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Control of Tumor Progression by Extracellular Matrix Molecule Fragments, the Matrikines

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Abstract

Tumor microenvironment is a complex system composed of a largely altered Extracellular Matrix (ECM) with different cell types that determine tumor progression. Upon the influence of hypoxia, tumor cells secrete cytokines that activate stromal cells to produce proteases and angiogenic factors. The proteases degrade the stromal ECM and participate in the release of various ECM fragments, named matrikines or matricryptins, capable to control tumor invasion and metastasis dissemination. The putative targets of the matrikine action are the proliferation and invasive properties of tumor or inflammatory cells, and the angiogenic and lymphangiogenic responses. In the present review, we will describe pro-tumorigenic effects triggered by soluble elastin or Elastin-Derived Peptides (EDPs), as well as the anti-tumorigenic or anti-angiogenic activities the matrikines derived from basement membrane associated collagens and several proteoglycans such as perlecan or lumican. Matrikines constitute a new family of potent anticancer agents that could be used under various therapeutic strategies: i) induction of their overexpression by cancer cells or by the host, ii) use of recombinant proteins or synthetic peptides or structural analogs designed from the structure of the active sequences. Matrikines could be used in combination with conventional chemotherapy or radiotherapy to limit tumor progression.

Keywords: Tumor microenvironment; Extracellular matrix; Matricryptins; Control of tumor progression

Introduction

Tumor progression is a multigenic and multistep process that involves many interactions between tumor cells and the surrounding microenvironnement. The latter consists of a highly modified extracellular matrix and cells (fibroblasts, endothelial cells, immune cells, etc.). Tumor microenvironment appears to be critical for the future of cell signaling cascades. Tumor cells and stromal cells exert cross-talks influencing behavior of each other. The cellular cross-talks trigger cell activation and the formation of a microenvironment that determines the proliferation of tumor cells, their invasive properties and therefore their metastatic potential [1]. These interactions also lead the tumor cells to secrete proteases that degrade ECM macromolecules and release ECM-stored growth factors. In particular, fibroblasts can be activated by growth factors such as TGFβ, chemokines as SDF1 or even proteases (MMP-2, -9 or MMP-14), that degrade ECM macromolecules, triggering an increased cell proliferation and ECM protein synthesis, such as type I collagen, tenascin C or fibronectin. These activated fibroblasts share phenotypic morphology with myofibroblasts, mainly the expression of α smooth muscle actin, and are named CAF (cancer associated fibroblasts) [2,3]

Fibroblasts activated by the tumor microenvironment are largely responsible for tumor-associated changes in ECM. These changes include upregulated ECM synthesis, posttranslational modifications of ECM and extensive remodeling of ECM macromolecules by MMPs. The altered ECM then influences tumor progression by architectural and signaling interactions [4]. Using mass spectrometric analysis, it was demonstrated in cancer xenograft models that both tumor cells and stromal cells contribute to the secretion of proteins making up the tumor ECM. Several proteins, such as periostin, not secreted in normal skin, become expressed by tumor cells and the stroma during tumor progression and metastasis [5]. In addition, the proteins secreted by the tumor cells may vary with their metastatic potential. The matrix components secreted by stromal cells also change in response to the metastatic potential of the tumor cells, indicating significant cross-talk between tumor and stromal cells [5]. The interstitial matrix is a major ECM, comprising fibrillar collagens, fibronectin and proteoglycans. It provides a structural bed to the cells and binds growth factors or cytokines. The synthesis and remodeling of the fibrillar type I collagen increases in tumors and is required for angiogenesis. The architecture of type I collagen also changes, with a progressive modification of fibers orientation, promoting cell migration along the collagen fibers, or by enhancing integrin signaling [4].

In addition to the microenvironment architectural structure changes, tumor angiogenesis constitutes another important mechanism which plays a crucial role in tumor progression. When the tumor reaches a critical size of a few millimeters in diameter, hypoxia, acidosis and nutrient deprivation lead to an "angiogenic switch" characterized by alteration in gene, microRNA [6], and growth factor expression and secretion. Hypoxia is the main endogenous stimulus of tumor angiogenesis, and VEGF is one of its target. Endothelial cells are activated by angiogenic growth factors, in particular VEGF. They acquire a proliferative capacity and synthesize proteases that degrade the pre-existing basement membrane and allow them to migrate within the tumor.

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In tumor progression, the cell–matrix interactions can be controlled by the ECM macromolecules either by intact ECM molecules or through some of their constitutive domains, released by limited proteolysis or by exposing cryptic sites. These domains, named matrikines, are protein domains exerting a biological activity [7]. The term of matricryptin was also proposed when the protein domain has a biological activity not carried by the native protein and unmasked by proteolysis [8]. Various matrikines have been described in the literature as endogenous inhibitors of angiogenesis [9]. Some of them derive from elastin or laminins and exert pro-angiogenic or pro-tumor activities, whereas others exert both anti-angiogenic and anti-tumorigenic properties. In the present review, we will describe pro-tumorigenic effects triggered by soluble elastin or Elastin Derived Peptides (EDPs), as well as the anti-tumorigenic or anti-angiogenic activities the matrikines derived from basement membrane associated collagens and several proteoglycans such as perlecan or lumican.

Pro-Tumor Matrikines

Elastin

Elastin, an insoluble ECM macromolecule matured from tropoelastin, constitutes the main amorphous component of elastic fibers, responsible for the tissue elastic properties [10]. Elastin turn-over is almost absent in normal physiological conditions explaining the half-life of elastin of about 74 years [11]. However, large amount of elastin peptides are produced during several pathological and physiopathological processes [12-14]. The elastokine word has been proposed to define bioactive peptides derived from elastin by proteolytic cleavage [15]. MMPs, such as MMP-2, MMP-9, MMP-7 and the macrophage metalloelastase MMP-12 are efficient elastases expressed in diverse pathologies associated to strong elastin degradation, as well as leukocyte elastase, cathepsin G and L [16-18]. K-elastin corresponds to a heterogeneous mixture of EDPs obtained by potassic solubilisation of elastin [19]. These peptides exert a variety of bioactivities in normal and tumor cells. Some of them contain the GXXPG motif that enables them to bind on cell surface to the elastin binding protein but also to αVβ3 integrin and galectin-3 [20-22]. All the EDPs in which the central residues are not glycine, adopt a canonical (or very close to) type VIII β-turn structure on the GXXP sequence, crucial for biological activity [23]. Any residue located before the GXXP motif (XGXXP) increases the β-turn stabilization, whereas the residue located after GXXP (GXXPX) has no significant structural effect [24].

Tropoelastin and EDPs promote proliferation of human tumor cells as described on astrocytoma cell lines [25]. EDP treatment increases invasive properties by upregulating the expression of MMP-1 and MMP-2 in human fibrosarcoma HT-1080 cells; the effect was reproduced by the synthetic VGVAPG peptide [23,26,27].When bound to S-Gal elastin receptor, EDPs enhance melanoma cell invasion in a three-dimensional type I collagen matrix by upregulating MMP-2 activation [28]. They also induce NF-κB activation, leading to IL-1β upregulation in invasive melanoma cells [29]. *In vivo*, the increased levels of EDPs facilitate the invasion of melanoma cells by exerting chemotactic effects [21]. The increased migration of tumor cells may be explained by an increase in the expression of CXCR-4 and CXCL-12 chemokines and of the elastin-degrading MMP-2 and MMP-3 or an increase in the expression of different adhesion molecules. K-elastin and the synthetic peptide $(VGVAPG)_3$ increase the invasiveness of malignant glioma cells by upregulating MMP-2 expression and by inducing the synthesis of MMP-12 [30]. K-elastin peptides also increased the invasiveness of invasive lung tumor cells without affecting noninvasive cells and triggered a secretion of pro-MMP-2 and urokinase plasminogen activator (uPA) with an increase in pro-MMP2 activation [31]. All these effects were not inhibited by two Elastin Receptor Complex antagonists (lactose and the peptide V14) or by αVβ3 integrin- and galectin-3 blocking antibodies. Synthetic peptides such as VGVAPG, used to specifically target EBP and Gal-3, and GRKRK, used to target αVβ3 integrin, failed to reproduce κ-elastin effects whereas the nonapeptides AGVPGLGVG and AGVPGFGAG, used to target a yet unknown, lactose-insensitive nonapeptide receptor, partially mimicked them [31].

Basement Membrane Collagen Derived Anti-Tumor Matrikines

Basement membranes are highly specialized ECM that represent a frontier between the epithelium and the underlying matrix. They consist of type IV collagen associated with collagens XV, XVIII and XIX, structural glycoproteins (laminins, nidogen/entactin,) and proteoglycans, as perlecan [32]. They not only provide a mechanical support for cells, but they may also serve as a reservoir of growth factors and cytokines. After release by proteases such as MMPs, these growth factors and cytokines may control various cell functions. By interaction with the cells, they regulate biological activities such as migration, proliferation or cell differentiation [33].

Collagen IV

Collagen IV, the major component of basement membranes, is formed by the association of three α(IV) chains among six possibles, α1(IV) to α6(IV), each encoded by a specific gene [34]. While α1(IV) and α2(IV) chains are ubiquitous, the other α(IV)chains, in smaller proportion, are expressed in specialized basement membranes [35]. Various matrikines or matricryptins derive from the different NC1 C-terminal domains of the different α(IV) collagen chains.

Arresten, the NC1α1(IV) domain, exert anti-angiogenic activity by binding to α1β1 integrin and inducing an intracellular transduction signal leading to the inhibition of HIF-1α factor [36,37]. The inhibition causes a tumor growth decrease in various cancer and liver metastasis models [38,39].

Canstatin, the NC1α2(IV) domain, is an endogenous inhibitor of angiogenesis. *In vitro*, it inhibits the proliferation and migration of endothelial cells and their protein synthesis [40,41]. The N-terminal part (residues 1-89) of canstatin is responsible for cell apoptosis induction while the C-terminal part (residues 157-227) specifically inhibits endothelial cell proliferation [42,43]. Canstatin also induces a decrease in angiopoietin-1 expression in endothelial cells and lymphatic endothelial cells under hypoxic conditions [44]. The induction of apoptosis involves two signaling pathways, a first one depending on a Fas/Fas ligand pathway with activation of caspases 8 and 3, and a second one initiated by the binding of canstatin to αVβ5 integrin [45,46]. Canstatin inhibits tumor growth in various *in vivo* cancer models when overexpressed by tumor cells [40,44,45].

Tumstatin, the NC1α3(IV) domain, exerts both anti-angiogenic and anti-tumor activities by two distinct sequences [47]. The sequence 54-132 named Tum-5, is responsible for the anti-angiogenic activity by induction of apoptosis in endothelial cells. Its binding to the αvβ3 integrin, independently of the RGD sequence induces a transduction pathway similar to that induced by canstatin, with down-regulation of the mTOR pathway and protein synthesis [48]. In the C-terminal part of tumstatin, a second sequence corresponding to residues 185-203, has a strong anti-tumor activity, demonstrated in murine and human melanoma models, either by using synthetic peptides reproducing

the sequence or by inducing its overexpression by cancer cells [49-51]. This sequence also inhibits the proteolytic cascades of tumor progression, MMPs and plasminogen activation. This sequence binds to αvβ3 integrin, independently of the RGD sequence, and triggers an intracellular transduction pathway involving the early phosphorylation of FAK and PI3 kinase [52].

Tumstatin is produced *in vivo* by cleavage of collagen IV by MMP-9, as demonstrated by using MMP-9 knockout mice. By ELISA, the serum concentration of circulating tumstatin was determined in mice (300-360 ng/mL) [53]. In our laboratory, we found mouse serum tumstatin concentrations of 600 ng/mL [54]. The concentration of circulating tumstatin was also determined in human (10 to 150 ng/mL), confirming its *in vivo* production and physiological interest in the control of tumor growth [55].

An anti-angiogenic activity has been demonstrated in the chicken chorioallantoic membrane model for the recombinant NC1 domains derived from the different α(IV) collagen chains, but no activity was found for the NC1α4(IV) domain [56]. However, its overexpression induced in human melanoma cells by stable transfection causes an anti-proliferative effect on these cells and a significant inhibition of their invasive properties. This decrease in invasive properties is due, at least in part, to a reduction of the amount of active MMP-14 at the migration front, inducing a non-migratory cell phenotype. In a xenograft model of human melanoma in mice, the NC1α4(IV) domain, named tetrastatin, induces a decrease of more than 80% in tumor growth [57].

Only few studies have been devoted to the NC1 α5(IV) domain, although its strong anti-angiogenic activity was demonstrated in the chicken chorioallantoic membrane model [56]. Peptide sequences of this domain, named pentastatin 1, 2 and 3 respectively, inhibit *in vitro* proliferation and migration of endothelial cells [58]. Pentastatin 1, corresponding to residues 1516-1535 of the α5(IV) chain has a strong anti-angiogenic activity in an *in vivo* angiogenesis model in mice and reduces tumor growth in a xenograft model of non-small cell lung cancer [59].

Hexastatin, the α6(IV) NC1 domain, inhibits endothelial cell proliferation, adhesion and migration as well as neovascularization in matrigel plugs in normal C57Bl/6 mice. Similarly, it reduces tumor growth in Lewis lung carcinoma and in Rip1Tag2 transgenic mice which develop spontaneous pancreatic carcinoma [60].

Intracellular transduction pathways triggered by collagen IV-derived matrikines essentially result in the inhibition of FAK/PI3K/Akt pathway, preventing the release of the translation initiation factor eIF4E and leading to the inhibition of protein synthesis through the mTOR pathway [46,48]. Tumstatin also inhibits NF-kB signaling resulting in inhibition of COX-2 mediated signaling [46].

The destruction of the basement membrane is the first step in epithelial cancer invasion and metastasis. Tumor sections from patients with lung carcinoma show an expression of tumstatin around some cancer clusters [61]. In 34 patients with lung carcinoma, a strong expression of tumstatin is associated with a lesser degree of tumor vascularization [62]. In patients with non-small lung cancer, tumor tumstatin-mRNA expression was significantly related to tumor pathologic stage and patients with low tumstatin-mRNA expression had poorer overall survival and disease-free survival than those with high expression [63]. As well, the loss of α5(IV) and α6(IV) chains from the epithelial basement membrane at the early stage of cancer invasion has been reported in several types of cancer [64,65]. In hepatic bile duct carcinoma, the absence of α2(IV) and α6(IV) chains corresponds to a significantly poorer prognosis [66]. Nevertheless, in gastric carcinomas, an overexpression of COL4A3 appears to be negatively associated with a favorable prognosis and an aberrant COL4A3 expression might play an important role in the pathogenesis and subsequent progression of gastric carcinoma [67].

Collagens XV and XVIII

These two collagens constitute the multiplexin family. Collagen XV is mainly located in the basal neuronal, mesenchymal, vascular membranes, and some epithelial basement membranes. Proteolysis of the C-terminal NC1 domain gives rise to a matrikine, restin, which exerts an anti-tumor effect based on its anti-angiogenic properties [68].

Collagen XVIII, initially described as a heparan sulfate proteoglycan, presents a high structural homology with collagen XV [69]. The cleavage of its C-terminal NC1 domain by different MMPs (MMP-2, -7, -9, -14) or other proteases gives rise to a 20 kDa matrikine, endostatin [70]. Anti-tumor and anti-angiogenic activities of endostatin have been widely described in literature and will not be described here [71,72].

Collagen XVIII also contains cryptic polypeptide modules, such as an N-terminal variant containing a frizzled module (FCZ 18), sharing a structural identity with the extracellular cysteine-rich domain of the frizzled receptors. This domain inhibits *in vivo* cell proliferation and tumor growth in mice through the Wnt/β-catenin signaling pathway [73,74].

Collagen XIX

Collagen XIX is a minor FACIT collagen associated with type IV and XVIII collagens in basement membranes. It is a homotrimer of three α1(XIX) chains [75]. Type XIX collagen expression is ubiquitous during embryogenesis, but its expression in adult is restricted to specialized basement membranes like vascular, neuronal, mesenchymal or epithelial tissues [76]. It seems to play an important role in muscle differentiation [77] and in the formation of hippocampal synapses [78].

The short NC1 (XIX) C-terminal domain is composed of 19 residues and inhibits the migration and invasion capacities of melanoma cells *in vitro* without affecting their proliferation [79]. It exerts also a strong inhibition of *in vivo* tumor growth in a murine melanoma model with a decrease in tumor vascularization. NC1(XIX) inhibited *in vitro* pseudotube formation in matrigel by human microvascular endothelial cells. This effect was accompanied by an intense inhibition of MMP-14 and VEGF expression [80].

Collagen XIX disappears from basement membrane during breast cancer progression at invasive stages [81].

A competitive ELISA assay was developed to determine NC1 (XIX) concentration in the sera of patients. NC1(XIX) was easily detectable in the sera [82].

Proteoglycans and Proteoglycan-Derived Matrikines

Initially thought to act exclusively as structural components, proteoglycans are now recognized as key players in cell functions such as proliferation, differentiation, survival, adhesion, migration, or inflammatory response, due in part to their ability to sequester cytokines and growth factors. The expression of proteoglycans is largely altered in various cancers [83-85]. Proteoglycan-derived peptides such as endorepellin, a perlecan fragment, lumcorin derived from lumican,

and decorin-derived peptides were found to play a role in the control of tumor progression, angiogenesis, and metastasis by exerting anti-tumor properties [86-91].

Endorepellin, a perlecan-derived peptide

Perlecan is a large proteoglycan, present in almost all basement membranes where it interacts with laminin-1 and collagen IV, as well as with β1-integrins [92]. The regulatory role of perlecan in tumor progression was demonstrated in human colon carcinoma xenograft and melanoma allograft models: the suppression of perlecan expression caused substantial inhibition of tumor growth and angiogenesis [84]. Perlecan can be pro-angiogenic by direct interaction with VEGFR2 pathway. The role of perlecan in regulating the angiogenic switch results from its opposing terminal angiogenic act**i**vities [93]. The N-terminus, which includes three heparan sulfate chains, harbours a number of angiogenic growth factors including FGFs, progranulin and VEGFA, in close proximity to their functional receptors [94-97]. In contrast, the limited proteolysis of its C-terminus by BMP-1 or cathepsin L liberates a bioactive angiostatic fragment named endorepellin to designate its intrinsic repulsive activity against endothelial cells [98,99]. Its angiostatic activity exists through binding to α2β1 integrin that induces a signaling cascade leading to actin cytoskeleton collapse and activation of the tyrosine phosphatase SHP-1, which in turn dephosphorylates several tyrosine kinase receptors, including VEGFR2 [100,101].

Lumcorin, a lumican-derived peptide

Lumican is a member of the Small Leucin Rich Proteoglycan (SLRP) family able to regulate cell proliferation, adhesion, migration and tumor invasion in melanoma [86,102-106]. Its core protein increases melanoma cell adhesion [107] while, in its glycosylated form, lumican inhibits melanoma cell migration and invasion [102-104]. It inhibits anchorage-independent cell proliferation, migration, or invasion and increases melanoma cell apoptosis. In *an in vivo* mouse melanoma model with lumican-overexpressing B16F1 melanoma cells, tumor progression is significantly inhibited [102]. Through binding to α2β1 integrin, it inhibits melanoma cell migration *via* alteration of actin network and focal adhesion complexes [104, 106, 108]. Lumican also exerts angiostatic properties by inhibiting endothelial cell invasion, angiogenic sprouting and vessel formation in mice [105,109-112]. This inhibitory effect on endothelial cell migration is associated with the downregulation of the expression and activity of MMP-9 and MMP-14 [111]. In our laboratory, within the Leucin Rich Repeat 9 (LLR9), we identified a 17 amino acid sequence inhibiting *in vitro* melanoma cell migration and reproducing the anti-migratory effect of lumican. This sequence was named lumcorin (fragment of lumican core protein) [113].

Lumican acts as an endogenous inhibitor of TGF β2 pathway, resulting in modulation of downstream effectors, such as pSmad 2 or β1 integrin and phosphorylation of p125FAK in osteosarcoma cells [114]

Lumican expression in pancreatic cancer correlates with an advanced stage and retroperitoneal and duodenal invasion [115]. The expression of lumican protein did not correlate with prognostic factors in breast carcinoma [116], but reduced lumican protein expression is associated with a poor outcome in breast cancer [117].

Decorin-derived peptides

Decorin, another member of the SLRP family, is involved in tumor progression, angiogenesis and metastasis [87,88]. Decorin inhibits tumor cell growth, migration, angiogenesis, endothelial cell proliferation and motility and alters endocytosis [88,118,119]. It acts as a tumor suppressor by interacting with EGF Receptor (EGFR), ErbB, c-Met, Insulin-IGF Receptor (IGFR), TGFβ Receptor (TGFβR), and α2β1 integrin respectively. This induces the $p21^{WAF-1}$ inhibitor of cell cycle progression, proteasome degradation, activation of PI3K/Akt/mTOR and PI3K/Smad signalling [88]. Decorin peptides derived from its LRR5 present anti-angiogenic properties [91]. Among them, a LRR5-derived 26 amino acid peptide and its 13-mer C-terminal part decreases VEGF-stimulated migration of endothelial cells by inhibiting VEGF-stimulated endothelial nitric oxide synthase activation and NO release [120].

Matrikine-Based Therapeutic Strategies

Numerous preclinical trials using matrikines to limit tumor progression have been conducted in various experimental cancer models in mice. They used different strategies:- *in vivo* matrikine overexpression using viral constructions or plasmid DNA electrotransfer -injections of recombinant proteins or synthetic peptides.

Collagen IV derived matrikines

The *in vivo* overexpression of canstatin in mice was obtained by an adenovirus encoding a fusion protein canstatin-human albumin or a fluorescent protein GFP-canstatin. The intratumoral injection of adenovirus causes a decrease in tumor growth [45,121]. Another construction, based on a plasmid containing the cDNA encoding the Tum-1 fragment of tumstatin and injected at regular intervals induces a significant decrease in tumor growth [122].

To avoid the side effects and the need for repeated injections, the use of DNA electrotransfer in muscle cells confirmed the anti-angiogenic and anti-tumor effects of canstatin in murine cancer models [123]. Similarly, in our laboratory, the *in vivo* overexpression of tumstatin or tetrastatin induced by DNA electrotransfer caused a strong decrease in tumor growth and increased mouse survival in a melanoma model [56].Collagen IV derived matrikines were produced in different cell systems. Their peri- or intra-tumor injections decreased tumor growth in experimental models of cancer in mice [40,124,125].

Short peptide sequences are responsible for the anti-angiogenic and anti-tumor activities of tumstatin:

The 74-90 sequence, named T7 peptide, is responsible for the anti-angiogenic activity [126]. A synthetic peptide reproducing a part of T7 peptide induces apoptosis in endothelial cells and inhibits tumor growth of gastric carcinoma in mice [127,128].

The 185-203 sequence, is responsible for the anti-tumor activity [49]. Intravenous injection of the peptide inhibits tumor growth of melanoma or gastric carcinoma in mice [128,129]. Within this 185-203 sequence, the biological activity is contained in the 7 N-terminal amino acid sequence (CNYYSNS) [130,131]. By molecular dynamics simulation, we showed that they form a β-turn [130]. A YSNSG cyclopeptide, forming a constrained β-turn was designed. In a model of melanoma, its inhibitory effect was higher than that of the native linear peptide, due to an increased stability [132,133].

Preclinical studies in mice performed by using a matrikine, eg canstatin or tumstatin in combination with conventional chemotherapy or radiotherapy showed a potentiating effect compared to each treatment used separately [45,123,126,131,134,135].

Proteoglycan derived matrikines

Systemic delivery of recombinant endorepellin to mice bearing orthotopic squamous carcinoma xenografts or syngeneic lung carcinoma tumors, caused a marked reduction of tumor growth, tumor metabolism and angiogenesis [136].

In a syngeneic mouse melanoma model, tumor progression was significantly reduced in tumor obtained by subcutaneous injection of lumican overexpressing melanoma cells [102]. Lumican is expressed in various cancer tissues but both positive and negative correlations with tumor aggressiveness have been reported and are largely discussed in [86].

As described for collagen IV-derived matrikines, similar tools have been used to demonstrate the anticancer effects of decorin in various cancer animal models, including adenoviral-mediated decorin gene delivery or systemic administration of recombinant decorin. A tumor xenograft approach obtained by injection of decorin-expressing cells showed a large decrease in tumor growth with a reduced neovascularization [137]. Systemic recombinant decorin delivery or *de novo*-induced expression of decorin inhibited tumor progression in different animal cancer models and induced a downregulation of the endogenous expression of VEGF and FGF2 [138]. In addition, decorin largely prevented lung metastasis in breast or osteosarcoma models [119,139]. In experimental combined therapy strategies, decorin exerts opposite effects: it synergizes with carboplatin to inhibit ovarian cancer cell growth, while it antagonizes the effects of carboplatin and gemcitabine on pancreatic cancer cells [88].

In tumors, proteoglycans may serve as preferred targets of chemotherapeutic drugs in order to improve their potential and minimize side effects. For example, the binding of a quaternary ammonium on an alkylating agent allows a specific address of this molecule on tumor proteoglycans in a rat chondrosarcoma [140].

The elastin peptides, including the previously described exert pro-tumor effects by increasing the activation of the proteolytic cascades involved in tumor progression. The determination of their receptors on cancer cell surface and the characterization of their spatial structures (presence of β turn for example) will permit to design structural analogs capable to act as antagonists to block signal transduction pathways induced by EDPs and thus to limit their pro-tumor effects.

Clinical trials

Clinical trials have been conducted or are underway with endostatin, but they proved to be ineffective. Currently, several clinical trials are underway in China, with Endostar, derived from endostatin, alone or in combination with conventional chemotherapy in patients with non-small lung cancer cells or colorectal and gastric cancers [141].

Conclusions

In vitro and preclinical studies in mouse cancer models highlight the strong potential of matrikines for new anti-cancer agent development. Their ability to inhibit the proliferative and invasive properties of cancer cells and their anti-angiogenic activity are opening new opportunities to limit tumor progression. In addition, their endogenous origin contributes to a better tolerance, limiting side effects. The characterization of the active minimal sequences will allow to design structural analogs and improve their bioavailability and pharmacokinetic properties. The binding of these matrikines or their analogs on cell surface receptors such as αvβ3 integrin, will also develop strategies to target specific cancer cells and activated endothelial cells, to directly address chemotherapeutic molecules on their target cells and to decrease the doses and side effects. Matrikines and derived molecules are a new family of potent anti-cancer agents for use in therapeutic strategies combined with conventional chemotherapy or radiation and open up real prospects against tumor progression.

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