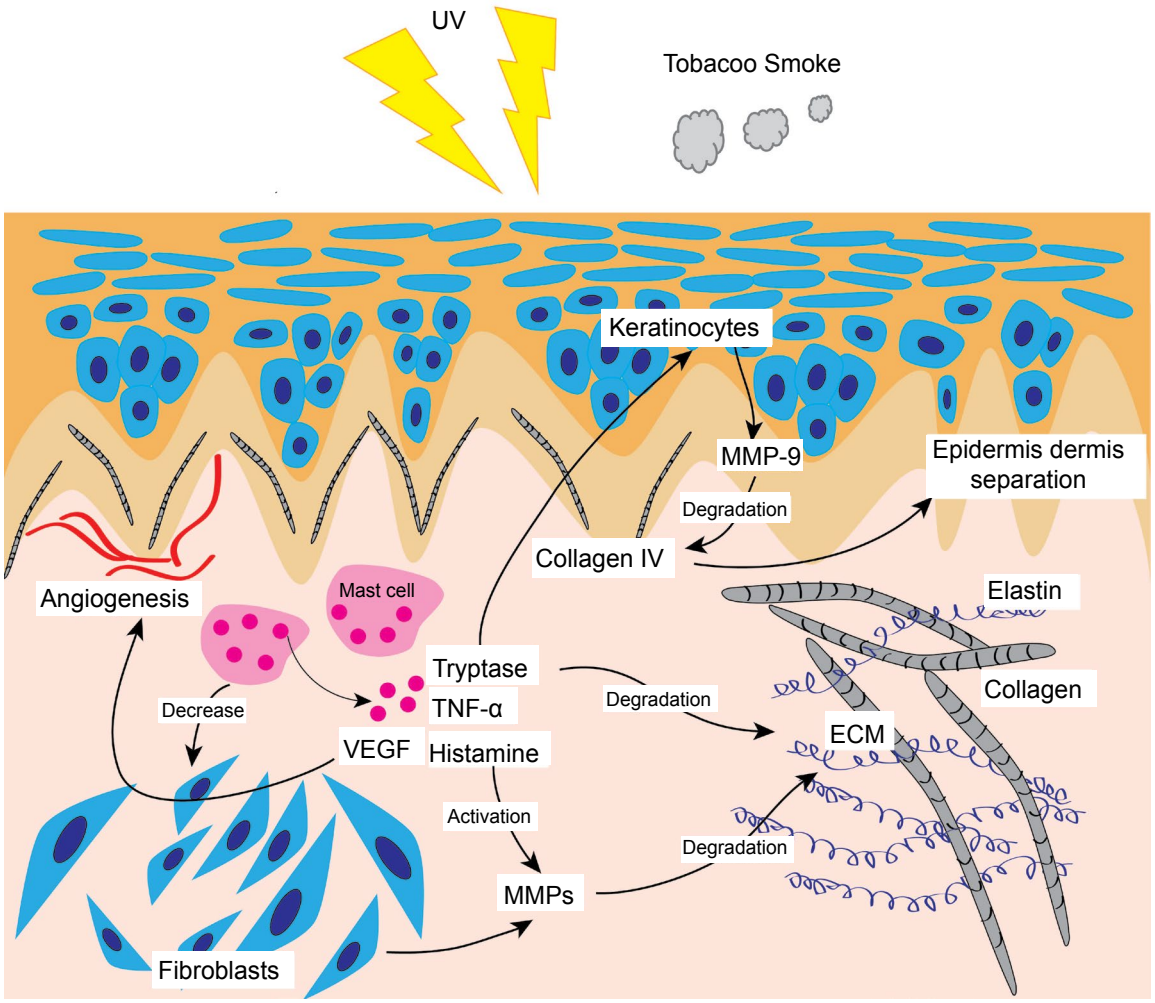


**Figure 1:** Schematic representation of mast cell activity in skin.

inflammation which finally leads to quantity increase of mast cells [26].

The appearance of photo aged skin is histologically identical to chronic inflammatory skin without any external inflammatory signs, which consists with the increase of mast cells after UV irradiation and suggests the important role of mast cell in skin inflammatory processes [27]. Inflammation is doubtlessly proved to be one of key factors resulting in skin aging.

Ultraviolet B contributes to 'sun burn' in human skin which is characterized by activated dermal blood vessel, altered traffic of Langerhans cell and acutely released TNF-α. The source of TNF-α is partly activated mast cells resided in skin [28]. The finding of decreased dermal mast cell prevalence in TNF-α- or TNF receptors-knockout mice [29] supported the hypothesis that TNF-α functions as a mast cell mitogenic factor. TNF-α is a cytokine triggering inflammatory responses that occur in the skin. TNF-α can induce the production of MMP-9, an enzyme responsible for skin aging, through regulating the expression of the MMP genes. MMP-9 is able to cause skin damage and inhibit the self-repair mechanism of skin tissue [30]. Increased number of mast cells is possibly resulting in earlier period of inflammations [31] and the release of inflammatory factors can upregulate MMP-9 [32]. The underlying mechanism is the upregulated MMP genes by transcription factors as activating protein-1 (AP-1) [33] and nuclear factor kappa B (NF-κB) of which the activity to bind to MMP-9 DNA sequence can be increased by TNF-α and then lead to over production of MMP-9 (Figure 1) [30].

## Mast Cell and Angiogenesis

Mediators as fibroblast growth factor (FGF), transforming growth factor (TGF)-β, TNF-α, tryptase and heparin released from mast cells adjacent to blood vessels play a vital role in facilitating angiogenesis and neovascularization of remodeled skin.

Angiogenesis is the process that new blood vessels sprout from existing blood vessels of which the blood supply is poor. With the stimuli like UV radiation, infrared rays and heat, cutaneous new blood vessels increase. Newly formed vessels are leaky and immature. Inflammatory cells escaped from these vessels result in cutaneous inflammation and further degradation and reconstruction of dermal ECM. Large amount of high toxic compounds released from new blood vessels to skin tissue may also induce skin damage and aging [34,35]. Angiogenesis has been proved to be functionally associated with photoaging-related wrinkle formation [36].

UV radiation caused skin photoaging is partly resulted from the increased number of mast cells in human skin after UV irritation [37]. UV radiation can lead to the increased level of vascular endothelial growth factor (VEGF). VEGF is one of the chemotactic factors contained in mast cell andis also one of the molecular features of photo aged skin [38]. As an important regulator of angiogenesis, VEGF is able to induce mast cell migration at picomolar concentrations. Over expressed VEGF contributes to a 35% increase in mast cell prevalence in the papillary dermis and also increases the density of blood capillaries in dermis (Figure 1) [39]. Mediators released from activated mast cells can also stimulate keratinocytes to release excessive amount of VEGF which results in increased numbers of tortuous and hyperpermeable blood vessels due to enhanced skin vascularization [40].

## Natural Mast Cell Stabilizers

### Quercetin

Quercetin is one kind of polyphenolic compounds naturally existed in fruits, vegetables, nuts, seeds and herbs [41,42] with various pharmacological effects as anti-oxidant, anti-inflammatory and mast cell stabilizing abilities [43]. Quercetin was reported effectively equivalent with cromolyn, one kind of mast cell stabilizers, in inhibiting histamine and prostaglandin 2 (PGD2) release but much more effective in reducing inflammatory cytokines release from human mast cells [44], of which the underlying mechanism may be the attenuation of NF-κ and p38MAPK signaling pathways in mast cell [45]. NF-κB and p38MAPK are well known involved in skin photoaging [46]. Quercetin is capable of regulatinginterleukin (IL)-6, IL-8, TNF-α, histamine and tryptase release from mast cells [44] and accordingly attenuates atopic dermatitis symptoms [47]. A murine study demonstrated that water in oilmicroemulsion containing quercetin reduced the incidence of histological skin alterations, mainly the connective-tissue damage, induced by UVB irradiation [48].

### Resveratrol

Resveratrol, a stilbenoid is a polyphenolic compound found predominantly in various plants, including grapes, berries and peanuts. Resveratrol has been well-studied to possess anti-inflammatory and anti-oxidant properties against aging. Resveratrol was confirmed to protect skin against photo damage through enhancing skin moisture and elasticity, reducing depth and length of wrinkles and decreasing intensity of spots [49-51]. *In vitro* test revealed that resveratrol directly inhibited degranulation of RBL-2H3 mast cells and human skin mast cells [52,53]. Resveratrol was reported to decrease the phosphorylation of ERK 1/2 in activated human mast cell-1(HMC-1) cells and inhibit NF-κB activation, which in turn lead to suppressed expression of TNF-α, IL-6, IL-8 and cyclooxygenase (COX)-2 [54]. And thus resveratrol plays a role in regulating mast cell mediated inflammatory processes that result in tissue damage including skin.

### Angelica sinensis

The root of angelica sinensis is one of the most commonly used traditional Chinese medicine that processes multiple medical actions, for instance, antitumor, antiaging, antioxidant, immunoregulation etc. Angelica sinensis is also used for treating skin disorders.Topical application of angelica sinensis on skin of mice with atopic dermatitis was proved to regulate the level of substance P and distribution of mast cells in the skin. Angelica sinensis also inhibits the activation of NF-κB, IκBα and MAPKs (ERK1/2, p38, and JNK) which are known to be associated with inflammatory cytokines secretion [55]. Angelicapolysaccharide, one of the important and active constituents of angelica sinensis, has recently come of note as its wide range of pharmacological activities. Investigation demonstrated that angelica polysaccharide could inhibit the releases of proinflammatory cytokines from mast cells including histamine which is the notable markers indicating the degranulation of mast cells [56].

## Conclusion

With development of technology and progress in civilization, human activities are increasingly changing the natural environment. As the external organ of human body, skin bears the brunt of environmental changes and shows the aging appearance. People struggle to explore the causes and mechanisms underlying skin aging and fight for a youthful skin appearance. In recent years, mast cells resided in dermis has attracted attention by many investigators. Reports showed that mast cells were rarely observed in dermis of fetus and young people but more often observed in dermis of aged people [27], which indicates the potential role of mast cell in regulating skin aging. Mast cells have been demonstrated to play a role in ECM remodeling, inflammation and angiogenesis in skin which are closely associated with skin aging processes. Thus, the essential factor implicated in aging and tissue damage in skin may possibly relate to mast cells. There are many natural products play stabilizing roles to inhibit mast cell from degranulation and block the downstream reactions induced by cytokine release.The exploration of natural mast cell stabilizers may do great to prevent or slow the skin aging process.

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