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Review Article

Beneficial Regulation of Matrix Metalloproteinases for Skin Health

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Matrix metalloproteinases (MMPs) are essential to the remodeling of the extracellular matrix. While their upregulation facilitates aging and cancer, they are essential to epidermal differentiation and the prevention of wound scars. The pharmaceutical industry is active in identifying products that inhibit MMPs to prevent or treat aging and cancer and products that stimulate MMPs to prevent epidermal hyperproliferative diseases and wound scars.

1. Introduction

Matrix metalloproteinases (MMPs) are essential to the remodeling of the extracellular matrix. While their upregulation facilitates aging and cancer, they are essential to epidermal differentiation and the prevention of wound scars. The pharmaceutical industry is active in identifying products that inhibit MMPs to prevent or treat aging and cancer and products that stimulate MMPs to prevent epidermal hyperproliferative diseases and wound scars.

2. Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a group of zinc-dependent extracellular proteinases, also called matrixins or collagenases, which remodel the extracellular matrix (ECM) [1–10]. The ECM gives tissue its structural integrity and predominantly comprises of the fibrillar collagens, basement membrane, and elastin fibers composed of elastin and fibrillin [11–13]. There are three predominant groups of MMPs: collagenases, gelatinases, and stromelysins [1–13]. The collagenases (MMP-1, -8, -13, and -18) cleave interstitial (structural) collagens, with MMP-1 as the predominant one. Gelatinases, primarily MMP-2 and MMP-9, degrade basement membrane collagens and degrade denatured structural collagens. The stromelysins (MMP-3, -10, -11, and -19) degrade basement membrane collagens as well as proteoglycans and matrix glycoproteins. The other MMP classes include membrane-type MMPs (MT-MMP: MMP-14, -15, -16, -17, -24, and -25) that activate MMPs, matrilysins that degrade the basement membrane (MMP-7 and -26), elastase that degrades primarily elastin (MMP-12), and others (MMP-20, -21, -22, -23, -27, and -28). MMPs are regulated in expression or activity at several different levels: gene expression, activation, and cellular inhibition of activity by tissue inhibitors of matrix metalloproteinases (TIMPs), especially TIMP-1 and TIMP-2 [12]. Epithelial cells, fibroblasts, neutrophils, and mast cells are some of the cell types that produce MMPs [1–13].

Transforming growth factor-β (TGF-β) is a predominant regulator of the expression of MMPs and the ECM [1, 2, 12]. It is secreted extracellularly in a latent form and activated by proteases to form the mature TGF-β that binds to its receptor complexes to activate Smads and thereby the regulation of various genes, including MMPs, collagen, and elastin [1, 2, 12]. TGF-β has differential effects in different cell types [1, 2, 12]. It inhibits MMP-1 and stimulates collagen, MMP-2, and TIMPs in fibroblasts, whereas in keratinocytes it stimulates the expression of MMPs and inhibits cell growth [1, 2, 12].

3. Skin Aging and Carcinogenic Effects of Matrix Metalloproteinases

3.1. Skin Aging and Its Prevention. Skin aging is the result the intrinsic chronological aging process superimposed by environmental factors, predominantly exposure to ultraviolet (UV) radiation (photoaging) [1, 2, 11–17]. UV radiation shifts the cellular balance to oxidative stress, inflammation, immunosuppression, and inhibition of TGF-β [1, 2, 12]. In addition, UV radiation stimulates proinflammatory and proangiogenic cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF) [1, 2]. Cellular damage in photoaged skin includes cell loss, DNA damage, lipid peroxidation, and compromise of skin barrier function [13].

Alterations in collagen and elastin of the ECM are primarily responsible for the clinical manifestations of skin aging such as wrinkles, sagging, and laxity [1, 2, 11–13, 17, 18]. The atrophy of collagen and elastin fibers in skin aging is predominantly from the increased expression of their degradative enzymes, collagenases (MMP-1), gelatinases (MMP-2 and -9), and elastases [1–13]. Collagen fibers are degraded by MMP-1 and MMP-2 and the elastin fibers by elastases, MMP-2, and MMP-9 [12].

Natural products that have been identified in our laboratory to inhibit MMPs and elastase and simultaneously stimulate collagen and elastin are *Polypodium leucotomos* extract, lutein, and xanthohumol [12–18]. These products consist of polyphenols, carotenoids, or flavonoids with antioxidant, anti-inflammatory, photoprotective, or anticarcinogenic properties [12–18].

P. leucotomos is rich in polyphenols [1]. It directly inhibits activities of MMPs [12]. *P. leucotomos* inhibits expression of MMPs in epidermal keratinocytes and fibroblasts and stimulates fibrillar collagens, elastin, and TGF-β in dermal fibroblasts [12, 13]. In addition, it inhibits cellular oxidative stress and thereby membrane damage and lipid peroxidation [13]. Furthermore, it functions as a sunscreen [14, 15].

Lutein is a non-provitamin A carotenoid that inhibits epidermal hyperproliferation, expansion of mutated keratinocytes, and the infiltration of mast cells in response to solar radiation, and thereby photoaging [16]. The mechanism to lutein's antiaging and antiphotoaging effects includes the inhibition of MMP-to-TIMP ratio in dermal fibroblasts and the inhibition of cell loss and membrane damage in ultraviolet radiation-exposed fibroblasts [17].

Xanthohumol, a flavonoid, directly inhibits MMPs (-1, -3, and -9) and elastase activities while dramatically increasing the expression of types I, III, and V collagens, elastin, fibrillin-1, and fibrillin-2 in dermal fibroblasts [18].

3.2. Skin Cancer and Its Prevention. Carcinogenesis is characterized by development of tumors from genetic alterations and immunosuppression. The mechanisms also include oxidative stress from reactive oxygen species, inflammation and DNA damage [19]. Malignant tumors metastasize, with MMPs playing a central role [19]. Cancer invasion and metastasis of various cancer types parallelly increased expression of MMPs [19]. MMPs activate growth factors such as TGF-β and VEGF to induce angiogenesis [19]. Furthermore, MMPs contribute to cancer progression by degrading the ECM, basement membrane, and E-cadherin molecules that hold cells together [19–22]. In our laboratory we have investigated two categories of agents that may prevent or facilitate carcinogenesis through the regulation of expression of MMPs: (a) plant extracts or vitamins and (b) hormones.

The plant extracts or vitamins examined in our laboratory for MMP regulation in cancer cells are *P. leucotomos,* lutein and ascorbic acid [12, 17, 23, 24]. *P. leucotomos* inhibits MMP-1 expression transcriptionally, through AP-1 promoter sequence, and stimulates the expression of TIMP-2 in melanoma cells [4]. *P. leucotomos* in addition inhibits TGF-β, known to stimulate MMPs in cancer cells [12]. In photo-carcinogenesis experiments with rats, lutein inhibits tumor multiplicity, volume, and tumor-free survival time [16]. Furthermore, lutein inhibits MMP-1 and stimulates TIMPs (-1 and -2), to reduce MMP/TIMP ratio and thereby carcinogenesis [17]. Ascorbate has dose dependent differential effects on cancer cell growth versus expression of MMPs/metastasis potential [23, 24]. At lower concentrations, ascorbate inhibits cell growth with dramatic increases in the expression of MMPs, which are inhibited by cotreatment with *P. leucotomos* or gene silencing with MMP siRNA [23, 24].

4. Beneficial Effects of Matrix Metalloproteinases

4.1. Epidermal Differentiation and Wound Repair. Hyperproliferative diseases of the skin are associated with reduced MMPs [25]. The expression of MMP-9 is reduced in psoriatic keratinocytes, with hyperproliferative keratinocytes [26]. Hyperproliferative skin diseases are also associated with reduced generation of ceramides (the major lipids of the stratum corneum) or increased ceramidase activity [27–29]. Ceramides are intracellular messengers of the sphingomyelin cycle that activate protein kinase C-alpha and stress-activated protein kinases to induce apoptosis and epidermal differentiation [30]. The experiments in our laboratory indicate that ceramide induces MMP-1 expression in keratinocytes through the activator protein-1 (AP-1) sequence and simultaneously inhibits keratinocyte cell viability by apoptosis [25]. The mechanism of MMP-1 gene regulation by ceramide may be through the stimulation of TGF-β, known to inhibit epidermal cell viability [25].

MMPs are essential to wound healing. They remove wound debris, facilitate epithelization, and prevent wound scars from excess collagen [31–34]. In our laboratory, copper is effective in inducing wound healing whereas the antibodies to TGF-β associated with wound scars are ineffective [31–34].

The biologically active concentrations of copper range from 1 to 200 μM in tissue engineering for wound care, without toxicity [35]. The lower copper concentrations (0.3–3 μM) stimulate activity of MMPs whereas the higher

concentrations (1–100 μM) stimulate the expression of MMPs in fibroblasts [31]. Adult wound scars are attributed to increased TGF-β expression and subsequent collagen deposition [33]. However, TGF-β antibodies cause feedback stimulation of TGF-β [32, 33]. The feedback stimulation of TGF-β in turn inhibits MMPs and stimulates TIMPs in fibroblasts, with further scarring potential [32, 33].

5. Summary

MMPs are potent proteases that remodel the ECM. It is central to the aging and cancer process. *Polypodium leucotomos* extract, lutein, and xanthohumol are effective in inhibiting expression and/or activities of MMPs, and thereby aging and cancer. Conversely, MMPs can prevent psoriasis and wound scars. Ceramide stimulates expression of MMP-1 and simultaneously inhibits cell viability. Copper stimulates MMPs, which may be its mechanism to improve wound healing. However, the antibodies to TGF-β cause feedback stimulation of TGF-β, and further scarring potential.

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