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Review

The Elastin Connection and Melanoma Progression

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Abstract. *Matrikines, i.e. matrix fragments with cytokine-like properties, have been ascribed a major role in regulating tumour progression. The invasive front of melanoma is characterised by intense fragmentation of dermal elastic fibres. Elastase-mediated elastolysis liberates elastin fragments, i.e. elastokines, that stimulate several aspects of melanoma progression such as to enhance melanoma cell invasion through type I collagen or increase angiogenesis. Induced-membrane-type1 metalloprotease (MT1-MMP) expression following elastin receptor (S-Gal) occupancy by elastokines is responsible for those biological activities. Several matrix-derived peptides with a GXXPG consensus sequence adopting a type VIII β-turn conformation were as potent as elastokines in promoting angiogenesis in a Matrigel assay, and galectin-3 also contains several similar repeats within its N-terminal domain. We propose that S-Gal might constitute a novel therapeutic target for controlling melanoma progression.*

Cutaneous melanoma is mainly characterised by its strong tendency to form metastases (1, 2); it may develop either *de novo* from melanocytes or may originate from precursor lesions such as dysplastic or congenital nevi (3). In recent years, the variability of the tumour microenvironment has been ascribed a major function in cancer progression (4, 5). This notion of plasticity applies to cells from tumour stroma, to cytokines, chemokines or growth factors expressed by either neoplastic or non neoplastic cells, but also to matrix constituents (5-8). The invasive front of melanoma is an area of intense proteolysis that locally transconforms matrix macromolecules revealing hidden cues within multimacromolecular complexes such as basement membranes, collagen or elastic fibres. Importantly, those matricryptic sites display biological activities distinct from their original matrix counterparts (8, 9). Sustained proteolysis further liberates these cryptic fragments, which consequently will modulate the phenotype of neighbouring cancer or stromal cells. The fragments, thus behaving as cytokine-like polypeptides, were designated as matrikines (10). Proteolytic degradation of any matrix constituent can give rise to the formation of matrikines and, strikingly, distinct generated fragments from one molecule might influence tumour progression in an opposite way. The type IV collagen molecule is perhaps the best illustration of such a paradox. The structural network of type IV collagen, the main component of the basement membrane, is constituted from the association of 3 distinct α chains (11). Within its triple helical domain, several peptide sequences distributed along the α_1 (IV) chain, *i.e.* CB3, α_1 (IV) 531-543 regions or the C-terminal α_1 (IV) sequence encompassing residues 1263-1277, were described as triggering melanoma cell adhesion, activation or motility (12, 13). On the contrary, matrikines from the NC1 domains of type IV collagen, α_1 (IV), α_2 (IV) or α_3 (IV), exhibit antimelanoma tumour growth and antiangiogenic properties and were named arresten, canstatin and tumstatin, respectively (8, 14). Such particularity also holds true for laminins and for other basement membrane components (14). However, it needs to be emphasised that the instructional signals for cells might be different depending upon the mode of presentation of the matrikines to cells, thus reflecting the importance of the conformational dependency of this class of compounds (7, 8). Therefore, the ability of a melanoma cell to cross the dermo-epidermal junction will largely depend on the balance between the levels of these distinct matrikines. To our knowledge, such a contribution of mixed-type matrikines to the fate of a melanoma cell has not been addressed.

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Table I. *Stimulation of matrix metalloproteinase (MMP) and inhibitor (TIMP) expression by elastin-derived peptides (kE : kappa-elastin).*

	Melanoma cells (M3DA): kE coating (50 μg/cm^2)	Human skin fibroblasts (kE=50 μg/ml)	Human dermal endothelial cells (kE=50 μg/ml)
MMP-1	1.0	6.0* (Western) 6.4** (ARNm)	1.0
MMP-2	2.0 (av.)***	1.7*** 1.00**	2.7*** 1.7**
MMP-3	Not determined	>6.0*;**	Not determined
MMP-9	Not determined	1.0	Not detected
MT1MMP	>3.0*	1.8**	1.9***
TIMP-1	~1.5***	>3.0***	1.0
TIMP-2	>3.0***	2.6**	1.0
αVβ3	1.0	Not determined	1.0

Data refer to fold increase: *as determined on immunological basis (Western, Elisa); **as determined by Northern blot or RT-PCR analyses; ***as determined by gelatin zymography.

Initial studies by Breslow (15) indicated that the incidence of recurrent metastases increased significantly as melanoma reached the sub-epidermal and dermal layers. Implicitly, it suggested that the major structural elements of these layers, namely collagen and elastic fibres, could facilitate melanoma progression. We and others have recently pinpointed the importance of a 3-dimensional array of type I collagen fibres in providing an invasive character to melanoma cells and unravelled part of the mechanisms involved (16-18). Here, we aimed to depict the contribution of elastin in melanoma progression, also focusing on the particular importance of the elastin receptor (S-Gal) as a potential pharmacological target.

Alteration of human skin elastic fibres in patients with melanoma

Elastic fibres give human skin its resilience and long range deformability and passive recoil (19). The macromolecular composition of elastic fibres varies throughout the skin lifespan, with decreasing amounts of microfibrils to amorphous cross-linked elastin from epidermis to dermis (20). The reticular dermis comprises thick bundles of elastic fibres which run parallel to the dermo-epidermal junction; these fibres are extended within the papillary dermis by a continuous perpendicular array of elaunin fibres that finally form a thinner oxytalan fibre cascade penetrating within the dermo-epidermal junction (20). Elastic fibres are characterised by their extreme molecular complexity and the precise function of molecules associated with microfibrils, located at the elastin-microfibril interface or involved directly in elastogenesis, is far from being totally elucidated (21). Decades ago, elastic fibre formation was shown to involve the deposition of tropoelastin on to a preformed mantle of microfibrils (22). Recent available evidence indicated that fibrillin-1 and MAGP-1 constituted the main scaffold for vectorial cross-linked elastin formation (23), although small leucine-rich proteoglycans such as decorin and biglycan might also participate in the formation of such composite biomaterial (24). Thus, elastic fibres need to be considered, in the same way as basement membranes, as a complex structural element which, on proteolysis, will lead to the formation of matrikines exhibiting distinct biological activities. The presence of matricryptic sites or formation of matrikines within elastin-associated molecules has not been considered, although decorin was found to initiate a sustained down-regulation of the EGF receptor, a mechanism which might impart its beneficial influence on tumour growth *in vivo* (24, 25). The unmasking of cryptic sites or/and liberation of matrikines, if any, from amorphous elastin might be impeded by at least two mechanisms. First, the microfibril cover might offer elastin protection against proteolysis; also, the extreme hydrophobicity and cross-linked character of elastin confer to the polymer a high resistance to protease degradation (26). Nevertheless, elastin fragments have been detected in the circulation (27); *in vivo*, elastin can be degraded by potent serine proteases sequestered in the azurophilic granules of polymorphonuclear neutrophils, *i.e.* elastase, cathepsin G and proteinase-3 (26). Elastolysis might also involve cysteine proteases such as cathepsins L and K, and several members of the matrix metalloproteinase (MMP) family, with a central role in the metastatic process (28-30). Among that clan, gelatinase A (MMP-2), matrilysin (MMP-7), gelatinase B (MMP-9), macrophage elastase (MMP-12) and membrane-type1 metalloprotease (MT1-MMP) were described as displaying elastin-degrading capacity (31). A number of investigations have delineated the critical importance of MMP-2 and MT1-MMP in melanoma progression (32-34). For instance, a correlation between high MMP-2 expression and low survival rate was found, which was independent of the Clark and Breslow microstage (35). On the contrary, MMP-9 expression was detected only during the horizontal growth phase of the tumour, suggesting that this protease contributed to early events in melanoma progression (36). Intense fragmentation of elastic fibres was evidenced in the invasive front of melanoma *in vivo*, most importantly in tumours with a high Breslow index (37). These observations corroborated the data from a recent comprehensive study including 108 patients with a follow-up period of up to 15 years, where the complete absence of elastic fibres in the melanoma's depth was associated with an adverse prognosis (38).

Triggering of cell activation following elastin receptor (S-Gal) occupancy by elastin fragments i.e. elastokines. The existence of an elastin receptor was earlier suspected from a series of

Table II. *Relationships between induced MMP-1 production by fibroblasts and CD spectra of elastin-derived peptides.*

	$[\theta]_r$	MMP-1
Elastin peptides	(deg.cm^{2}dmole^{-1}x10^{-3})	(ng/h/10^5 fibroblasts)
VGVAPG	–11.5	0.48 (0.02)
$(VGVAPG)_2$	–14.9	0.98 (0.18)
$(VGVAPG)_3$	–16.2	1.42 (0.3)
kE	Not det	1.8 (0.3)

θ refers to mean residue molar ellipticity (200 nm); Not det: not determined.

experiments revealing that elastin fragments from acid or alkaline degradation of insoluble elastin or elastase digests could induce cell chemotaxis (39), proliferation (40) and could modulate ion fluxes (41, 42). Importantly, tropoelastin, but also amorphous elastin, were similarly shown to bind to several cell types including melanoma cells (43-45), suggesting that the recognized epitope was not cryptic either in the isolated precursor molecule, or in its mature counterpart. However, either S-Gal (see below) during elastogenesis or associated microfibrils in the mature elastic fibre could hide the cell-recognizing sequence. An elastin-binding protein (EBP) was further isolated from the plasma membrane of several cell types (46), which proved to be identical to an enzymatically-inactive, alternatively-spliced variant of β-galactosidase (S-Gal) (47). Such splicing leads to an enzymatically-inactive protein while retaining its galactosugar-binding domain; EBP behaves as a galectin, which initially acts as a chaperone molecule for tropoelastin, impeding its intracellular degradation and coacervation. In its route to plasma membranes, S-Gal is associated with a lysosomal protective protein (PP), displaying an S-Gal protective function as well as a catalytic activity overlapping that of cathepsin A (E.C.3.2.1.23) (48). This complex further comprises N-acetyl α neuraminidase (Nam; EC 3.2.1.18), whose activity depends on its association with PP (49). Other constituents, like galectin-3 might be part of this miniproteome. Since tropoelastin contains several S-Gal binding motifs (Table I), several PP-Nam dimers could bind to one tropoelastin molecule. Tropoelastin dissociation from S-Gal was found to involve galacto-pyrosides containing pyranosides, whose excess however, as observed in patients with Hurler's disease, can impair elastic fibre assembly (50). S-Gal, residing on the cell surface, could further act as a receptor for defined elastin motifs; such an elastin receptor notion was first introduced by Robert and colleagues, who demonstrated that elastin-derived peptides (EDPs) could stimulate calcium fluxes in different cell types (51). Since then, efforts have been made by several investigators to elucidate the signalling pathway triggered by S-Gal occupancy by elastin-derived peptides. The data obtained are rather confusing but, as a whole, it appears that, for many cell types, a specific ERK 1/2 activation pathway is mainly induced following binding of elastin peptides to its S-Gal receptor (52-54). Upstream activating elements might include Ras-dependent and Ras-independent pathways; in fibroblasts, S-Gal occupancy by EDP was found to promote a novel Ras-independent ERK 1/2 activation mechanism in which the class IB p110γ PI3K/Raf-1/MEK1/2 and PKA/B-raf/MEK1/2 cooperate to achieve sustained ERK 1/2 activation (53). On the contrary, in aorta smooth muscle cells, EDPs triggered a Ras-Raf-MEK 1/2 – ERK 1/2 cascade (54). It needs to be delineated that all EDP-mediated biological effects so far reported involved activation of G proteins and opening of L-type calcium channels (26, 41, 42, 51). The molecular mechanism involved in transducing the message from the elastin receptor system comprising S-Gal, PP and Nam, to G proteins is still an unresolved issue. Possibly, the role of Nam could be envisaged since its cytoplasmic tail contains a recognition sequence for the src family kinase (49); also neu-1 encoded sialidase was involved in cellular signalling during the immune response (55). Further, and of major importance, the transactivation of tyrosine kinase receptors was recently reported to represent a general aspect of GPCR signalling (56, 57). Indeed, transactivation of PDGFr has been observed in SMCs following EDPs binding to S-Gal (54). Probably, the elastin-driven transactivated receptor, *i.e.* EGFr, PDGFr, VEGFr, HGFr, IGF1r..., that supported GPCR signalling can vary among cell types but, since increased Ca^{2+} concentration was reported to be a key mediator in EGFr transactivation by various ligands, it might be hypothesised that such a mechanism represents one aspect of elastin signalling.

Modulation of matrix metalloproteinases (MMPs) expression and activation by elastokines

Taking into account the previously reported correlation between the presence of S-Gal on melanoma cell lines and their propensity to metastasize to the lung (41), as well as the intense elastolysis observed at the invasive front of melanoma (37), we first investigated the EDP's potential to enhance type I collagen invasion of S-Gal-expressing melanoma cell lines (37). To that end, transwell assays were performed in which melanoma cells were embedded within a type I collagen 3-dimensional matrix and cell invasion further monitored in the presence or absence of EDPs. In such a system, EDPs binding to S-Gal was found to significantly enhance type I collagen invasion by melanoma cells (37). Neoangiogenesis appears as an essential determinant in cancer progression and several studies indicated that it might represent an independent prognostic

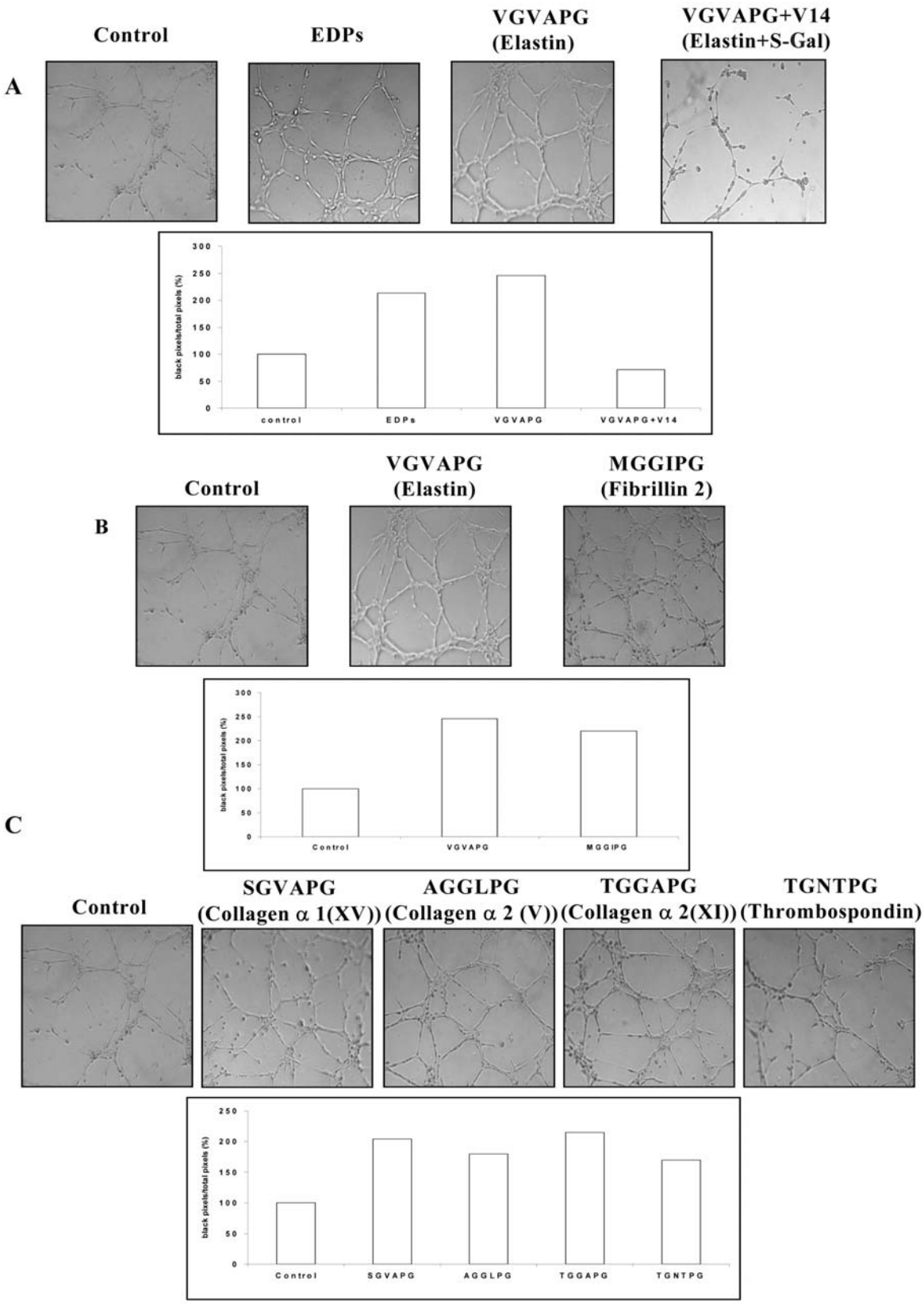
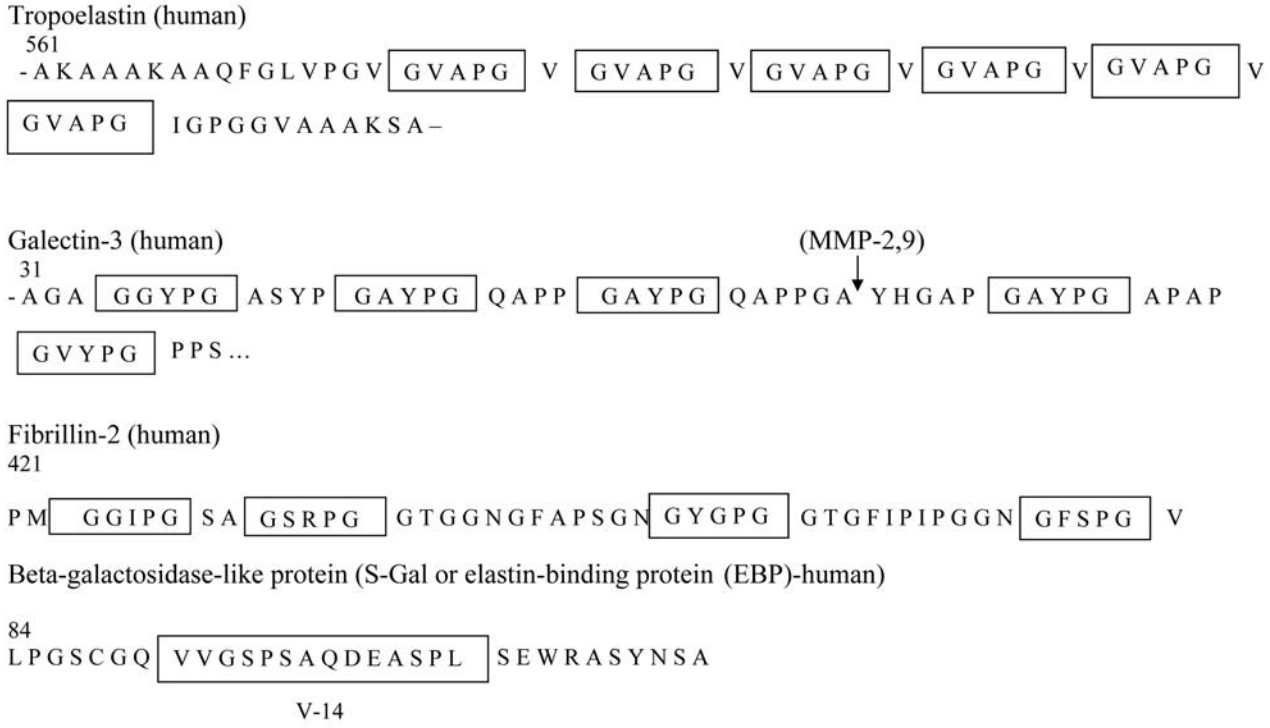


Figure 1. *Influence of several matrikines with GXXPG consensus sequence on in vitro angiogenesis.(Human microvascular endothelial cells: HMEC-1 were used in the Matrigel assay). Pseudotubes formation was quantified as described (60).*

Table III. *GXXPG-containing domains in human tropoelastin, galectin-3 and fibrillin-2. S-Gal specific sequence, from alternative splicing, together with elastin reactive domain (14 amino acids) is also indicated.*



variable in vertical growth phase melanomas (58, 59). EDPs were as potent as VEGF in promoting an angiogenic phenotype, either *in vivo* using the chick chorio-allantoic membrane (CAM) assay or *ex vivo* by following pseudotube formation in matrigel (60). Current evidence indicates that melanoma cells negotiate skin barriers, *i.e.* dermo-epidermal junction, epidermis and dermis, by mobilizing a series of proteolytic cascades which, somehow, appear redundant since individual enzymes lack any specificity towards a particular matrix constituent. Considering the well-documented importance of MMPs in tumour progression, the influence of EDPs on the production of MMPs and their inhibitors (TIMPs) by melanoma cells and their stromal counterparts, *i.e.* skin microvascular endothelial cells and fibroblasts, was analysed (Table II). The data deserve a series of considerations: i) Whatever cell types, MMP-9 expression was not affected by EDPs. ii) For fibroblasts and melanoma cells, a high concentration of peptides are necessary (>10 μg/ml) to induce a response and the presentation of the agonist (coating for melanoma cells) appears to be an important parameter. It suggests that those elastin fragments exerted only a local MMP regulatory role on the corresponding cell type. This was in accordance with the close association between melanoma cells or/and fibroblast and altered elastic fibres with mottled appearance, as revealed ultrastructurally from the skin of patients with advanced melanoma (37).

On the contrary, EDP-mediated MT1-MMP/MMP-2 up-regulation in endothelial cells was observed for a concentration of peptides as low as 10 ng/ml, a level previously reported to also increase nuclear and cytoplasmic free calcium concentrations in umbilical venous endothelial cells (61). Depending upon the physiopathological conditions, circulating EDPs levels range from 10^{-2} to 10^{-6} mg/ml, indicating that an active concentration of EDPs on neoangiogenesis might certainly reach endothelial cells from initial melanoma or fibroblast-catalyzed elastolysis. iii) For any cell type, S-Gal activation was found to enhance MT1-MMP expression in a significant manner. MT1-MMP belongs to the plasma membrane-tethered MMP subfamily (8, 9); its expression is negligible within nevi but is increased significantly in the invasive front of tumours, particularly in melanoma with a Breslow index greater than 5 mm (18). This type I transmembrane MMP is converted intracellularly into a partially activated form by furin convertase and autoproteolysis further catalyses the formation of a fully active enzyme. Enzyme oligomerization, through hemopexin or/and cytoplasmic domain interactions, was reported to play a crucial role in concentrating active

enzyme at the front of migrating cells. Such a mechanism is equally important in directing pro MMP-2 activation (62, 63). Importantly, MT1-MMP and MMP-2 both display collagenolytic and elastinolytic activities, so that intense dermal destruction might take place at those protrusions formed in invading endothelial and melanoma cells. Besides, MT1-MMP proved to shed CD44 and to activate αVβ3 through αV cleavage, thus promoting the directional migration of activated cells (62, 63). Furthermore, its importance in facilitating the penetration of cross-linked type I collagen in a rich antiprotease environment by fibroblasts from tumours and endothelial cells was recently evidenced (64, 65). In that respect, it has to be considered that the TIMP-2 level precisely controls MT1-MMP activity as well as MMP-2 activation and activity (62, 63). Culturing melanoma cells within a 3-dimensional type I collagen matrix was found to down-regulate TIMP-2 production, an effect which was exacerbated in the presence of elastin or its fragments (37). It might involve increased inhibitor endocytosis (17), although the precise molecular mechanism underlying this phenomenon remains undefined.

Relationship between elastin, S-Gal and galectin-3

Aiming at defining the structural requirements of EDPs in eliciting MMP up-regulation, peptides corresponding to circular permutation of the VGVAPG motif were used. It was established that those peptides maintaining a GXXPG sequence, adopting a type VIII β-turn conformation, were all active as MMP inducers in fibroblasts and the HT 1080 fibrosarcoma cell line (66). Such a consensus sequence is recovered in other matrix macromolecules and corresponding peptides were as potent as the VGVAPG elastokine in eliciting an angiogenic response in the Matrigel assay (see Figure 1). Interestingly, the basal formation of pseudotubes could be partly inhibited using V14 peptide (a peptide corresponding to the sequence of elastin within S-Gal) as an antagonist, suggesting that the LGTIPG- containing β1 chain of laminin-1 can directly bind to S-Gal and might participate in angiogenesis.

In most instances, matrikines are presented as repeats within their parent macromolecule. That holds true for tenascin-C, which contains multiple EGF-like tandem repeats (67), but also for tropoelastin, that possesses up to 7 contiguous GXXPG motifs (63). Strikingly, MMP up-regulation was directly related to the number of VGVAPG repeats (Table II), a finding probably involving the stabilization of the active conformation in a more rigid constraint.

Interestingly, GXXPG repeats are also encountered in fibrillin-2, another elastic fibre component, and in galectin-3 (Table III). Galectin-3, originally identified as the macrophage differentiation marker (Mac-2), belongs to the galactoside-binding lectin family including S-Gal, whose members share common sugar-binding specificity although presenting structural diversity. In most instances, galectin-3 expression is correlated with aggressiveness and the acquisition of a metastatic phenotype in several tumour types including melanoma (68). Galectin-3 interacts with a number of intracellular proteins, such as oncogenic Ras proteins, promoting the activation of Raf-1 and PI3 kinase and also affects cell cycle regulators (68, 69). Similarly to S-Gal, galectin-3 was found to bind intracellularly to tropoelastin but also to insoluble elastin, an association that can be impaired in the presence of lactose (70, 45). More intriguing is the presence of GXXPG clusters within the Pro- and Gly-rich short stretches fused onto the carbohydrate recognition domain of galectin-3 (68, 69). It raises the possibility that galectin-3 could, similarly to tropoelastin, interact with S-Gal. Whether galectin-3 intervenes in elastogenesis or in cell activation through S-Gal binding is still a matter of speculation. Interestingly, however, MMP-2 as well as MMP-9 were found to cleave galectin-3 at Ala_{62}-Tyr_{63} (71), suggesting that small peptides containing three repeats of GXXPG motifs might be liberated in the tumour vicinity (see Table III).

Conclusion

Matrikines originate from proteolytic degradation of extracellular matrix macromolecules. However, in several instances, the precise specificity of any given protease towards a particular matrix constituent, as well as the corresponding peptide bonds cleaved in living tissues, are still not defined. Therefore, a degrading approach (72) appears to be required when aiming to determine the contribution of this family of bioactive peptides to cancer biology. Nevertheless, the presence of matrikines such as endostatin and VGVAPG-elastin-derived peptides have been evidenced in the circulation (14), suggesting that they might play a role under physiopathological circumstances. Also, elastolysis by human neutrophil elastase (HNE) led to the release of fragments exhibiting bioactivity similar to the organo-alkaline digest of insoluble elastin or tropoelastin (63). It is suggested that this serine elastase solubilized elastin, while leaving intact GXXPG elastin motifs, consistent with the preferential cleavage site specificity of this enzyme towards insoluble elastin (62, 63). In addition, bioactive elastokines were generated following moderate HNE-mediated elastolysis (<10% of insoluble elastin degradation), thus favouring the physiopathological importance of this mechanism (63). Obviously that cannot be extended to other elastolytic proteases which, instead, could cleave elastin within GXXPG sequences, thus displaying, in that respect, a potential beneficial influence on melanoma progression.

As here stated, elastokine production would facilitate melanoma progression in those cancer cells expressing S-Gal elastin receptor. Furthermore, since elastokines have potent chemotactic activity for those melanoma cells (45, 73), elastin degradation at a distant organ such as the lung might contribute to metastasis.

As mentioned previously, proteolysis of any matrix macromolecule might generate matrikines with distinct biological activity. Recently, the C-terminal 16 residue of tropoelastin, encompassing the region encoded by exon 36, was shown to bind to integrin $\alpha_v\beta_3$ (74). The ability of such a domain to behave as a matrikine, with properties different from GXXPG (elastokines), might be considered.

S-Gal, therefore, appears to constitute a novel target for impairing cancer progression in elastin-rich tissue such as skin, lung and breast. Its involvement might even be extended to other cancer types, providing that galectin-3 repeats behave similarly to elastokines. An S-Gal-directed siRNA approach might be attempted to control the activity of those fragments. Alternatively, antagonist peptides from the V_{14} S-Gal sequence could be used as pharmacological agents; since such a sequence was found to bind to elastin but also to laminin-I with high affinity, it might confer to those molecules, if appropriately derivatized to also act as a protease inhibitor, protection against proteolysis.

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