Chapter 10

The Role of Furin in the Development of Skin Cancer

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Additional information is available at the end of the chapter

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1. Introduction

Skin cancer represents a major, and growing, public health problem, and is the most common type of cancer observed in Caucasians [1-3]. The three most common forms of skin cancer are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma. BCC and SCC are together known as non-melanoma skin cancers (NMSC), and are both derived from keratinocytes whereas melanomas are derived from melanocytes [3-6]. SCCs can undergo metastasis; BCCs rarely do, while melanomas can be highly metastatic [5, 6].

The ultraviolet (UV) radiation component of sunlight is acknowledged to be the main carcinogen implicated in the formation of skin cancer. UV radiation can be divided into three components: UVC (100-280 nm), UVB (280-320 nm) and UVA (320-400 nm). Ozone depletion, seasonal and weather variations affect the amount of UV radiation reaching the Earth's surface [7]. UVC and most of the UVB radiation emitted from the sun is blocked from reaching the Earth's surface by the ozone layer. The component of UV light that reaches the Earth's surface consists of 90-95% UVA and 5-10% UVB [3, 8]. The penetration of shorter-wavelength UVB radiation is predominantly confined to the epidermis while UVA penetrates into the dermis because of its longer wavelength [9].

UVB can cause sunburn, inflammation, DNA mutations and membrane damage as well as skin cancer [8, 10, 11]. It is known that UVB directly damages DNA and can induce Reactive Oxygen Species (ROS) by interactions with chromophores in the skin [12]. The DNA damage caused by UVB irradiation typically results in the formation of cyclobutane pyrimidine dimers (CPD) and pyrimidine (6-4) photoproducts. The mutations are frequently found in the p53, p16, PTCH and INK4α/CDKN2A genes of skin cancer patients [13, 14]. Inflammation plays a significant role in creating an environment where cells possessing mutated DNA can become carcinogenic. UVA can cause premature skin ageing, wrinkle formation, blotching and induces sunburn cell formation in the epidermis, as well as skin cancer [8, 10, 15]. It affects keratinocytes

at a transcriptional level by altering the expression of genes involved in apoptosis, cell cycle, DNA repair, signal transduction, RNA processing and translation, and metabolism [9]. UVA can cause DNA damage by generating ROS [12] resulting in genomic damage e.g. single-stranded breaks, protein-DNA crosslinks, and oxidative base damage (i.e. 8-oxo-7,8-dihydroxyguanine) [16]. It can also initiate signal transduction pathways [13, 17] as well as inducing the expression of cytokines such as Interleukin (IL)-6, heme oxygenase-1, and cyclo-oxygenase [18] as well as inflammatory mediators such as tumor necrosis factor-α (TNFα) [15, 19].

While UVB has been thought to be the main contributor toward skin cancers, based largely on the DNA action spectrum of UV radiation, UVA has more recently been acknowledged as playing an important role in this process [9, 11, 20]. While UVA does not produce an inflammatory response like that of UVB, it produces ROS and as such activates many of the same signalling pathways [13]. It is clear that doses of UVB, UVA and solar stimulated UV that are too low to cause inflammation can induce mutations in epidermal cells. However, this does not exclude a role for ROS from inflammatory cells contributing to skin carcinogenesis, but it may be important for tumour progression [20]. UV-induced inflammation seen in the skin involves the action of many molecules. Of these inflammatory molecules TNFα plays a major role in UV-irradiated inflammation in the skin [15, 19]. TNFα is cleaved from its membrane-bound precursor by the action of the metalloprotease, Tumour Necrosis Factor-α Converting Enzyme (TACE) [21, 22]. While UVB radiation increases the release of TNFα from skin cells, it is not known whether this is due to increased TACE activity and/or expression. However, before TACE is activated it is cleaved from its proform by the action of furin, a proprotein convertase [23, 24]. Furin can cleave other proteases such as matrix metalloproteases (MMPs) [23, 24]. Exposure to UVB radiation also increases MMP activity in skin cells [25]. While furin is expressed in skin cells, the effect UV radiation has on its expression and/or activity and that of the proteases it activates is not fully known. As a result of elevated furin levels in a mutated cell, enhanced TACE activity would see an increase in the secretion of TNFα thereby sustaining a localised inflammatory environment allowing for the development of carcinogenic cells. As furin activates MMP activity, these carcinogenic cells have the potential to become metastatic. This review investigates the role that furin plays in the activation of TACE and MMPs and the effect that this has on a skin cells exposed to UV radiation, as well as that its role in cancer cells which undergoes metastasis, and how an understanding of the role played by this proprotein convertase, may assist in the design of new inhibitors which have therapeutic potential.

2. UV-induced inflammation

High doses of UV can induce inflammation in the skin that results in the appearance of macrophages and other leucocytes [15, 26]. Along with the activation of these cells, many mediators of inflammation are also seen including; prostaglandins [18], nitric oxide (NO) [27] and ROS [12, 17], and cytokines such as interleukin (IL)-1, interferon (IFN)-γ, and TNFα [14, 19, 28, 29]. ROS can cause DNA strand breaks as well as lipid peroxidation, membrane and protein damage [12, 30]. The effects of UV radiation on the levels of these proinflammatory molecules in skin cells are seen in Table 1 [8, 15, 31-33].

Inflammatory mediators such as IL-1, TNFα and IL-6 have been postulated to play a major role in both melanoma [34] and NMSC formation [26, 35, 36]. Male mice are known to be more sensitive to UVB-induced skin carcinogenesis than female mice [4], which is consistent with human studies showing men having a higher incidence of skin cancer than women [20]. Damian *et al*. [20] found that while women developed a larger inflammatory response to UVB radiation, men had lower antioxidant levels in the skin resulting in a higher level of oxidative damage to DNA, and were more sensitive to UV immunosuppression. This suggests that UV-induced immunosuppression and DNA damage plays a greater role in the formation of skin cancers in men compared to women [20]. IL-1α and IL-1β are both induced in keratinocytes exposed to UVB radiation [31, 37]. IL-1α has been shown to enhance the expression and release of TNFα from UVB-irradiated keratinocytes [38, 39], while IL-1β enhances the expression of matrix metalloprotease (MMP)-9 in these irradiated cells [40]. Apart from IL-1β, UVB can stimulate MMP-9 expression in human skin via the induction of Activator protein-1 (AP-1) and NFκB activities [41].

Mediator	Produced By	Function	References
TNFα	Keratinocytes Mast cells Dermal fibroblasts Langerhans cells	Langerhans cell migration, sunburn cell information, stimulates prostaglandin (PG) synthesis, changes in adhesion molecule expression	[15, 31, 33]
IL-1α	Keratinocytes Langerhans cells	Simulates PG synthesis, increases TNFα and IL-6, inhibited by IL-1 receptor antagonist	[15, 33]
IL-1β	Keratinocytes Langerhans cells	Langerhans cell migration	[15, 31, 33]
IL-6	Keratinocytes, Langerhans cells	Fever Severe sunburn	[8, 15, 33]
IL-10	Macrophages Melanocytes	Blocks cytokine production by T cells, macrophages and NK cells Decreases antigen presentation, Increases IL-1 receptor antagonist	[33] [8, 15, 32, 33]
IL-I2p40 (not bioactive)	Keratinocytes, Dendritic cell, Langerhans cells	Decreases Th1 response Decreases antigen presentation	[33]
IFNγ	T cells	Triggers apoptosis T-cell mediated tumour cell destruction	[33]
PGE_2	Keratinocytes, Mast cells	Erythema Decreases antigen presentation Increases IL-4, decreases IL-12	[15, 33]
Histamine	Mast Cells	Increases release of PG Inhibit lymphocyte functions like IL-2 and IFNγ	[8, 15, 33]

Table 1. Effect of UV radiation on the expression of bioactive molecules in human skin cells

UVB radiation can increase cyclo-oxygenase (COX)-2 expression and activity in keratinocytes [20, 28, 42]. High levels of COX-2 activity have been observed in human epithelial skin cancers [43]. Nonsteroidal anti-inflammatory drugs can inhibit COX-2 activity and subsequent PGE formation in the skin, and have been used in the treatment of actinic keratosis (AK) [44], BCC, SCC and melanoma [45]. This suggests a role for COX-2 in the formation of skin cancers, and high levels of activity have been observed in many of these tumours [46].

Upregulation of TNFα is a key early response observed in keratinocytes exposed to UVB radiation [8, 38, 47] and represents an important component of the inflammatory cascade in skin. The expression of TNFα mRNA was enhanced a few hours post-UVB irradiation in both keratinocytes and dermal fibroblasts [38, 47]. IL-1α was shown to stimulate TNFα expression in UVB-irradiated keratinocytes [47] and melanocytes [48]. While Bashir *et al.* [38] observed that TNFα expression in keratinocytes was only induced by UVB irradiation, others have shown that UVA can also induce expression in these cells [49, 50]. This increase in TNFα released by the cells is due to elevated gene transcription [38, 49]. The IL-1α formed in the skin, can in turn, induce mast cells to express inflammatory cytokines (e.g. TNFα and IL-1α), as well as prostaglandins which can enhance the inflammation caused by direct UV exposure on the epidermis [15, 20, 28, 51]. Histamine released from the mast cells can induce vasodilation of the surrounding blood vessels, which assists leucocytes in undergoing diapedesis and entering this region [20, 51]. UVB radiation can induce the synthesis and release of IL-6 and IL-8 from irradiated keratinocytes and fibroblasts [33, 36, 37, 51]. IL-8 assists in the homing of leucocytes, primarily neutrophils, from surrounding blood vessels into the inflamed region, while IL-6 can trigger the activation of monocytes and other infiltrating leucocytes to secrete cytokines and chemokines [51]. Figure 1 shows the complex interaction that occurs between different bioactive molecules in the skin following exposure to UV radiation.

TNFα can induce the expression of adhesion molecules and chemokines in surrounding epithelial cells, resulting in the recruitment of inflammatory leucocytes from surrounding blood vessels via diapedesis [15, 20, 51, 52]. These inflammatory cells in turn can express additional cytokines that form a positive feedback loop that further upregulates TNFα as well as downstream TNF⟨− induced chemokines, cytokines, and other pro-inflammatory mediators in irradiated skin [8, 38, 53]. The effects elicited by these infiltrating inflammatory cells occur some hours following exposure to UV irradiation, thereby prolonging the inflammatory response. UVB radiation also induces inducible nitric oxide synthase (iNOS) activity in dermal endothelial cells, through a TNFα-dependent pathway [38, 54].

TNFα plays a pro-inflammatory role in the skin due to; (a) the direct effects of UV radiation and (b) the indirect effects of inflammatory cells that chemotax to the skin. UV- and inflammatory cell-derived cytokines further enhance TNFα gene transcription in human skin cells [38], which can again increase its production by epidermal cells. In contrast, clustering and internalization of the TNF receptors may lessen the cell's response to TNFα, which may account for why the upregulation of TNFα mRNA is not sustained over time in culture [20]. For further information on the complex interplay of cytokines, chemokines and other mediators in UV-induced inflammation please refer to the following reviews [15, 20, 41, 42].

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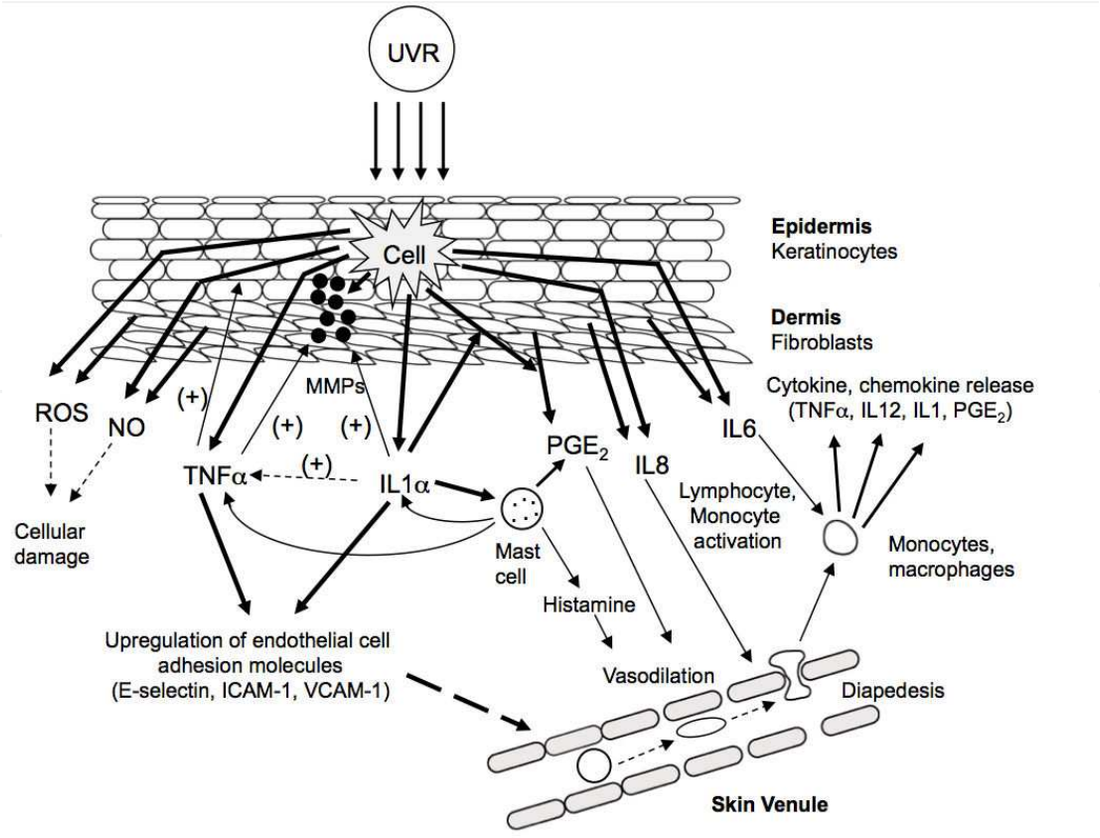

Figure 1. The inflammatory response seen in the skin following exposure to UV radiation. Inflammation can be induced as a direct result of UV exposure on epidermal cells, or due to the release of secreted molecules, which in turn induce the release of inflammatory mediators from the dermis, as well as attracting inflammatory cells from circulation into this region of the skin. The infiltrating monocytes and macrophages, which enter the irradiated skin tissue in turn, secrete mediators that prolong the inflammatory response. See text for details and references.

3. Tumor necrosis factor α

TNFα, is a member of the TNF ligand superfamily, and is a type II transmembrane glycoprotein of 234 amino acids possessing an extracellular carboxy-terminus and a cytoplasmic amino group [53, 55, 56]. It can exist in one of two forms; a 26 kDa membrane-bound form (mTNFα) and a 17 kDa soluble form (sTNFα). sTNFα is cleaved from its membrane bound precursor between Ala^{76} - Val^{77} by the action of the metalloprotease TACE [22, 55].

Numerous cells produce TNFα, including macrophages, leucocytes, dendritic cells, keratinocytes, melanocytes and fibroblasts [8, 47, 57, 58]. It plays a role in apoptosis, cellular proliferation, differentiation, inflammation, tumorigenesis, viral replication, immune response to extracellular stimuli, as well as in local and systemic inflammation [21, 53, 55-57, 59]. Most of the cellular actions described for TNFα correspond to its secreted, mature soluble form. There is increasing evidence that mTNFα is also biologically active [58]. Both forms of TNFα can specifically bind to one of two receptors: TNF-R1 (CD120a receptor), a 55 kDa protein; TNF-R2 (CD120b receptor), a 75 kDa protein [57]. The receptors are both transmembrane glycoproteins, and display a high degree of structural homology and are expressed on most cell types [60].

TNF-R1 is expressed on a wide range of cell types and its signalling mediates cytotoxicity, cell proliferation, antiviral activity and many of the proinflammatory actions of TNFα [58, 61]. TNF-R2 is expressed on a limited range of cells, including leucocytes, endothelial cells, Langerhans cells (LC) and epithelial cells but its actions are less clear [58, 61]. Membrane-bound TNF-R1 and TNF-R2 can be cleaved by TACE to release the soluble forms of these receptors and this process is activated by IL-10 [58]. The soluble forms of TNF-R may act as (a) an antagonist to the surface receptors by competing for sTNFα or (b) an agonist by stabilizing the TNF trimer; therefore maintaining saturating concentrations in extracellular fluids [58, 62].

When TNFα is bound to the TNF-R1 receptor it plays a role in UVB-induced apoptosis in keratinocytes [54, 63]. Transgenic mice deficient for either TNF-R1 and/or TNF-R2 have been shown to be less susceptible to UVB-induced skin tumours than were wild type controls [64]. Through the use of TNF-R1 [65, 66] and TNF-R2 [65] gene-targeted mutant mice, it has been shown that TNF-R1 plays a decisive role in the host's defence against microorganisms, while TNF-R2 plays a role in the induction of tissue necrosis. Through the use of agonist and antagonist antibodies, TNF-RI was shown to be the main mediator of TNFα action in the cell [67].

Dermal injection of TNFα resulted in the accumulation of dendritic cells in draining lymph nodes as well as in impairment of contact hypersensitivity (CHS) in the skin [60, 68]. This suggests that TNFα induces the migration of LC from the skin to the surrounding regional lymph nodes. Streilein and colleagues [69, 70] observed that UVB indirectly induced TNFα, which then caused morphologic and functional changes on LC resulting in the impairment of CHS, suggesting that TNFα plays a role in this process.

Studies using TNF-R1(-) mutant mice have shown that TNFα was not involved in UVB-induced immunosuppression [71]. UVB-induced immunosuppression is implicated in the pathogenesis of skin cancers, and is mediated in part by *cis*-urocanic acid (*cis*-UCA) [72, 73]. *trans*-Urocanic acid, a deamination product of histidine, is a major chromophore present at high concentrations in the stratum corneum [73]. Upon exposure to UV radiation, *trans*-UCA undergoes a photoisomerization to its *cis*-isomer until equilibrium is reached. In humans, this occurs after one minimal erythemal dose of UV radiation, which is the lowest dose that can induce a visibly perceptible erythema [72, 73]. *cis*-UCA does not exert its immunosuppressive effects via TNFα, but through other factors such as prostaglandin E_2 [72]. Amerio *et al*. [71] showed that in TNF-R1 and TNF-R2 double knockout mice, TNFα played a minimal role in UVB-induced immunosuppression and therefore cannot be considered as a major mediator of *cis*-UCA-induced immunosuppression. While TNFα does not play a major role in UV-induced immunosuppression [60, 71] it does play a significant role in UV-induced inflammation [20] as well as in other inflammatory diseases such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus and cancer [21, 38, 46, 74].

4. TACE

TNFα is cleaved from its proform by the action of the metalloprotease TACE [75]. This enzyme is a member of the disintegrin and metalloprotease (ADAM) family of proteases, and is

also known as ADAM 17 [22, 75-77]. ADAM proteases belong to the adamalysin/reprolysin subfamily of the metzincin superfamily, and contain a Zn^{2+}-dependent catalytic domain [75, 77].

TACE was first purified, characterized and cloned in 1997 and is a multi-domain type I transmembrane protein of 824 amino acids in length [22, 76, 78]. While its amino acid sequence shows relatively low homology to other ADAM family members, its structure contains all the domain regions, which are characteristic for this family of metalloproteases [22, 76, 79]. Structurally TACE consists of a signal peptide followed by a pro, catalytic, disintegrin, cysteine-rich, transmembrane and cytoplasmic domain [55, 80]. The catalytic domain contains the zinc-binding consensus motif HEXGHXXGXXHD involved in coordinating Zn^{2+} with His residues and creating the active site of the enzyme [79, 81]. The cysteine-rich domain may play a role in enzyme maturation or substrate recognition [75, 76].

TACE is synthesized as an inactive zymogen, which is subsequently proteolytically processed to the catalytically active form. In order for TACE to be activated its prodomain is removed at the furin cleavage site RVKR (Arg-Val-Lys-Arg) localized between the pro- and the catalytic domain, and is due to the action of a furin-type proprotein convertase [24, 77, 82-84]. In mammalian cells, proTACE is located in the endoplasmic reticulum and the proximal Golgi body whereas the mature form is located both intracellularly and on the cell membrane [83, 85]. TACE maturation is closely linked to the transport of proTACE through the medial Golgi, where upon exit, prodomain removal occurs before the enzyme reaches the cell's surface [77].

Apart from TNFα, TACE cleaves a wide range of molecules including transforming growth factor α (TGFα), amphiregulin, neuregulin, growth hormone receptor, TNF-R1, TNF-R2, L-selectin, amyloid precursor protein and IL-6R [77, 86-89]. TACE-knockout mice are far less efficient at processing TNFα on the cell membrane compared to wild type controls [75, 86]. This suggests that TACE is the main protease responsible for the processing of TNFα in the cell. Although some matrix metalloproteases (MMP) can cleave TNFα, the cleaved products are inactive due to hydrolysis occurring at different sites within the molecule [75, 81, 89].

Some metalloproteases are activated in epidermal cells following UV radiation [90-93]. Piva and co-workers found that there were a number of proteases whose activity was upregulated in UVC- or UVB-irradiated HeLa cells [91-93]. These enzymes included aminopeptidases and a "TGFαase" [91, 92]. On re-evaluation of their data, the TGFαase in questions is most likely TACE, because (a) the later enzyme is known to cleave TGFα among other growth factors [81, 88] and (b) the substrate used in these studies was a nonapeptide based on the N-terminal cleavage site of TGFα [90-93]. In cells undergoing UV-induced apoptosis, the level of cell surface protease activity (aminopeptidase and "TGFαase") was shown to be higher than that seen in viable or necrotic cells [91, 93]. The results of these studies were the first to show that TACE activity was elevated in cells exposed to UV radiation. Recently Skiba *et al*. [29] reported that UVA and UVB irradiation increased TACE mRNA levels in HaCaT cells, with higher induction induced by UVA. The expression patterns for both UVA- and UVB-irradiated cells in general appeared to be constant, although mRNA levels were significantly higher than controls throughout the 48 h post-exposure period [29].

In UV-irradiated HaCaT cells, TACE was responsible for the increased cleavage of EGF family members [28, 94]. Inhibition of TACE by metalloprotease inhibitors reduced the release of these growth factors, resulting in an increase in apoptotic cell death [28, 94]. It appears that TACE mediates a EGF receptor/AKT signalling pathway in these cells that is activated as a result of its cleavage of EGF family members. In HaCaT cells exposed to UVA-radiation TACE mediated EGF receptor activation and cell cycle progression, which suggests that UVA, at non-lethal doses, has the potential to be a skin cancer promoter [28, 94]. TACE has also shown to be overexpressed in some tumours [21, 46, 56], as well in a large number of skin cancer cells lines compared to their non tumorous counterparts [28, 94]. It is also known that members of the EGF family are overexpressed in skin cancers [95], and this could be a mechanism by which skin cancer growth is stimulated by autogenic growth factors. The results of these recent studies suggest that inhibition of TACE following UV radiation may prevent the stimulation of surviving irradiated cells. This has the potential in reducing the incidence of skin cancer that may arise from prolonged sun exposure. It is not clear if the increase in TACE activity seen in UV-irradiated skin cells is due to increased numbers or a higher level of activity. Furin is known to activate TACE [83, 85, 96] as well as matrix metalloproteases (MMP) [97, 98] and may indirectly play a role in this process.

5. Furin

Furin, also known as PACE, is a 94 kDa, type I transmembrane, Ca^{2+}-dependant serine protease. It is a member of the proprotein convertase (PC) family which is related to the bacterial subtisilin enzyme [23, 97-99]. The PC family consists of seven distinct members (furin and PC1-PC7) that vary in regards to their tissue and subcellular distribution as well as enzymatic and biochemical properties [23, 24, 97, 100]. Furin, PACE 4, PC5/6 and PC7/8 are widely expressed in the epidermis whereas PC2 and PC1/3 are limited to neuroendocrine tissues and PC4 is restricted to the testis [23, 24, 98]. The PC enzymes recognize basic motifs, cleaving after paired basic residues (PC2 and PC1/3); or after a canonical Rx (R/K) R (Arg-x-(Arg/Lys)-Arg) motif (furin and PACE4) [24, 97, 98, 100-102]. Both PC7 and furin share cleave similar substrates and the selectivity of which depends on their cellular localization. As their cytosolic domains regulate intracellular trafficking it is likely that the cellular localization of PC7 differs to that for furin [85].

Structurally furin and other PCs consist of a signal peptide followed by pro, catalytic, middle, and cytoplasmic domains, respectively [24]. The signal peptide directs the translocation of the peptide chain to the endoplasmic reticulum and the secretory pathway [82, 97, 103]. The pro-region is cleaved in the endoplasmic reticulum, where it then associates with the catalytic domain and helps to guide the protein through this region to the Golgi apparatus where it becomes catalytically active [97, 103]. The trans-membrane region anchors the enzyme in the membrane of the trans Golgi network (TGN) or on the cell membrane. The cytosolic tail contains the information necessary for furin's sorting to various intracellular compartments [82, 97, 103]. In the epidermis, furin can exist either as: (a) a mature 97 kDa membrane bound enzyme or (b) a smaller 75 kDa form that lacks the transmembrane domain [97]. This suggests that post-translational cleavage at the C-terminus occurs within in the cell [97, 98, 103]. Furin

and other PC family members process inactive precursor proteins to their functional or mature form, and these include growth factor receptors, growth factors, hormones, plasma proteins, and MMPs [23, 24, 97, 98, 103] as seen in Table 2. PC family members play crucial roles in a variety of physiological processes and are involved in the pathology of diseases such as cancer and viral infection [23, 101, 103-106].

Functional group	Substrate	References
Serum proteins	Von Willebrand Factor	[107]
	Coagulation factor IX	[108]
Signalling peptides	Endothelin-1	[103, 109]
Growth factors	TGFβ	[103, 110]
	Vascular endothelial growth factor (VEGF)	[111]
	β-Nerve growth factor	[112]
Membrane proteins	MT1-MMP	[86, 113, 114]
	TACE	[77, 99, 115]
Transmembrane receptors	Notch1 Receptor	[98, 116]
	Insulin growth factor 1 receptor	[117]
Extracellular matrix proteins	N-Cadherin	[113, 118]
	Integrin α-chain subunits	[119]
Viral proteins	Ebola virus glycoprotein	[103, 120]
	Papillomavirus minor capsid protein L2	[121]
Bacterial toxins	Anthrax toxin	[122]
	Clostridium septicum alpha-toxin	[103, 123]

Table 2. Some biological molecules cleaved by furin

As a result of the role furin plays in many disease states, considerable effort has been directed at designing specific inhibitors that may have therapeutic applications. The first furin inhibitors that were synthesised where peptidyl chloromethyl ketones [124]. The next major furin inhibitor that was developed, decanoyl-Arg-Val-Lys-Arg-chloromethylketone (dec-RVKR-cmk, or CMK) was less cytotoxic and is cell permeable and has been used in many experimental studies [86, 106, 125]. It was recently shown to reduce the incidence of skin cancer in transgenic mice by inhibiting PACE4 as well as other PCs [126]. However a limitation of CMK's use is that it is not furin specific, and is also known to inhibit other proprotein convertases [86, 102, 127]. Zhu *et al*. [127] has recently developed an antibody-based single domain nanobody which is a furin specific inhibitor. Through the use of this and other furin-specific inhibitors, it will be possible to delineate the role furin plays in the processing of specific substrates within in the cell. This will help in development of specific inhibitors, which will have therapeutic potential in the treatment of a variety of diseases.

Furin and other PCs have been shown to be involved in the maturation of both TACE and MMP within skin cells. ProTACE is processed by both furin and PC7 to its mature form thereby increasing its proteolytic activity [83, 85]. The maturation of TACE occurs as it transits through

the Golgi compartment where the prodomain was removed by a furin-type proprotein convertase [77, 84, 85]. As increased amounts of mature TACE are detected in furin over-expressing cells, it appears that proTACE is a better substrate for furin than it is for PC7 [85]. A similar observation has been seen in cells overexpressing TACE [58, 83, 99] where furin was shown to be responsible for its cleavage [83, 99]. This finding was confirmed using cell permeable furin inhibitors CMK and PDX in Cos7 cells [83] and keratinocytes [98] where reduced levels of mature TACE were formed.

Furin mRNA, protein and enzyme activity has been observed in human epidermal keratinocytes [29, 98, 111, 128, 129]. Skiba *et al*. [29] found that UVA and UVB radiation immediately increased furin mRNA levels in HaCaT cells. UVB irradiation induced higher levels of furin mRNA expression [29]. The time course for furin mRNA levels in cells irradiated with low dose of UVA or high dose of UVB was similar to that for TNFα, whereas maximal mRNA induction of both genes were detected 8 h post-irradiation [29]. Although UV irradiation does appear to have an effect on furin gene expression, no direct relationship was apparent between TACE and furin mRNA induction. A recent study has shown that following exposure to UVA and UVB, furin levels in HaCaT cells fell with respect to time [49, 129]. However, it was unknown whether this was due to the loss of the pro or mature form of the enzyme. Through its effect on stimulating MMPs, as well as activating TACE and the resultant effect this has on TNFα released by the cell, furin activity has an influence on the inflammation seen in the skin following exposure to UV radiation as seen in Figure 2.

Furin/PC processing of substrates has been shown to also contribute to tumour progression, aggressiveness, metastasis, and angiogenesis [23, 24, 104-106]. Tumour invasion and metastasis represent a multistep process that depends on the activity of many proteins [46, 101, 104, 130]. Proteolytic degradation of the ECM components is a central event of this process. Several classes of proteases, including MMPs, serine proteases and cysteine proteases have been implicated in the tumour cell invasive process [104, 130, 131]. Of these, MMPs appear to be primarily responsible for much of the ECM degradation observed during invasive processes [111, 130, 132-134]. They can contribute to tumour growth not only by degradation of the ECM but by the release of sequestered growth factors or the generation of bioactive fragments VEGF, bFGF or TGFβ, the suppression of tumour cell apoptosis and the destruction of immune-modulating chemokine gradients [131, 132, 135]. Furin also cleaves a number of MMPs from their proform, and activating them as a result [23, 86, 102, 105].

6. MMPs

MMPs belong to the family of zinc-dependent endopeptidases collectively referred to as metzincins. The metzincins can be subdivided into four families: seralysins, astacins, ADAMs/adamalysins, and MMPs [130, 136]. So far to date, 28 members of the MMP family have been identified [130, 135, 136] which are primarily responsible for most of the ECM degradation observed during the invasive processes. MMPs are produced by skin cells (fibroblasts, keratinocytes, melanocytes) as well as macrophages, endothelial cells and mast cells [10, 25, 81, 137].

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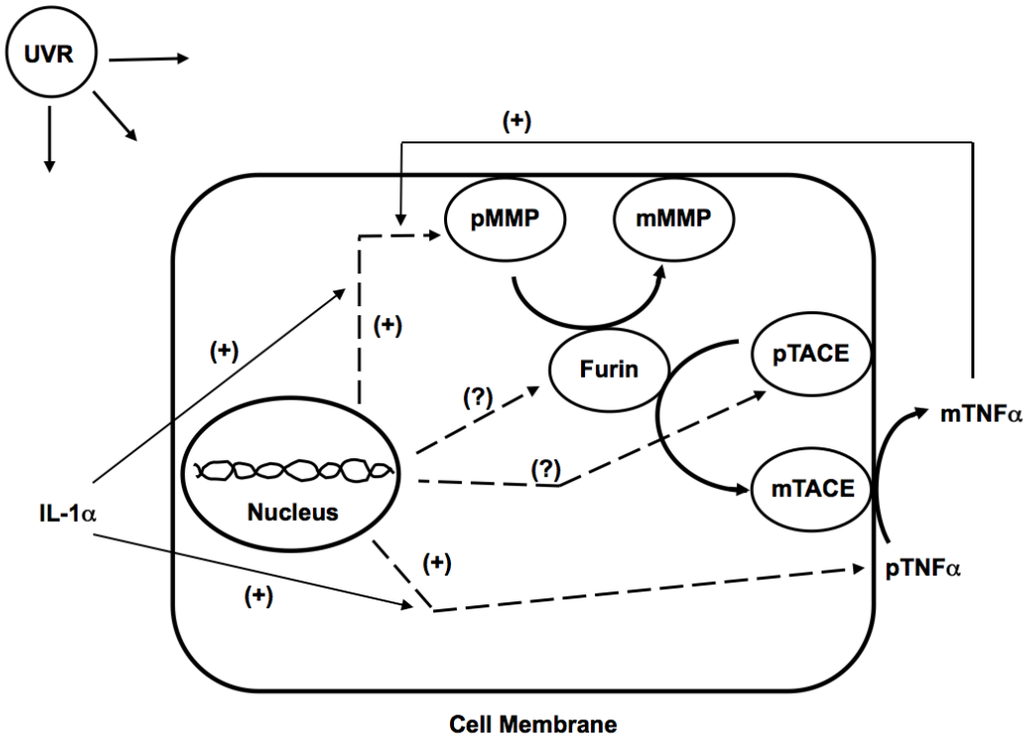

Figure 2. The role furin plays in the maturation of TACE and MMPs in skin cells. Furin cleaves and activates TACE, which in turn can process TNFα from its proform. Keratinocytes secrete TNFα following exposure to UVB radiation, and this is enhanced if IL-1α is present. Furin also cleaves MMPs from their respective proforms, and the expression and activity of these proteases are elevated when the cells have been exposed to UVB radiation, and they are enhanced if either IL-1α (MMP-9) or TNFα (MMP-2) is present. The effect of UVB radiation on the expression of the enzymes and pTNFα in the cell is represented by dashed lines, if it is enhanced it is represented by (+), and if it is unknown (?)

MMPs are also implicated in cell migration, proliferation, and tissue remodelling and thereby may also play a role in growth and development, angiogenesis, and atherosclerosis [138, 139].

Structurally MMPs consist of a signal peptide followed by pro, catalytic, hemopexin and cytoplasmic domains, respectively [130]. MMPs cleave peptides and proteins, which have a myriad of functions that are independent of their proteolytic activity [140]. They have distinct but often overlapping substrate specificities, hence leading to the absence of distinct phenotypes in most genetically-engineered mice with knockdown of specific MMPs [140].

MMPs are generally expressed in very low amounts and their transcription is tightly regulated either positively or negatively by cytokines and growth factors such as IL-1, IL-4, IL-6, TGFβ, or TNFα [130, 135, 141, 142]. Some of these regulatory molecules can be proteolytically activated or inactivated by MMPs (via a feedback loop). MMPs are synthesized as latent proenzymes, which are converted into mature, catalytically active forms in the TGN by PCs [111, 139]. Activation of MMPs following secretion from the cell depends on disruption of the prodomain interaction with the catalytic site, which may occur either by conformational changes or proteolytic removal of the prodomain. With the exception of MMP-2, the mechanism for *in vivo* activation of secreted MMPs is not well understood [135].

In normal skin, MMPs are not constitutively expressed but can be induced temporarily in response to exogenous signals such as UVR [10, 25, 143]. Elevated levels of MMP activity in human skin, as a result of prolonged periods of sun exposure, confirm that it plays a major role in photoageing [10, 25, 28]. Onoue *et al*. [144] suggested that MMP-9 secreted from keratinocytes after UVB irradiation might result from apoptotic events. UV radiation is known to elevate the expression of MMP-1, MMP-3 (stromelysin-1) and MMP-9 in human skin *in vivo* [25]. All three MMPs (1, 3 and 9) can degrade most of the proteins found in the extracellular matrix [25]. MMP-1, which is produced by both dermal fibroblasts and epidermal keratinocytes, cleaves type 1 collagen into specific fragments. These fragments can then be further hydrolysed by MMP-2 and MMP-9 [137, 145]. Steinbrenner *et al*. [137] found that UVA irradiation dose-dependently decreased the steady-state mRNA levels of MMP-2 and MMP-9 and lowered the gelatinolytic activity of both enzymes in cell culture supernatants. Of interest is that *in vivo*, following exposure to UV radiation only keratinocytes express large levels of MMP on the cell membrane [146], but when fibroblasts grown in culture are irradiated they express higher levels of MMP on their plasma membrane [147]. The reasons for the discrepancies between the responses of human skin cells under *in vivo* and *in vitro* conditions are not known.

TNFα has been shown to induce proMMP-2 in human dermal fibroblasts [8], while IL-1α induced proMMP-9 levels in fibroblasts and keratinocytes [148]. In mesenchymal cells TNFα was shown to stimulate MMP-2 activity by activating a proteolytic cascade involving furin and MT1-MMP [139]. It is not known if TNFα activates MMP activity in epidermal cells via a similar mechanism. MMP-9 [144], has been shown to play an important role in the pathophysiologies of many skin conditions such as wound healing [145], and angiogenesis [87]. Activation of pro-MMP2 takes place at the cell surface and involves interactions with active MT1-MMP, which is itself activated through rapid trafficking to the cell surface and proteolytic processing [139]. Maquoi *et al*. [114] demonstrated that furin-inhibitor reduces the level of mature MT1-MMP, which is paralleled by a decrease in pro-MMP-2 activation as well as in cell invasiveness, confirming the furin plays a role in this process. Direct cleavage of proMMP-2 by furin in the TGN has shown to inactivate this matrix metalloprotease [149]. Therefore changes to the level of MMP-2 activity on the surface of the cell can be directly or indirectly regulated by furin either through cleavage in the TGN to reduce activity or indirectly via MT1-MMP, which increases activity. The mechanism by which this is regulated is not clear.

7. Role of furin in skin cancer

Low doses of UV radiation while they are not inflammatory, can cause mutations in skin tissue [9, 19, 30] or in cultured fibroblasts [150]. Constant exposure to UV radiation will not only result in mutations in p53 [150, 151] but in other genes including p16, PTCH, B-Raf, which will result in these cells becoming carcinogenic [6, 152, 153]. Apart from causing these mutations, UV radiation enhances the release of inflammatory molecules (e.g. TNFα, IL-1α, ROS, chemokines) from the skin (see section 2 for details). The result of which is the creation of an environment that allows for these mutated skin cells to become cancerous over time [15, 19, 21, 46, 56]. As a result of increased levels of MMP activity on the cell membrane, either as a

result of UV exposure or other factors, these skin cancer cells may become metastatic as a result of epithelial to mesenchymal transition (EMT) [154].

In the progression of a mutated cell to that of a tumorigenic or metastatic cell, PCs have been shown to cleave a range of precursors of growth factors, their receptors, adhesion molecules, proteases and MMPs. Some of these molecules include cadherins, TGFβ, platelet derived growth factor as well as insulin-like growth factor 1 and its receptor [23, 101, 106, 117, 155]. Tumour progression and metastasis may enhanced by a number of factors such as (a) hypoxia-induced upregulation of furin activity within the solid tumour mass [105], (b) changes in cell adhesion through PC cleavage and activation of integrins and related adhesion molecules [156], (c) furin processing of vascular endothelial growth factor resulting in increased angiogenic activity [157], and (d) furin enhanced expression of MMPs [84, 158].

Furin/PC expression and processing can increase the incidence and severity of the cancer phenotype [104, 111]. Aberrant furin expression has been observed in a number of tumours including those from the breast [159], ovary [160], liver [125], brain [161], skin [111, 132] and from other tissues [23, 128, 162, 163]. Bassi *et al*. [101] observed that PACE4 transgenic mice were more susceptible to epidermal carcinogenesis and tumour progression compared to controls. These transgenic keratinocytes had higher rates of processing of MT1-MMP and MT2-MMP resulting in increased collagen degradation.

MMP-2 (gelatinase A) and MMP-9 (gelatinase B) have been frequently associated with the invasive and metastatic potential of tumour cells [10, 104, 111, 130, 132, 133, 137]. The expression of MMP-2, is regulated independently of MMP-9 [144]. The close correlation observed between MMP-2 activation and metastatic progression in various tumours suggests that it may act as a "master switch" triggering tumour spread [114]. The expression of MMP is low in keratinocytes but elevated in BCC and SCC [49, 164, 165]. In SCC, MMP proteins (1, 2, 3 and MT1-MMP) are expressed both in tumorous and stromal cells [165], while MMP proteins (1, 2, 3 and 9) are observed in BCCs and melanomas [165, 166]. This expression correlates with the progression and the metastatic potentials of these tumours [106, 135, 165, 167]. UVR can participate to the development of skin cancer by the activation of MMPs. Two molecular mechanisms contribute to the UV-induced MMPs expression. First, the activation of cell-surface receptors with subsequent activation of mitogen activated protein kinase (MAPK) cascade that in turn contributes to the transcriptional up-regulation of MMPs [168]. Second, through the expression of pro-inflammatory cytokines, which induce the expression of MMPs [46, 133, 142, 143]. The role of UV in the induction of MMPs is supported by two experimental findings. First, UV-irradiation of SCC cell lines results in an increased secretion of MMPs [49, 132]. Second, UV-induced phosphorylation of extracellular signal-regulated kinase (ERK) and stress kinases precedes the rapid stimulation of MMPs in SCC cells [10]. If there are cells in the skin which become cancerous as a result of DNA damage, some may go onto become metastatic due to increased MMP activity [111]. This increase in levels of activated MMPs on the surface of the cell could be due to either increased expression of proMMP protein and/or increased furin activity. The role furin plays in the development of skin cancer suggests that it could be significant, and as such the development of specific inhibitors may offer a new therapy to treat such tumours.

Recently, Fu *et al*. [106] showed that in transgenic mice overexpressing furin, exposed to chemical carcinogens formed more and larger tumours than did control mice. This suggests that furin enhances skin cancer growth. Of interest was that these tumours were induced by chemical carcinogens and not by UV radiation. While enhanced furin levels were shown to enhance skin tumour development, in studies using cultured melanoma and glioma cells, furin inhibition was shown to reduce the processing of the pro-N-cadherin adhesion molecule, enhancing their migratory and aggressive nature [118]. The result of this study suggests that high furin levels may not enhance the metastasis of some tumours. Huang *et al*. [125] when investigating the expression of furin in hepatocellular carcinoma and surrounding tissue in humans, observed that if this ratio was >3.5 this resulted in higher patient survival rates compared to those who had ratios <3.5. This suggests that furin may play a dual role in cancer development, though the exact nature of which is not clear at this stage. Further study on this is warranted, and may result in a better understanding of its role in cancer development, and from which it may be possible to develop specific furin inhibitors which could be used clinically to treat these tumours.

8. Conclusion

While it has been shown that UVA and UVB radiation cause different effects on the immune response this could be related to the activity of cell surface metalloproteases found on skin cells. Although the effect of TNFα in UV-induced inflammation has been well documented, little is known if the changes in TACE activity are due to increased protein levels or changes in enzyme activity. The inflammatory environment, seen in the skin, following exposure to UV radiation is known to stimulate the development of mutated cells which possess DNA damage caused directly by UV radiation or indirectly through the generation of ROS. Apart from processing TNFα, TACE also cleaves EGF family members, which would stimulate the growth of these mutated cells, which over time may become cancerous. As TNFα is a powerful inflammatory cytokine, considerable research has been under taken to develop specific TACE inhibitors [55, 56, 80]. Such inhibitors may play an important role in preventing the development of UV-induced skin cancers. An increased knowledge of the roles played by metalloproteases in tumour progression, combined with the use of more selective inhibitors, could lead to effective use of these compounds in cancer therapies [55].

Similar to that of TACE, MMPs are also activated by UV radiation and also play a crucial role in skin tumour cell development and metastasis. Furin and other PCs have been shown to play an important role in activating both TACE and many MMPs in skin cells. Whereas the overexpression and activity of furin exacerbates the cancer phenotype, inhibition of its activity decreases or nullifies its effects, and thus, the development and use of specific inhibitors may also be a viable route to cancer therapy [23, 86, 102, 127].

It is known that UV induces furin mRNA in skin cells, though protein levels do not appear to change with respect to time, which suggests a rapid turnover of the enzyme. Further study is needed on how UV radiation activates furin, TACE and MMPs in skin cells. These proteases

play an important role in the changes observed in those epidermal cells exposed to UV radiation. The development of specific furin inhibitors has the potential to reduce the carcinogenic effects of sunlight by preventing the activation of TACE and MMPs and their subsequent downstream effects. Such compounds may have the potential to offer new therapies both in the prevention and treatment of skin cancer.

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