Chapter 6

Skin Ageing and Cancer

Guolong Zhang, Peiru Wang and Xiuli Wang

Additional information is available at the end of the chapter

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Abstract

Human matrix metalloproteinases (MMPs) belong to the M10 family of the MA clan of endopeptidases. They are ubiquitarian enzymes, structurally characterized by an active site where a Zn^{2+} atom, coordinated by three histidines, plays the catalytic role, assisted by a glutamic acid as a general base. Based on their structure and substrate specificity, they can be categorized into five main subgroups, namely (1) collagenases (MMP-1, MMP-8 and MMP-13); (2) gelatinases (MMP-2 and MMP-9); (3) stromelysins (MMP-3, MMP-10 and MMP-11); (4) matrilysins (MMP-7 and MMP-26) and (5) membrane-type (MT) MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24 and MMP-25). MMPs can act on extracellular matrix (ECM) and non-ECM components affecting degradation and modulation of the ECM, growth-factor activation and cell-cell and cell-matrix signalling. In skin, MMPs are secreted by different cell types such as fibroblasts, keratinocytes, macrophages, endothelial cells, mast cells, and eosinophils. This chapter reviews the role of MMPs in maintaining skin homeostasis, skin ageing and skin cancer.

Keywords: MMP, skin ageing, photoageing, cutaneous melanoma, cutaneous squamous cell carcinoma, basal cell carcinoma

1. Introduction

Human skin is the largest organ in the human body. The primary function of the skin is to provide a protective barrier against environmental insults, such as heat, solar ultraviolet (UV) irradiation, infection, injury and water loss. The skin is composed of two layers: the epidermis and the dermis [1]. The epidermis is primarily composed of keratinocytes, which produce keratins, intermediate filaments that provide mechanical stability. The dermis is largely composed of dense collagen-rich extracellular matrix. Dermal collagen represents by far the most abundant ECM protein and constitutes the bulk of skin (90% dry weight) [2]. Dermal ECM is essentially responsible for the skin's tensile strength and mechanical properties. In human skin dermis,

collagen-rich ECM is synthesized, organized and maintained by dermal fibroblasts [3]. Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases, which are involved in remodelling of connect tissue of many organs, including the skin [4]. More than 24 MMPs have been identified in human beings, most of which consist of multidomains [5]. MMPs activity is regulated at multiple levels: gene expression, zymogens activation and inhibition by specific inhibitors [4]. In skin, MMPs are produced by several different types of cells such as fibroblasts, keratinocytes, macrophages, endothelial cells, mast cells and eosinophils [6]. MMPs play an important role in maintaining skin homeostasis and various pathophysiological conditions, such as skin ageing, wound healing and skin cancer. The aim of this chapter is to provide a concise overview of the research progress on MMPs in skin ageing and skin cancer.

2. MMPs in skin development and cutaneous wound healing

The active and continuous changes in cell-cell adhesion, cell migration, cell proliferation, apoptosis and remodelling that are required for normal skin development involve MMP gene expression and activation of pro-MMPs. Degradation of dermal ECM is required for epidermal expansion and appendage development during embryogenesis and for the cyclic growth of hair follicles in adult skin. Starting from the third month of gestation, immunostaining for MMP-1 has been detected in basal epidermal keratinocytes and dermal fibroblasts, as well as in cells in and around developing hair follicles [7]. As the development proceeds, the amount of MMP-1 protein decreases, and in adult human skin, MMP-1 is not expressed in intact human epidermis, whereas occasional fibroblast-like cells in the reticular dermis express the mRNA and protein [8]. Matrilysin has been detected in epidermal layers of fetal skin and in cells of early appendageal buds [9]. As skin development continues, matrilysin disappears from epidermal keratinocytes and then expresses in outer root sheath of hair follicles as well as secretory portion of the eccrine glands. Immunostaining for MMP-9 is detected in mesenchymal cells of upper dermis in fetal skin [10], whereas in adult skin, MMP-9 mRNA is detected in the lower epidermis [10]. MMP-2 is constitutively expressed by dermal fibroblasts and occasional basal keratinocytes in normal adult skin [10]. MMP-3 and MMP-10 mRNAs are not expressed in normal intact epidermis or dermis [11], but are occasionally detected in normal hair follicles [6]. MMP-14 expression in fibroblasts plays a crucial role in collagen remodelling in adult skin and largely contributes to dermal homeostasis underlying its pathogenic role in fibrotic skin disease [12]. MMP-21 were present in inflammatory or stromal cells in ageing mice while dysplastic keratinocytes and invasive cancer were negative, suggesting that MMP-21 does not associate with invasion of squamous cell carcinoma (SCC) but may be involved in keratinocyte differentiation [13].

The hair cycle is an intrinsic and cyclic system of regenerating tissue, which is composed of the anagen (phases of rapid growth; 1–3 weeks), catagen (phases of apoptosis-driven regression; ~2 days) and telogen (phases of relative quiescence; ~2 weeks) phases [14]. The hair cycle is considered to be a process of tissue regeneration associated with ECM degradation and remodelling [15]. Increasing evidence demonstrates that MMPs have been suggested to be associated with the hair cycle in vitro and in vivo. Yamazaki et al. reported that MMP-2 was expressed

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strongly in anagen tissue and slightly in telogen tissue, and topical application of 1% minoxidil sulphate to the anterior dorsal skin of rats in telogen stimulated hair growth and increased the mRNA expressions of hepatocyte growth factor (HGF) and MMP-2 [16]. After stimulation with epidermal growth factor (EGF), tumour necrosis factor-alpha (TNF-α) or interleukin-1 alpha (IL-1α), MMP-9 production was strongly increased in human hair follicles cultured in vitro. Using immunohistochemistry, MMP-9 was detected in the lower part of the inner root sheath (Henle's layer) of normal human anagen hair follicles [17]. These findings suggest that MMP-2 strongly expressed in anagen and may act as hair growth regulatory molecules, whereas the mechanism of the association is largely unknown. Hou et al. further confirmed that MMP-2 and MMP-9 may serve as an important role in the hair growth cycle. The different expressions of MMP-2 and MMP-9 in different stages of hair cycle significantly influenced the collagenase IV expression, which in turn plays an important role in regulating hair cycle by inducing vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF)-1 and transforming growth factor β (TGF-β) expression [15, 18]. So far, there have been no reports of other MMPs associated with hair cycle.

Moreover, there is increasing evidence that MMPs play a crucial role in cutaneous wound healing. MMP-1 expression occurs as a rapid response to wounding and is exclusively expressed in basal keratinocytes at the migrating epithelial front in wounds without basement membrane [19]. Initial expression of MMP-1 is dependent on α2β1 integrin, whereas sustained expression of MMP1 involves cross-talk between the α2β1 integrin and the EGF receptor [20]. Expression of MMP-1 can also be modulated by numerous proinflammatory mediators such as interleukin-1 and TGF-α [21]. Activity of both MMP-2 and MMP-9 can be detected in wound fluids of human mucosal epithelium, suggesting a role for these MMPs in wound healing [22]. Addition of exogenous MMP-2 to primary human nasal epithelial cultures promotes wound closure, which supported the idea that MMP-2 might has a role in wound healing [23]. In mice, expression of MMP-9 is observed at the leading edges during wound closure. MMP-9 knock-out mice display delayed wound closure, suggesting a role for MMP-9 in keratinocyte migration [24]. As is well known, angiogenesis is an important step during wound healing. Both MMP-2 and MMP-9 play a role in physiologic angiogenesis, suggesting that MMP-2 and MMP-9 can have a critical role in this process. MMP-3 and MMP-10 have a differential pattern of expression, with MMP-3 being expressed by a proliferating population adjacent to the wound edge, whereas MMP-10 is expressed at the leading edge, where it colocalizes with MMP-1. Keratinocytes expressing MMP-3 are in contact with an intact basement membrane, while MMP-10 expression is induced in keratinocytes migrating on type I collagen [11]. MMP-10 expression seems to be regulated by cytokines such as EGF, TGF-β1 and TNF-α [25]. MT1-MMP localizes at the migrating front in migrating keratinocytes, accompanied by pro-MMP-2 activation, a coordinated process involving two molecules of MT1-MMP and also TIMP-2 [26]. MT1-MMP may be involved in the regulation of epithelial cell proliferation after tissue injury through a mechanism involving keratinocyte growth factor (KGF) receptor expression [27]. In-vitro data show that MT1-MMP can cleave syndecan-1, CD44 and laminin-332, accelerating migration of different epithelial cells [28, 29]. MMP-8, which is mainly expressed by neutrophils, was discovered to be the most abundant collagenase in human cutaneous excisional wounds [30]. In wound healing, MMP-8 can compensate for loss

of MMP-13 expression in MMP-13-defficient mice, and MMP-8 knockout mice demonstrate a significant delay in wound healing [31]. MMP-12 is produced by macrophages in the wound area in acute murine excisional wounds, being detected mainly around the blood vessels [32]. These results, together with more recent data showing that MMP-12 can generate angiostatin, suggest a potential role of MMP-12 in angiogenesis [33]. MMP-13 is expressed in mice at the leading edge of cutaneous wounds. Data obtained with MMP-13 knockout mice suggest that MMP-13 plays a role in keratinocyte migration, angiogenesis and contraction in wound healing [34]. Metalloproteinase-19 has been detected in proliferating epithelium, fibroblasts, capillary endothelial cells and also macrophages in skin wounds [35]. Overexpression of MMP-19 in a epidermal keratinocyte cell line in vitro increased cellular proliferation, migration and adhesion to type I collagen through a mechanism involving the insulin-like growth factor (IGF)-binding protein-3 and the IGF-I receptor [36]. MMP-26, the smallest MMP, has been shown to be expressed during re-epithelialization in cutaneous wound healing. Its expression has been detected in migrating keratinocytes at the wound edge [37]. MMP-28 seems to be expressed by proliferating keratinocytes distal from the wound edge. It is suggested that MMP-28 may be needed to restructure the basement membrane or to degrade cellular adhesion proteins between keratinocytes in order to supply new cells for the migrating front [38].

3. MMPs in skin ageing

3.1. Ageing of human skin

Ageing of human skin can be caused by passage of time (intrinsic or chronological ageing) or environmental factors such as light, heat, cold, etc. (extrinsic ageing or photoageing). Intrinsic skin ageing is a slow, spontaneous, progressive, cumulative and degradative process represents as both epidermal and dermal atrophy. Clinical changes of intrinsic skin ageing show only finely wrinkled at old age (>70 years). The histopathology manifests epidermal atrophy, flattening of the rete ridges and dermal ECM reduction [3].

Chronic exposition to solar UV irradiation is the major extrinsic factor accelerates skin ageing. Usually, photoageing also means extrinsic skin ageing. Clinically, photoageing is recognizable by fine and coarse wrinkles, blotchy dyspigmentation, telangiectasia, sallowness, increased fragility and rough skin texture [39]. Histologically, the epidermal becomes thick during photoageing; the dermal connective tissue is composed of damaged and disorganized collagen fibrils and massive accumulation of aberrant elastic material, referred to as "solar elastosis" [3]. The action spectrum for UV-induced skin damage is divided into (320–400 nm) and UV-B (290–320 nm). The 95% of the UV radiation reaching the Earth's surface is UVA, which is only slightly affected by ozone levels. Although, the amount of UVB reaching the earth's surface is lesser than that of UVA, its intensity is high enough to induce photoageing and skin cancer [39]. In past decades, several studies reported that solar UV irradiation induce different kinds of MMPs leading to photoageing.

Dermal ECM in particular the collagen and elastic fibres changes, is the major alteration in both intrinsic ageing and photoageing. Imbalance of collagen synthesis and breakdown

causes alternations of dermal collagen. In both extrinsic and intrinsic ageing, elevated levels and activities of cutaneous MMPs have been demonstrated [3, 40].

Type I collagen is the most abundant subtype of collagen found within dermal ECM connective tissue of human skin, followed by small amounts of type III collagen. Collagen precursor molecules (procollagen) are synthesized by dermal fibroblasts and are secreted into extracellular spaces, where it is enzymatically processed to mature collagen. Mature collagen spontaneously forms fibrils, which are stabilized by cross-links. Collagen fibrils are largely responsible for the strength and elasticity of skin. The half-life of collagen fibrils is about 15 years [41]. Therefore, fragmented collagen fibrils accumulate with the passage of time and have long-lasting consequences on skin structure and function. Breakdown of collagen is normally regulated by activity of MMPs and their natural inhibitors, tissue inhibitor of metalloproteinases (TIMPs). MMP-1 (collagenase) initiates cleavage of type I fibrillar and type III fibrillar at a single site within central triple helix. Once cleaved by MMP-1, collagen can be further degraded by MMP-3 (stromelysin) and MMP-9 (gelatinase). Elevated levels and activities of cutaneous MMPs are important in the development of age-related changes in skin [42].

3.2. Source of MMPs in human skin

In the skin, most of the epidermal cells are kerationocyte and dermal cells are fibroblast. In vitro data showed both keratinocyte and fibroblast can secrete MMPs, including MMP-1 (collagenase), MMP-3 (stromelysins) and MMP-9 (gelatinases). Cell culture and skin equivalent model studies have concluded that dermal fibroblasts are the major source of MMPs that are expressed in response to UV irradiation [43]. While, based on in situ hybridization and immunohistology, Fisher et al. reported that keratinocytes are the major cellular source of MMPs in UV-irradiated human skin in vivo [44]. They dissect epidermis and dermis from human skin by laser capture microdissection (LCM) and detect the MMP expression by real-time RT-PCR. MMP-1, 3 and 9 induced by 2 minimal erythema doses (MED) UV were primarily secreted by the epidermis, rather than dermis [41]. The reasons for the discrepancies between responses of human skin cells in vivo and responses of cultured skin cells in vitro are not well known. Although UV-induced MMPs (MMP-1, 3 and 9) are mainly produced by the epidermis, the secreted enzymes diffuse into the dermis and degrade collagen, as shown by in situ zymography [41]. Maybe dermal fibroblasts play a role in modulation of MMPs activities. It is also possible that dermal cells may also play a role in epidermal production of MMPs, through indirect paracrine mechanisms, by release of growth factors or cytokines, which in turn modulate MMP production by epidermal keratinocytes.

Besides keratinocytes and fibroblasts, neutrophil and macrophage are also important source of MMPs during UV irradiation or other pathological process in human skin. Fisher reported that MMP-8 (neutrophil collagenase) is present in human skin, 24 hours following UV irradiation, as a result of influx of neutrophils from the circulation [45]. Rijken et al. reported that neutrophils are major acute infiltrating cell in dermis after solar UV irradiation and these infiltrating neutrophils are a key source of in vivo MMP-1 and MMP-9 [46]. Keratinocytes and fibroblasts also produce MMPs but to a lesser extent [46]. Chung reported that macrophage-derived MMP-12 (macrophage elastase) mRNA maximally (11.9-fold) was induced by ultraviolet within 16 h in human skin in vivo [47]. Tewari confirmed that MMP-12 induction by UVA1 at 6 hours and contributing to elastin degeneration in late solar elastosis [48].

3.3. Role of MMPs in intrinsic skin ageing

Due to the limitation of experiment model for intrinsic ageing, details of molecular mechanism of MMP activation during chronological ageing are less clear than those in photoageing. Quan et al. screened basal mRNA expression levels of MMP family members in normal healthy, sun-protected, adult human skin. Among the 24 MMP genes in human beings, transcripts for MMP-8, 10, 12, 20 and 26 were not detected. Transcripts for other MMPs (MMP-1, 2, 3, 7, 9, 11, 13, 15, 16, 17, 19, 21, 22, 23, 24, 25, 27, 28) except MMP-14 were near the level of detection, approximately 1000-fold lower than internal control, housekeeping gene 36B4. Basal expression level of MMP-14 mRNA was approximately 35-fold higher than other detectable MMPs [41]. In both extrinsic and intrinsic ageing, elevated levels and activities of cutaneous MMPs have been demonstrated. MMP-1, MMP-2 and MMP-9 mRNA expressions are significantly elevated in sun-protected skin from patients older than 60 years of age compared with the 18- to 29-year-old age group [40, 49]. In parallel, aged skin was found to contain reduced levels of TIMPs both in normal skin and during acute wound repair [44]. Transcription factor AP-1 and $\alpha 2\beta 1$ integrin, which are key regulators of MMP-1 expression, are also elevated in fibroblasts in aged human skin in vivo [49]. In elder skin, reactive oxygen radicals produced during the mitochondrial oxidative energy metabolism, in particular in case of reduced antioxidant capacity, also contribute induction of MMPs [49, 50]. In addition, age-associated impaired ECM causes further fibroblast dysfunction in a self-sustaining loop. Fragmentation of collagen fibrils and collagen mass loss impairs fibroblast attachment with the collagenous ECM and then reduces spreading. The reduced mechanical force within fibroblast causes reduced collagen production from fibroblast and upregulates MMP expression especially MMP-1, which collectively causes further deterioration of the ECM [51–53]. In old cutaneous dermis, collagen fragmentation promotes oxidative stress and elevates MMP-1 production in fibroblasts from old skin [49]. Fibroblast cultured in three-dimensional collagen lattices with exogenous MMP-1 mimics the ECM microenvironment in old human dermis. And the fibroblast elevated levels of MMP-1, AP-1 and $\alpha 2\beta 1$ integrin and the antioxidant MitoQ can significantly reduce MMP-1 expression [49]. Reduced spreading/mechanical force of fibroblasts in aged skin induces MMP-1 expression through regulating c-Jun/AP-1 and elevating PGE2 production [53, 54]. The above studies reveal a novel mechanism by which alteration of fibroblast shape/mechanical force regulates MMP-1 expression through several pathways, such as c-JUN/AP-1, COX2-PGE and oxidative stress. Increasing mechanical force of old skin dermis by cross-linked hyaluronic acid filling can stimulate collagen synthesis and block MMP elevation partially [55].

3.4. Role of MMPs in photoageing

Both UVA and UVB can cause MMPs induction in human skin. In 1996, Fisher et al. first time showed induction of MMP mRNA expression and activities in human skin by low-dose UVB irradiation in vivo. Even 0.1 minimal erythema dose (MED) of UVB stimulates MMP expression and activities significantly. The 0.1 MED never causes perceptible erythema and is equivalent to 2–3 min solar irradiation on a summer day [56]. After UVB irradiation, the changes of AP-1 transcription factors became detectable within a few minutes and reached a maximum level at 60 min. Induction of MMP levels and activities was detectable approximately 16 hr.

post UVB irradiation, reached a maximum platform at 24 hr. and gradually disappeared after 48–72 h [56]. Usually, suberythemal dose of UV induces collagenase (MMP-1), a gelatinase (MMP-9) and a stromelysin (MMP-3) from keratinocytes and fibroblasts in vivo. High dose of UV irradiation induces more profound changes in MMPs expression and activity because it recruits more inflammatory cells, including neutrophil granulocytes, mast cells, monocytes-macrophages, lymphocytes and Langerhans cells [57, 58].

After UV irradiation, neutrophils are mainly MMP derived inflammatory cells and recruited in acute phase. Usually, neutrophil-derived MMPs are stored in granules ready for secretion [59]. Neutrophils can secrete MMP-1, MMP-8 and MMP-9. Macrophage-derived MMP-12 (macrophage elastase) mRNA maximally (11.9-fold) was induced by ultraviolet within 16 h in human skin in vivo [47]. Other UV-inducing MMPs like MMP-13, 10 and 7 are also reported.

The MMP induction was shown to be strongly dependent on the skin type: UVA or UVB/UVA irradiation of individuals with darkly pigmented skin resulted in only modest or little MMP induction, even if high UV dose was applied.

Among the UV-induced collagen, MMP-1 is the only enzyme able to initiate cleavage of collagen triple helix within type I and type III collagens, which are the two major fibril-forming molecules in the skin. Only the degrade fibrillar collagens initiate by MMP-1 can be cleaved by MMP-3 and MMP-9. The activity of MMP-1 remains under tight control even after UV irradiation [60]. After acute UV irradiation, only a small part of MMP-1 becomes active, whereas the majority of MMP-1 still inactive [60].

Besides MMP-1, MMP-8 (neutrophil collagenase) and MMP-13 (collagenase 3) also belong to collagenases being able to degrade native collagen without unwinding the triple helical assembly of the substrate [61]. They share similar configuration and enzymatic functions and only have small differences in substrate specificity. Recent studies suggest an induction of MMP-8 by UV irradiation but upregulation was minimal and plays a limited role in UV-mediated collagen damage in the skin [62]. MMP-13 shows less cleavage activity for type I collagen and type III collagen than MMP-1. However, it is 5–10 times more potent in cleaving type II collagen, a major collagen present in the cartilage [61]. Hence, MMP-8 and MMP-13 contribute very little to collagen damage in photoageing.

MMP-3 (stromelysin-1) and MMP-10 (stromelysin-2) belong to stromelysins, differ from collagenases and cannot digest intact type I collagen. They cleave various ECM proteins and are involved in the activation of pro-MMPs. The primary function of MMP-3 is the activation of pro-MMPs such as collagenases, gelatinase B and matrilysins during ECM turnover. In particular, the production of fully active MMP-3 is essential to partially activate pro-MMP-1 [61, 63, 64]. MMP-3 can degrade a large number of ECM proteins, such as type IV, V, IX and X collagens, gelatin, fibrillin-1, fibronectin, laminin and proteoglycans. The catalytic function of MMP-10 for type IV and type V collagens is quite weak compared to the MMP-3 activity [61, 65].

MMP-9 (gelatinase B or 92-kDa type IV collagenase) and MMP-2 (gelatinase A or 72-kDa type IV collagenase) belong to gelatinases, which can degrade type IV, V, VII and X collagens, fibronectin and elastin [64, 66]. They are essential in breakdown of fibrillar collagen fragments

that initially cleaved by collagenases. In photoageing, MMP-9 mainly degrades type IV collagen, an important component of the cutaneous basement membrane [67].

Besides collagen impairment during photoageing, degrading of elastin also contributes to photoageing. Elastin constitutes only 2–4% of the total protein content of the skin; however, it is a major component that contributes to the function of recoil and resilience [68, 69]. UV-induced MMP-12 contributes to solar elastosis, which refers to the collection of dystrophic elastotic material in the dermis [48]. MMP-12 (macrophage metalloelastase) and MMP-7 (matrilysin) can degrade elastin efficiently after UV irradiation. MMP-12 is secreted by both macrophages and fibroblasts after UV irradiation. MMP-12 can cleave many other substrates belonging to the ECM, such as collagen type IV fragments, fibronectin, fibrillin-1, laminin, entactin, vitronectin, heparin and chondroitin sulphates. MMP-12 is also responsible for the activation of other pro-MMPs, such as pro-MMP1, MMP-2, MMP-3 and MMP-9 [61, 68]. MMP-7 can also cleave many other substrates of the ECM, such as collagen type IV, entactin, fibronectin, laminin and cartilage proteoglycan aggregates [61, 70].

Although UV is the most important factor causing extrinsic skin ageing, other factors such as smoking may also contribute to skin ageing through induction of MMPs. Indeed, it has been shown that tobacco smoking-induced MMP-1 causes extrinsic skin ageing in vivo [71].

MMPs induction by UV is related with reactive oxygen species (ROS). UV irradiation stimulates excess intracellular ROS including singlet oxygen, superoxide anion, hydrogen peroxide and hydroxyl radicals. ROS activates the mitogen-activated protein kinase (MAPK) family pathways. Then, transcription factors AP-1 and NF-κB are activated and regulated MMP-1, MMP-3 and MMP-9 resulting in the degradation of collagen [72, 73]. AP-1 also inhibits transforming growth factor-beta (TGF-β) signalling. TGF-β is an important regulator of type I procollagen synthesis in human skin [74]. Stimulation of MMP-1 and MMP-3 expression occurred via the upregulation of transcription factors AP-1 and NF-κB both in cultured keratinocytes and fibroblasts [75, 76]. AP-1 and MMP activities are also upregulated in the aged human skin in vivo [75]. Other influence factors generating ROS also induce AP-1- and NF-κB-mediated transcriptional activation and regulation of MMP gene expression. These pathways are shared by intrinsic and extrinsic skin ageing. Thus, even under physiological condition, low level of reactive oxygen species is constantly produced by the skin cells. The effects of ROS do not depend on their origin and all of them will lead to MMP activation and shift the MMP/TIMP balance. Treatment targeted to ROS generation can inhibit MMPs and prevent skin ageing. In recent years, it is demonstrated that many botanical supplements have effects of suppressing UV-B-induced ROS and MMPs expression, such as *Galla chinensis* [77], *Ixora parviflora* [78] and *Coffea Arabica* et al. [75].

There are a few medicines known to inhibit MMPs in human skin [51]. Topical application of tretinoin may suppress AP-1 and effectively inhibit a number of MMPs in both photoageing [44, 79] and intrinsic ageing [80]. Vitamin A antagonizes decreased cell growth and elevated collagen-degrading MMPs and stimulates collagen in aged skin. Doxycycline inhibits MMP activity at subantimicrobial doses used in many experimental systems. It is used clinically to treat periodontal disease. It is the only MMP inhibitor widely available clinically without major side effects [81]. Its topical application to the skin may also be beneficial against dermonecrosis induced by Loxosceles spider venom [82]. Interferon-γ and heparin have been reported inhibition of MMPs via inhibition of transcription levels.

3.5. Conclusion

MMPs are involved in various forms of skin ageing. It have been demonstrated that in both extrinsic and intrinsic ageing, reactive oxygen species are induced by physiological function of the organism or the extrinsic toxic effects like UV irradiation or tobacco smoking. Reactive oxygen species stimulate expression and activation of MMPs via AP-1 and NF-κB pathway. Meanwhile, MMP inhibitors and collagen synthesis are suppressed. MMPs can degrade all kinds of dermal ECM proteins such as collagen and elastin. Incomplete repair and chronic imbalance of ECM synthesis and degradation lead to disorganization of collagen and elastic fibres. The details of molecular events in skin ageing and MMP behaviours not completely understood. Although some MMP inhibitors are found to prevent skin ageing, more work should be done to reveal more mechanisms.

4. MMPs in skin cancer

Skin cancer is the most common type of malignancy, especially in the Caucasian population. There are three main types of skin cancers: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and cutaneous melanoma (CM). The first two together along with a number of less common skin cancers are known as non-melanoma skin cancer (NMSC) [83]. CM is the most aggressive, SCC is more likely to spread and BCC grows slowly and can also damage the tissue around. Two essential steps in tumour development are degradation of the basement membrane and invasion of the surroundings tissue by tumour cells, and MMPs maybe play an important role in them [84].

4.1. MMPs in cutaneous melanoma

CM is the most severe skin cancer characterized by a bad prognosis at metastatic stages due to resistance to most classical chemotherapies [85]. Degradation of basement membranes and ECM is an essential step in melanoma cell migration, invasion and metastasis formation. MMPs families are the main degrading substances involved in this process. Studies show that MMPs expression is not only restricted to tumour cells but also found in stromal cells. In addition to disrupt matrix proteins, MMPs can also cleave non-matrix components such as cytokines and growth factors. The modifications generated by the remodelling of matrix and non-matrix components can influence melanoma cell proliferation, adhesion, vascularization, survival, proteases expression and migration. The major findings about the expression and roles of some MMPs in melanoma are summarized according to their subgroup.

4.1.1. Collagenases

Three collagenases have been identified so far: collagenase 1 (MMP-1), collagenase 2 (MMP-8) and collagenase 3 (MMP-13) [84]. In 1980, MMP-1 was firstly detected in the stromal cells adjacent to melanoma metastases but not tumour cells and normal skin [86]. MMP-1 expression by stromal fibroblasts has also been implicated in the processing of PAR1, a thrombin receptor, thereby promoting the metastatic potential of cancer cells [87]. Their findings supported the hypothesis that collagenase facilitates connective tissue breakdown, which is associated with

tumour invasiveness and metastatic spread. Further research found detection of MMP-1 at the edges of tumours and increased expression during melanoma progression [88]. Montgomery et al. found MMP-1 was also detected in a highly metastatic human melanoma cell line (M24met) together with MMP-2 and MMP-9 [89]. Furthermore, MMP-1 is detected in melanoma cells in advanced melanoma [90]. In terms of its expression, MMP-1 displays several promoter polymorphisms. Several studies had confirmed that the extra guanine (G) at -1607 bp was associated with enhanced transcription of MMP-1, increased enzymatic activity [91, 92] and also deep invasive melanoma [92]. Pearce et al. had assessed the functional effects of several single nucleotide polymorphisms (−1607GG > G, −839G > A, −755G > T, −519A > G, −422 T > A, −340C > T and 320C > T) on MMP1 gene promoter activity in cell lines of melanoma (A2058 and A375). Their results suggest that the polymorphisms exert haplotype effects on the transcriptional regulation of the MMP1 gene in cancer cells and indicate a need to examine haplotypes rather than any single polymorphism in genetic epidemiologic studies of the MMP1 gene in cancers [93]. The further research confirmed that the above polymorphisms correlate with ulceration patient status, but did not significantly associate with overall survival and other clinical factors [94], suggesting that MMP-1 promoter polymorphisms may individually or jointly play roles in the development of CM [95]. According to the literature, almost all the past studies showed that the expression of MMP-1 was positively correlated with melanoma invasion and metastases [96]. Nikkola et al. found the expression of collagenase-1 (MMP-1), stromelysin-1 (MMP-3) and collagenase-3 (MMP-13) in 70 melanoma metastases obtained from 56 patients treated with combined chemoimmunotherapy. They found that patients with MMP-1-positive metastases had significantly shorter disease-free survival compared to patients with MMP-1-negative metastases [97]. Despite a broad acceptance that MMP-1 plays a central role in invasion and metastasis, one study had found that high MMP-1 expression correlates with a favourable chemoimmunotherapy response in human metastatic melanoma [98].

In contrast to the other collagenases, MMP-8 had a very limited tissue distribution, thought to be restricted to neutrophils and chondrocytes. Giambernardi et al. firstly observed MMP-8 expression in human melanoma cells in 1998 [99]. This observation led them to assess in more detail the expression of MMP-8 in normal and malignant melanocytic cells. They found that MMP-8 was expressed by 11 of 12 human melanoma cell lines tested and all 10 primary melanomas examined, but was not expressed by four primary neonatal melanocyte strains. In contrast to its restricted tissue expression postpartum, MMP-8 was present in multiple embryonic tissues, including neural crest cells. The production of MMP-8 by migrating neural crest cells may contribute to their ability to degrade fibrillar collagen matrices while in transit [100]. Unlike the other MMPs, most studies showed that MMP-8 may have anti-tumour properties. Gutiérrez-Fernández et al. proposed that MMP-8 is a tumour protective factor, which also has the ability to reduce the metastatic potential of malignant cells in both mice and human [101]. In human melanoma, 23% somatic mutations of MMPs have been identified and 5 of these were found in the MMP-8 gene that lost thereby enzymatic activity [102]. MMP-8 gene variation might associate with an increased risk of malignant melanoma, which suggests that wild-type MMP-8 has the ability to inhibit melanoma progression, thus providing definitive evidence that MMP-8 is a tumour-suppressor gene [103]. On the controversy, high serum MMP-8 level is also associated with earlier recognized histopathology markers of melanoma

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progression and haematogenous spreading of melanoma through vascular invasion [104]. Although Syrjänen et al. had reported that patients with high serum MMP-8 levels may benefit from adjuvant IFN-α therapy [105], Prošvicová et al. reported that MMP-8 does not seem to function as a tumour suppressor in the most recent study [106]. In all, MMP-8 seems to have two different effects and needs further investigation in the future.

MMP-13 was shown to be expressed during invasive vertical growth phase of melanoma, but its expression is higher when the tumour starts to invade surrounding tissues [88]. Further studies also confirmed MMP-13 involved in BCC progression, invasion and metastasis [107, 108]. Moreover, MMP-13 can also mediate melanocytes and melanoma growth in vitro studies [109]. To confirm the role of stroma-derived MMP-13 in the invasion process, Zigrino et al. also investigated the invasiveness of melanoma cells upon intradermal injection in mice with complete inactivation of MMP-13. Their data suggest an important role of MMP-13 in tumour growth and an unexpected role in organ-specific metastasis of melanoma cells [110]. The recent research showed that MMP-13 has a dual effect in melanoma, as it promotes invasion and metastasis by cleaving laminin-5 (Ln-5) into small fragments but disrupts vasculogenic mimicry formation [111]. However, host-derived MMP-13 exhibits a protective role in lung metastasis of melanoma cells by local endostatin production [112].

4.1.2. Gelatinases

MMP-2 and MMP-9, also known as gelatinases A and B, were detected by immunohistochemical staining in stromal and/or melanocytic cells in melanoma [113] and stromal cells as the major source for it [114]. Using in situ enzymatic assays, proteolytic activity of MMP-2 and MMP-9 was predominantly localized in peritumoural areas while no activity was observed within the tumour cell nests [115]. MMP-2 cleaves fibronectin into small fragments to enhance the adhesion and migration of human melanoma cells [116]. There is growing evidence that MMP-2 is an important factor for promoting cancer cell invasion and independent predictive factor for lymph node involvement [117]. The pro-tumour function of several molecules (NADPH oxidase 1 [118], angiotensin II [119], hyaluronan-binding protein 1 [120], osteopontin [121] and interleukin-8 [122]) was also MMP2-dependent. The expression of MMP-2 in CM could be a useful diagnostic and prognostic indicator in melanoma [123, 124]. However, MMP-2 serum level appears to be of limited clinical value in monitoring [125, 126]. At the genetic level, functional promoter polymorphisms −1306 C/T and −735 C/T were known to modify the gene transcription but not associated with melanoma progression [127].

Among all the members of the MMP family, MMP-9 is of crucial importance in tumour invasion and metastasis. MMP-9 was significantly higher in melanoma patients than in controls [128]. Transfection of sense MMP-9 can enhance growth and invasion of melanoma cells, further confirming its important role in tumour invasion and metastasis [129]. MMP-9 may also act as tumour suppressor by processing matrix macromolecules. Enzymatic activity of MMP-9 towards the basement membrane collagen type IV was shown to generate a proteolytic active fragment, tumstatin, which suppresses activity of endothelial cells and inhibits pathological angiogenesis [130]. Circulating MMP-9 levels had shown low sensitivity and specificity and did not seem to be good tumour markers in patients with melanoma [131].

Nikkola et al. reported that MMP-1, MMP-9 and MMP-13 play important roles at different phases of metastatic melanoma spread and serum MMP-9 could particularly have clinical value in identifying patients at high risk for melanoma progression [132]. There was no strong evidence that MMP-9 SNPs play a role in melanoma progression [133].

4.1.3. Stromelysins

MMP-3, MMP-10 and MMP-11 correspond to stromelysins 1, 2 and 3, respectively. MMP-3, also called stromelysin-1, was one of the first proteinases found to be associated with cancer. MMP-3 was localized to the deeper margins of human melanoma [134] and confirmed to correlate with shorter disease-free survival [97]. However, Tas et al. proposed that neither of the serum levels of MMP-3 could be a good indicator of invasion and metastasis nor can be recommended as a tumour marker in the management of melanoma patients owing to lack of sensitivity and specificity by detecting serum MMP-3 levels in 70 patients with cutaneous malignant melanoma [135]. At the genetic level, functional promoter polymorphisms −1171 5A/6A was known to modify the gene transcription [127], but no strong evidence provided into the role of the MMP3 variants in melanoma progression [127, 136]. More researches are needed to confirm it specific roles in CM. Studies on the other two stromelysins, MMP-10 and MMP-11, in CM were very limited. It seems that the stromelysins are involved in the generalized growth and expansion of the neoplastic cell mass [107], but the possible correlation with CM is still unclear. MMP-11 is a fibroblastic factor expressed in stromal cells adjacent to carcinoma cells, but was not found in human melanoma [137].

4.1.4. Matrilysins

MMP-7 and MMP-26 belong to the group of matrilysins. Matrilysin (MMP-7) is expressed in various types of malignant tumours. Kawasaki et al. found MMP-7 expression in primary melanomas and in metastatic melanomas, but not in common naevi or Spitz naevi. Their observations indicate that MMP-7 may be associated with melanoma progression and may enhance melanoma tumour cell invasion [138]. However, a direct role for MMP-7 in melanoma development has not been shown. MMP-26 was not generally expressed in melanoma cells [139] but elevated in melanoma tissues, and it may serve as a molecular marker for the early diagnosis of melanoma [140].

4.1.5. MT-MMPs

Two types of MT-MMPs exist: four type I transmembrane proteins (MMP-14, MMP-15, MMP-16 and MMP-24) and two glycosylphosphatidylinositol (GPI)-anchored proteins (MMP-17 and MMP-25). MT1-MMP, also referred to as MMP-14, was the first discovered membrane-type MMP [141]. MT1-MMP expressing clones can induce rapid tumour growth and high tumour vascularization in nude mice [142]. It is expressed in tumour cells mainly at the leading edge of the invasive front of melanomas [115] and can serve as prognostic factor as its expression strongly associates with cancer progression and metastasis and poor prognosis of patients [143]. Activation of MMP-2 is mediated by binding to the complex of MT1-MMP with tissue inhibitor of MMP-2 (TIMP-2) on the cell surface [144]. Further study suggested that activation of MMP2 by MT1-MMP is

required to sustain RAC1 activity and promote MT1-MMP-dependent cell motility. These data highlight a novel MT1-MMP/MMP2/RAC1 signalling axis in melanoma that may represent an intriguing molecular target for the treatment of invasive melanoma [145]. Moreover, MT1-MMP can activate Notch1 in melanoma cells by directly cleave it to induce melanoma growth [146]. Recently, MT1-MMP has been found to also modulate gene expression. Shaverdashvili et al. identified the tumour suppressor gene SPRY4 as a new transcriptional target of MT1-MMP and a novel molecular effector of MT1-MMP that affect melanoma cell motility [147]. MMP-2 is considered to be activated by MT-MMPs and its expression in melanoma cells was involved in the degradation of ECM during melanoma growth and correlated with later melanoma metastasis. Thus, MT-MMPs and MMP-2 cooperate in the invasive and metastatic process of melanoma cells [123]. Recent research also showed that effective inhibition of MT1-MMP and MMP2 can effectively reduce melanoma cell growth, migration and invasion in vitro [148]. The information could help in developing new therapies designed to interfere with MMPs activation and management of cancer and metastases.

The expression of MT2-MMP (MMP-15) and MT3-MMP (MMP-16) was generally increased in primary and metastatic melanoma cells. A consistent colocalization of MT2-MMP/MMP-2 and MT3-MMP/MMP-2 in the nodular melanoma and metastatic melanoma cells was found by double immunofluorescence [123]. MT3-MMP was significantly upregulated in biopsies of human melanoma metastases and induced efficient invasion of the cells in fibrin, a provisional matrix component frequently found at tumour-host tissue interfaces and perivascular spaces of melanoma, which suggest that MT3-MMP functions as a matrix composition-dependent effector of melanoma cell invasion [149]. Further study showed that overexpression of MT3-MMP in human melanoma is associated with poor clinical outcome, collagen bundle assembly around tumour cell nests and lymphatic invasion [150]. So far, there is no report of MMP-17 and MMP-25 related to melanoma. Although more studies are required to unveil the roles of GPI-MT-MMPs in cancer, the data so far obtained suggest that these proteases influence cancer progression by mechanisms that are different from the TM-MT-MMPs. First, GPI-MTMMPs do not act as progelatinase activators; second, their ECM degradation profile appears to be very limited; third, GPI-MT-MMPs do not promote tumour cell migration and invasion and fourth, their inhibition profile appears unique [61].

4.1.6. Other MMPs

MMP-12, MMP-19, MMP-20, MMP-21, MMP-23, MMP-27 and MMP-28 have not been catalogued in any of the subgroups mentioned above. Zhang et al. found that MMP-12 expression in melanoma was significantly associated with tumour invasion and metastasis [151]. Müller et al. found that MMP19 expression was upregulated in the vertical growth phase and in metastases (mainly expressed close to tumour surrounding fibroblasts), suggesting participation of MMP19 in melanoma development and MMP19 as a candidate marker for identifying vertical growth phase melanoma and metastatic melanomas [152]. MMP-21 is upregulated at early stages of melanoma progression but disappears with more aggressive phenotype, suggesting expression of MMP-21 may serve as a marker of malignant transformation of melanocytes and does not associate with the presence of micrometastases [139]. Moogk et al. confirmed that MMP-23 was expressed in human melanoma by detecting MMP-23 expression

in primary melanoma patients who received adjuvant immunotherapy. The results showed an inverse association between primary melanoma MMP-23 expression and the anti-tumour T cell response, suggesting MMP-23 is a potential immunosuppressive target in melanoma [153]. MMP-28 was not generally expressed in melanoma cells [139]. To date, there was no report relating to MMP-27 and melanoma.

4.2. MMPs in basal cell carcinoma

BCC is the most common cancer in white-skinned individuals with increasing incidence rates worldwide. There are different histopathological subtypes, of which nodular is the most frequent, followed by superficial and infiltrative, and mixed types are frequently found as well. Most BCC occur in the head and neck region (i.e. sun-exposed), followed by trunk and extremities (i.e. relatively sun-unexposed) [154]. Although BCC is characterized by slow progression and low metastatic potential, it has a propensity to be locally destructive. If untreated, BCC may invade subcutaneous fat, muscles and even bones [154]. The invasion of tumour cells is a complex, multistage process, which is governed by complex interactions between various biomarkers, especially MMPs, cell-cell adhesion molecules (such as β-catenin) and chemokine receptor-ligand complexes (SDF-1/CXCR4) [155, 156].

4.2.1. Collagenases

MMP-1 is the primary collagenolytic enzyme in BCC and expressed at various intensities in epithelial tumour cells and surrounding stromal cells, including fibroblasts, inflammatory cells and vascular endothelial cells [157, 158]. The expression of MMP-1 is significantly enhanced at the invasive front of BCC, suggesting its role in the initial steps of tumour proliferation; even when potentially important variables such as age and individual variability are controlled for, tumour-specific effects on the expression of MMP-9 and MMP-1 also need be taken into consideration [159]. In order to determine correlations between invasiveness and histologic differentiation, the expression of MMP-1, MMP-3, Ki-67, p53, EGFR and CD44v6 was detected in 108 cases of BCC using tissue array. The results showed that the loss of palisading arrangement in BCC was correlated with the MMP-1 expression of stromal cells [160]. Odds ratio for development of morpheaform and recurrent BCC was 6.2 for positive MMP-1 immunostaining in epithelial tumour cells, suggesting MMP-1 is associated with morpheaform and recurrent BCC [161]. MMP-13 is involved in the degradation of ECM and its expression is associated with malignant transformation in skin carcinogenesis [155, 162]. The expression of MMP-13 is not confined to tumour cells alone, as its expression is also upregulated in stromal cells surrounding epithelial tumours, including fibroblasts, inflammatory cells and endothelial cells [163]. The further study found endothelial cells-derived MMP-13 is associated with endothelial cell proliferation and vascular differentiation, suggesting MMP-13 maybe is an efficient therapeutic target for future treatment of BBC [162]. The CXCR4 ligand, stromal cell-derived factor 1 alpha (SDF-1α), directed BCC invasion and that this was mediated by gelatinase activity of MMP-13 [155]. By immunohistochemistry, MMP-13 was detected in the cytoplasm of the malignant cells and occasionally in the surrounding stromal cells. Statistical analysis showed no significant association between MMP-13 immunostaining

and patients or tumour characteristics, but the expression of MMP-13 was more intense in the epithelial tumour cells located at the invading front [164]. Taken together, MMP-13 expression may serve as a prognostic marker for early tumour invasiveness and also an increased risk for BCC recurrence. Neutrophils are a major source of MMP-8. MMP-8 was indeed detected in BCC, but its source is more problematic as it diffusely presented only throughout the stroma. It is reasonable to suggest that circulating neutrophils present in the tissue at the time of biopsy might be responsible for this enzyme, but this does not rule out contributions by resident neutrophils [157].

4.2.2. Gelatinases

MMP-2 and MMP-9 play an important role in the development, progression, invasion and metastasis of BCC and proposed to be used as prognostic factors of BCC [165]. MMP-2 is a leading ECM degrading protease and upregulates in almost all cancers by creating a suitable microenvironment for the proliferation of cancer cells and epithelial-mesenchymal transition (EMT) [61]. MMP-2 is mostly secreted by stromal cells surrounding BCC tumours and rarely by keratinocytes and BCC tumour cells [166]. MMP-2 expression may contribute to the distinct invasive patterns seen in BCC as its expression was higher in the stroma of high-risk BCC when compared to low-risk BCC [167]. MMP-9 has been historically identified as a basement membrane degrading protease, due to its high affinity for collagen IV. Experimental models, mostly based on MMP-9 knockout mice, have provided unequivocable evidences about the pivotal role played by the enzyme in tumour growth, invasiveness and angiogenesis [61]. MMP-9 prominently expressed at the invading edge of the BCC and was mostly secreted by inflammatory cells, such as macrophages, rather than by tumour cells [158, 168]. Odds ratio for development of morpheaform and recurrent BCC was 5.8 for positive MMP-9 immunostaining in tumour stroma, suggesting MMP-9 expression in stromal cells is associated with morpheaform and recurrent BCC [161]. In order to compare the expressions of mRNA for metalloproteinases (MMP-2 and MMP-9) and type IV collagen in BCC and normal tissues from the tumour interface, Goździalska et al. detected the expressions of mRNA for MMP-2, MMP-9 and type IV collagen by RT-PCR. They revealed that MMP-2 and MMP-9 expressed significantly higher in nodular and infiltrative BCC than normal tissues adjacent to tumours, suggesting that MMP-2 and MMP-9 could be used as prognostic factors of BCC [165].

4.2.3. Stromelysins

MMP-10 was entirely negative in premalignant lesions and only detected in epithelial cancer cells. By statistical analysis, MMP-10 expression does not correlate with the invasive behaviour of tumours as assessed by their histology, but may be induced by the wound healing and inflammatory matrix remodelling events associated with skin tumours [169, 170]. MMP-11 seems to be associated with benign fibroblastic tumours and is a fibroblastic factor expressed in stromal cells adjacent to carcinoma cells. Thewes et al. found MMP-11 only expressed in fibroblasts surrounding malignant epithelial tumour cells in more than half of BCC. Of interest, different percentages of positive immunoreactivity were found between the lowest level

(29.4%) in the nodular-ulcerative subgroup and the highest level (65.4%) in the morpheaform subgroup [171].

4.2.4. Matrilysins

Expression of MMP-7 is low in the normal epidermis and is induced by physiological processes such as wound healing, but also malignant transformation of epidermal cells. Hartmann-Petersen et al. revealed that the intensity of MMP-7 was found in tumour cells of BCC. Furthermore, the activity of MMP-7 was associated with the hyaluronan (HA) receptor CD44 and its staining intensity was inversely correlated with that of CD44 in BCC [172]. MMP-26 expression is barely detected in BCC epithelium or stromal cells and is therefore not considered significant in the development of BCC nor in the process of angiogenesis [168, 173].

4.2.5. MT-MMPs

MT-MMP acts as a membrane activator of other soluble MMPs, such as MMP-2 [156, 167]. Oh et al. has detected MT1-MMP expression in various histological subtypes of BCC. The results showed that MT1-MMP immunoreactivity was increased in the high-risk BCC and at the invading front of mixed BCC tumour islands, suggesting MT1-MMP might be a novel marker for high-risk BCC [156].

4.2.6. Other MMPs

In BCC, MMP-12 was more often found in macrophages than in cancer cells, indicating that the level of human MMP-12 expression correlates with epithelial dedifferentiation and histologic aggressiveness [174]. MMP-21 protein was not detected in normal adult skin. However, it was present in invasive cancer cells of aggressive subtypes of basal and SCC [175].

4.3. MMPs in cutaneous squamous cell carcinoma

SCC is the second most common type of NMSC and characterized by malignant proliferation of epidermal keratinocytes. Its incidence rates appear to be increasing in many populations of European heritage [176]. Evidently, the primary cause of cutaneous SCC is cumulative lifetime sun exposure (especially UVB). Furthermore, ionizing radiation, immune suppression, chronic inflammation and human papillomavirus (HPV) infection may lead to the development of SCC. The prognostic risk factors include diameter, depth of invasion, histologic differentiation, rapid growth, anatomic site, immune suppression and etiology, so that tumours arising from scars and chronic ulcers tend to be aggressive [176]. Unlike BCC, SCC exhibits an increased risk of metastasis, although the rate of metastasis is much lower than that of melanoma [177]. Like BCC, MMPs also play an important role in the degradation of ECM and basement membrane [84].

4.3.1. Collagenases

MMP-1 mRNA was detected in tumour cells and/or in stromal cells in all cases of SCC, its expression could be an early event in the development of SCC [178]. Ultraviolet radiation may cause NMSC. In order to find out if UV irradiation modulates the expression of MMPs, Ramos et al. investigated it and found MMP-1 was upregulated 4 h after UVA and 16 h after UVB irradiation

of tumour cells [179]. Further clinical research revealed that MMP-1 is a significant marker associated with the invasiveness of SCC and also a poor clinical outcome. Thus, it will be helpful to evaluate the invasiveness by measuring the expression of MMP-1 in SCC [160]. Specific expression of MMP-13 by SCC cells in vitro and in vivo strongly suggests a role for MMP-13 in the high invasion capacity of SCC cells [180]. In patients with recessive dystrophic epidermolysis bullosa, MMP-13 expression is strongly positive in SCC but negative in benign hyperkeratotic lesions, suggesting MMP13 may be a useful differentiating marker between SCC and benign hyperkeratotic lesions [181]. Further studies showed that MMP-13 is also involved in the maintenance of angiogenesis through the release of VEGF from the tumour ECM [182]. Taken together, MMP-1 and MMP-13 are expressed mainly in stromal cells, particularly in tumour-associated fibroblast. Both MMP-1 and MMP-13 can cleave native fibrillar collagen and remodel the ECM thereby play a crucial role in tumour progression in vivo [183]. MMP-8 expressed in tissue from head and neck carcinomas, but the amount of MMP-8 in them is rather low [184]. Further study found that MMP-8 was positive in peritumoural inflammatory cells in cutaneous SCC, but it was not associated with the overall survival of patients with cutaneous SCC [185].

4.3.2. Gelatinases

The expression of MMP-2 greatly increased in tumour stroma and parenchyma of SCC and may contribute to the distinct invasive patterns seen in SCC [167]. MMP-9 showed positive staining mainly in the granular layer of normal epidermis. While in SCC and BD, MMP-9 showed positive staining in the dysplastic lesions even in the basal layer [186]. Borchers et al. reported that interactions between malignant keratinocytes and adjacent stromal fibroblasts are critical in directing expression of MMP-9 to the tumour-stroma interface in human SCC tumours [187], and also MMP-9 was found to be focally expressed by neoplastic epithelial cells of cutaneous carcinomas at the infiltrative edges in microinvasive carcinomas and in dyskeratotic foci in Bowen's disease and widely invasive carcinomas [188]. The expression of MMP9 was higher in SCC compared to BCC and AK [189], and also may contribute to the more aggressive behaviour of SCC in immunosuppressed patients [190]. Nan et al. observed that the MMP9 Arg668Gln polymorphism was significantly associated with a decreased risk of SCC, but no correlation to BCC and melanoma [191]. The reduced expression of collagen IV combined with an increased expression of both MMP2 and MMP9 could account for the increased metastatic potential of SCC vs. BCC through an increased invasion of the ECM and the vascular space [192]. To investigate the expression of MMP-2 and MMP-9 in NMSC and compare their expression between different tumour types with clinicopathological factors, a study of 11 normal skin, 29 Bowen's disease and 40 SCC samples for MMP-2 and MMP-9 expression was carried out using immunohistochemistry and in situ hybridization. The results showed that there was a correlation between increased metalloproteinase expression and depth of lesion (MMP-2), inflammation (MMP-2 and MMP-9) and microvessel density (MMP-2 and MMP-9) [193]. These results provided additional evidence of the role of MMP-2 and MMP-9 in tumour invasiveness of keratinocyte-derived tumours.

4.3.3. Stromelysins

MMP-3 or stromelysin-1 is induced in the tumour stroma in the early stages of tumourigenesis. It can degrade a variety of matrix and non-matrix molecules such as growth factors,

HB-EGF and E-cadherin. Fibroblast-derived MMP-3 is a necessary mediator of tumour vascularization and tumour progression and thus plays an important role in mechanisms that modulate tumour metastasis [194]. The expression of MMP-3 was increased in both tumour cells and stromal cells in metastatic SCC and also correlated to that of MMP-1 localized at tumour mass and stroma of the invasive SCC [178]. McCawley et al. demonstrated that MMP3-null animals have an increased sensitivity to the development of SCC, suggesting that MMP3 has a protective role in SCC. However, not all cellular responses affected by a loss of MMP3 are tumour-protective, and tumour expression of MMP3 is coincident with an invasive tumour phenotype. Transgenic mice were generated with MMP3 targeted to keratinocytes to examine the biological role of tumour-produced MMP3 in their further study. Overexpression of MMP3 reduced tumour multiplicity in response to chemically induced SCC. Vascular density was increased with MMP3 overexpression; however, other cellular processes, including tumour growth and leukocyte infiltration, were unaffected. These studies suggest that keratinocyte expression of MMP3 promotes cellular differentiation, impeding tumour establishment during tumourigenesis [194]. MMP-10 or stromelysin-2, similar to other metalloproteases, facilitates the recruitment of infiltrating cells by remodelling the ECM. Moreover, MMP-10 upregulates several other MMPs such as MMP-1, MMP-7, MMP-9 and MMP-13 that are essential for tumour progression. The function of this protease is restricted to the initial process of tumour initiation, indicating that it might not be important in invasion or metastasis [13]. In 2001, MMP-10 was only detected in epithelial laminin-5 positive cancer cells in SCC, and its expression does not correlate with the invasive behaviour of tumours [169]. More precisely, MMP-10 is highly expressed in SCC stromal cells and is upregulated by tumour-associated cytokines, including TGF-β and TNF-α. The level of MMP-10 expression in tumour epithelium of grades III and II of SCC was significantly greater compared to grade I tumours [195]. Recently, Kadeh et al. also found high immunohistochemical expression of MMP-10 in tumour epithelium and stroma in SCC. Moreover, they also confirmed that the level of MMP-10 expression in tumour epithelium of grades III and II of SCC was significantly greater compared to grade I tumours [170]. Thus, MMP-10 was highly expressed in both tumour epithelium and stromal cells and may play a role in the initial stages of SCC progression [13], but does not correlate with the invasive behaviour of SCC [169]. MMP-11 found a positive immunoreactivity in fibroblasts surrounding malignant epithelial tumour cells in 4 of 25 (16%) SCCs, whereas the tumour cells themselves were negative [171]. Besides the above report, there was no other MMP-11-related study in SCC was found. Thus, the role of MMP-11 involved in SCC maybe so limited.

4.3.4. Matrilysins

MMP-7 can digest a wide range of ECM proteins and cleave several cell surface proteins, including E-cadherin and syndecan-1 [196]. In addition to enhance tumour invasion and metastasis directly, MMP-7 also exerts indirect effects through the activation of MMP-2 and MMP-9 [197]. Mitsui et al. found that the expression of MMP7 increased in invasive SCC and its expression was induced by IL-24. Moreover, blocking of MMP7 by a specific antibody significantly delayed the migration of SCC cells in culture. These results suggest that MMP-7 in SCC is derived by IL-24 and may play a role in SCC invasion [198]. MMP-7 was present in tumour cells and mainly located in the invasive front, suggesting play a role in promoting the growth

of cutaneous SCC [199]. MMP-26 is predominantly located in pre- and early-invasive areas in SCC and plays an essential role in the initial stages of skin cancer [200]. In addition, MMP-26 can also stimulate MMP-9 expression [190]. MMP-26 is upregulated in keratinocytes during early skin carcinogenesis and becomes downregulated during histological dedifferentiation of SCC. Thus, lack of MMP-26 in SCC could be a marker of aggressive growth [37].

4.3.5. MT-MMPs

MT1-MMP or MMP-14 plays an important role in the degradation of various ECM proteins and in activating pro-MMP-2 [201]. MMP-14 mRNA was detected both in epithelial cancer cells and stromal fibroblasts [169]. MMP-14 showed a statistically significant linear trend with decreasing values for tumoural and stromal expression with invasion suggesting that it might be of use as a prognosticator [202]. Both stromal fibroblasts and tumour cells in SCC, particularly at the invasive front of the tumour, secrete MMP-14. MMP-14 in tumour cells can induce tumour cell invasion, whereas MMP-14 in fibroblasts may be important in the stromal response to tumour cells that characterize the desmoplastic reaction [203].

4.3.6. Other MMPs

Several other MMPs are reported to be involved in the pathophysiology of SCC. MMP-12 expression by tumour cells in SCC of the vulva correlates with invasiveness, while macrophage-derived MMP-12 in tumour predicts better outcome. These results suggest a dual role for MMP-12 in tumour progression [204]. Unlike most MMPs, MMP-19 was present in the hyperproliferative (p63-positive), E-cadherin-negative epidermis at the tumour surface but downregulated in invasive cancer islands in SCC, suggesting MMP-19 maybe a protective factor and preventing the occurrence of SCC [205]. MMP-21, the newest member of the MMP gene family, has been suggested to play an important role in embryogenesis and tumour progression and to be a target of the Wnt, Pax and Notch signalling pathways. MMP-21 is present in invasive cancer cells of SCC and is upregulated by TGF-beta1 in keratinocytes [175]. It may be involved in keratinocyte differentiation but does not associate with invasion of SCC [13]. MMP-28 is the newest member of the matrix metalloproteinase enzyme family. Unlike many other MMPs, MMP-28 was not detected in the invading cancer cell nests of squamous cell cancers of various grades.

4.4. Conclusion

MMPs play an important role in tumour development, growth, angiogenesis and metastasis. Each of these proteinases has specific roles in determining the invasive capacity of the tumour. The expression and role of various MMPs in BCC, BCC and SCC were summarized in **Tables 1–3**. Different MMPs might form a network, in which each has a distinct role in the cleavage of a particular matrix component or activation of other MMPs. Stromal cells are the major source of MMPs, but tumour cells, fibroblasts and inflammatory cells all express a distinct set of MMPs capable of complementing the proteolysis needed in tumour progression. Hence, the function of distinct MMPs and their regulation should be considered the principal targets for development of antineoplastic drugs or chemotherapeutic agents.

Member	Expression	Role
Collagenases		
MMP-1	Expressed by stromal fibroblasts adjacent to melanoma metastases and also melanoma cells in advanced melanoma	Promotes progression, invasion and metastatic
MMP-8	Expressed by melanoma cells	Two different effects: (1) Tissue expressed MMP-8 inhibits melanoma progression; (2) Serum MMP-8 is a marker of melanoma progression and haematogenous spreading of melanoma through vascular invasion
MMP-13	Expressed by melanoma cells	A dual effect: (1) Stroma-derived MMP-13 promotes progression, invasion and metastatic; (2) Host-derived MMP-13 exhibits a protective role in lung metastasis
Gelatinases		
MMP-2	Expressed by stromal and/or melanocytic cells in melanoma, and stromal cells as the major source	Promotes cancer cell invasion and independent predictive factor for lymph node involvement
MMP-9	Expressed by stromal and/or melanocytic cells in melanoma, and stromal cells as the major source	Promotes invasion and metastatic
Stromelysins		
MMP-3	Expressed in deeper margins of human melanoma	Correlates with shorter disease-free survival
MMP-10	Expressed by malignant melanomas, especially in the ECM adjacent to blood vessels	Role was very limited
MMP-11	Expressed in stromal cells adjacent to carcinoma cells	Role was very limited
Matrilysins		
MMP-7	Expressed in primary melanomas and in metastatic melanomas	Promotes progression and invasion
MMP-26	Elevated in melanoma tissues, but not in melanoma cells	May serve as a molecular marker for the early diagnosis of melanoma
MT-MMPs		
MMP-14	Expressed by tumour cells mainly at the leading edge of the invasive front of melanomas	Strongly associates with cancer progression and metastasis and poor prognosis of patients
MMP-15	Expressed in primary and metastatic melanoma cells	Promotes invasion and associates with poor clinical outcome
MMP-16	Expressed in primary and metastatic melanoma cells	Promotes invasion and associates with poor clinical outcome
MMP-17	None reported to date	Unknown
MMP-24	None reported to date	Unknown
MMP-25	None reported to date	Unknown

Member	Expression	Role
Other MMPs		
MMP-12	Mainly expressed by tumour cells	Promotes invasion and metastatic
MMP-19	Upregulated in the vertical growth phase and in metastases (mainly expressed close to tumour surrounding fibroblasts)	Serves as a candidate marker for identifying vertical growth phase melanoma and metastatic melanomas
MMP-20	None reported to date	Unknown
MMP-21	Upregulated at early stages of melanoma progression but disappears with more aggressive phenotype	Serves as a marker of malignant transformation of melanocytes
MMP-23	Expressed by melanoma cells and also fibroblasts surrounding melanoma islands	Inversely associates with the anti-tumour T cell response
MMP-27	None reported to date	Unknown
MMP-28	Not generally expressed in melanoma cells	Unknown

Table 1. The expression and roles of MMPs in cutaneous melanoma.

Member	Expression	Role
Collagenases		
MMP-1	Expressed at various intensities in epithelial tumour cells and surrounding stromal cells including fibroblasts, inflammatory cells and vascular endothelial cells	Plays a role in the initial steps of tumour proliferation and associates with morpheaform and recurrent BCC
MMP-8	Diffusely presented throughout the stroma	Unknown
MMP-13	Expressed by epithelial tumour cells and stromal cells including fibroblasts, inflammatory cells and vascular endothelial cells	Serves as a prognostic marker for early tumour invasiveness and an increased risk for BCC recurrence
Gelatinases		
MMP-2	Mostly secreted by stromal cells surrounding BCC tumours	Plays an important role in the development, progression, invasion and metastasis
MMP-9	Expressed at the invading edge of the BCC and was mostly secreted by inflammatory cells such as macrophages, rather than by tumour cells	Plays an important role in the development, progression, invasion and metastasis
Stromelysins		
MMP-3	None reported to date	Unknown
MMP-10	Expressed by epithelial cancer cells	Maybe induced by the wound healing and inflammatory matrix remodelling events associated with skin tumours
MMP-11	Expressed by fibroblasts surrounding malignant epithelial tumour cells	Unknown

Member	Expression	Role
Matrilysins		
MMP-7	Expressed by tumour cells	Maybe associated with poor differentiation
MMP-26	Not expressed in BCC	Unknown
MT-MMPs		
MMP-14	Expressed by tumour cells mainly at the invading front of mixed BCC tumour islands	Serves as a novel marker for high-risk BCC
MMP-15	None reported to date	Unknown
MMP-16	None reported to date	Unknown
MMP-17	None reported to date	Unknown
MMP-24	None reported to date	Unknown
MMP-25	None reported to date	Unknown
Other MMPs		
MMP-12	More often found in macrophages than in cancer cells	Correlates with epithelial dedifferentiation and histologic aggressiveness
MMP-19	None reported to date	Unknown
MMP-20	None reported to date	Unknown
MMP-21	Presents in invasive cancer cells of aggressive subtypes	Maybe promote invasion
MMP-23	None reported to date	Unknown
MMP-27	None reported to date	Unknown
MMP-28	None reported to date	Unknown

Table 2. The expression and roles of MMPs in BCC.

Member	Expression	Role
Collagenases		
MMP-1	Expressed by tumour cells and stromal cells, mainly in stromal cells	Served as a significant marker associated with the invasiveness of SCC and also a poor clinical outcome
MMP-8	Lowly expressed by peritumoural inflammatory cells in SCC	Role is limited
MMP-13	Expressed by tumour cells and/or stromal cells, mainly in stromal cells	Promotes invasion and angiogenesis
Gelatinases		
MMP-2	Expressed by tumour stroma and parenchyma	Promotes invasion
MMP-9	Expressed in the tumour-stroma interface of SCC and also at the infiltrative edges of microinvasive carcinomas	Promotes invasion and metastatic

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Member	Expression	Role
Stromelysins		
MMP-3	Expressed by tumour stroma at the early stages of tumourigenesis and upregulated in both tumour cells and stromal cells in metastatic SCC	Promotes progression, invasion and metastatic
MMP-10	Highly expressed in stromal cells	Promotes progression
MMP-11	Expressed by fibroblasts surrounding tumour cells	Role is limited
Matrilysins		
MMP-7	Expressed by tumour cells and mainly located in the invasive front	Promotes invasion and metastatic
MMP-26	Upregulated in keratinocytes during early skin carcinogenesis and becomes downregulated during histological dedifferentiation of SCC	Plays an essential role in the initial stages of SCC
MT-MMPs		
MMP-14	Detected both in epithelial cancer cells and stromal fibroblasts	Promotes invasion
MMP-15	None reported to date	Unknown
MMP-16	None reported to date	Unknown
MMP-17	None reported to date	Unknown
MMP-24	None reported to date	Unknown
MMP-25	None reported to date	Unknown
Other MMPs		
MMP-12	Expressed by tumour cells and macrophages	A dual role: Expressed by tumour cells correlates with invasiveness, while macrophage-derived MMP-12 in tumour predicts better outcome
MMP-19	Expressed by the hyperproliferative, E-cadherin-negative epidermis at the tumour surface but downregulated in invasive cancer islands	Maybe a protective factor and prevent the occurrence of SCC
MMP-20	None reported to date	Unknown
MMP-21	Expressed by invasive cancer cells of SCC	Promotes progression and invasion
MMP-23	None reported to date	Unknown
MMP-27	None reported to date	Unknown
MMP-28	None expression in SCC	Unknown

Table 3. The expression and roles of MMPs in cutaneous SCC.

Author details

Guolong Zhang, Peiru Wang and Xiuli Wang*

*Address all correspondence to: wangxiuli20150315@163.com

Institute of Photomedicine, Shanghai Skin Disease Hospital, Tongji University School of Medicine, Shanghai, China

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