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INVITED REVIEW

Transglutaminases: key regulators of cancer metastasis

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Abstract The ability to metastasize represents the most important characteristic of malignant tumors. The biological details of the metastatic process remain somewhat unknown, due to difficulties in studying tumor cell behaviour with high spatial and temporal resolution in vivo. Several lines of evidence involve transglutaminases (TGs) in the key stages of tumor progression cascade, even though the molecular mechanisms remain controversial. TG expression and activity display a different role in the primary tumor or in metastatic cells. In fact, TG expression is low in the primary tumor mass, but augmented when cells acquire the metastatic phenotype. Nevertheless, in other cases, the use of inducers of TG transamidating activity seems to contrast tumor cell plasticity, migration and invasion. In the following review, the function of TGs in cancer cell migration into the extracellular matrix, adhesion to the capillary endothelium and its basement membrane, invasion and angiogenesis is discussed.

Keywords Polyamines · Transglutaminase · Invasion · Extracellular matrix

This work is dedicated to Alberto Abbruzzese, who died of cancer in 2011.

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Introduction

Despite the increased understanding of the basic biological processes that become altered in tumorigenesis and metastatic progression, cancer still remains one of the leading causes of mortality. The improvement in radiotherapeutical, chemotherapeutical and gene therapy treatments leads generally to marginal control of metastatic spread, or is limited to specific types of cancers. Therefore, there is a pressing need to investigate the molecular and cellular mechanisms of tumor growth and spread. The transition from the benign to the malignant phenotype is the key event for the metastatic progression of tumors. Malignancy is a state arising from the tumor host microenvironment where the host contributes to the induction, selection and expansion of the neoplastic cells, which continuously stimulate host stromal and vascular cells to assist them in conducting physiological invasion (Park et al. 2000). Several distinct phases characterize the metastatic cascade (Fig. 1). Malignant cells enter the circulation by invading blood vessels situated either within the substance of the primary tumor mass or near its advancing edge. Degradation of the basement membrane facilitates invasion into the vasculature or lymphatic system, which is followed by rolling and arrest of the malignant cells at a distant site. When tumor cells reach the capillaries of the target organ, they attach to the endothelial cell lining, often associated with a specific tissue type, depending on the cancer cell type. Invasion into the surrounding tissue then requires passage through the endothelial cell junctions and adhesion to the basement membrane and its following degradation, a process referred to as extravasation. Motility and invasion are bi-directional processes, as occurring before intravasation and after extravasation (Liotta and Kohn 2001). The degradation of basement membranes and extracellular

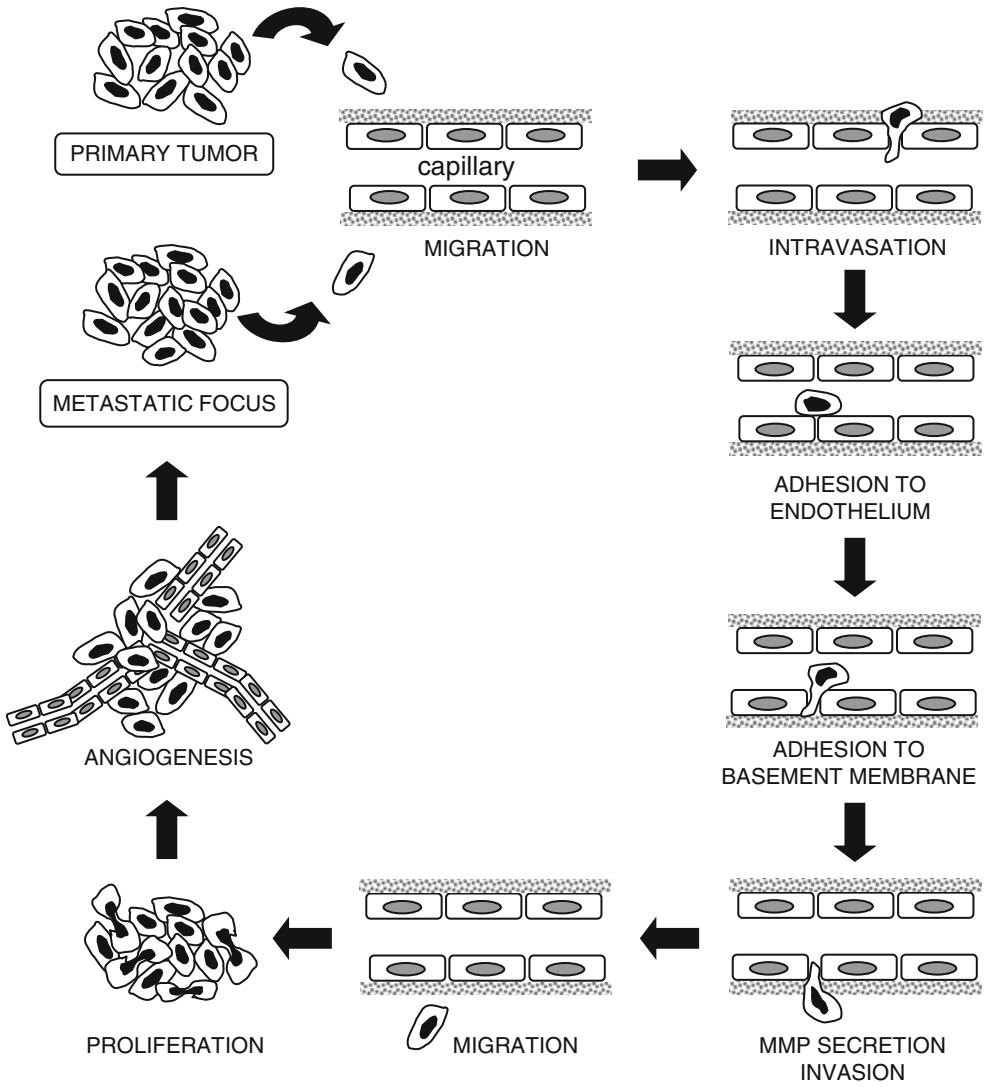

Fig. 1 The metastatic cascade

matrix (ECM) depends on the secretion of specific enzymes by tumor cells, named metalloproteinases (MMPs). The last stage is relative to the cells proliferation in the site organ. Here, tumor cells produce angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which stimulate stromal vascular cells causing vascular permeability, endothelial proliferation and invasion.

Transglutaminases (TGs) are a family of mammalian enzymes that modify proteins post-translationally in a calcium-dependent manner, leading to the formation of covalent ε(γ-glutamyl)lysine linkages (Folk 1980). TGs can catalyze the covalent incorporation of several low molecular weight amines into proteins in the form of amides of the γ-carboxyl group of a peptide-bound glutamic acid. TGs are widely distributed in various organs, tissues, and body fluids. They are distinguishable from each other to a large extent by their physical properties and body distribution. The cross-linked protein products are highly resistant to mechanical challenge and proteolytic degradation. Among the naturally occurring di- and polyamines, putrescine (PUT), spermidine (SPD) and spermine (SPM) are excellent substrates of TG in vitro (Beninati et al. 1988). The incorporation of these amines into proteins can occur through one or both of their primary amino groups. The result of these reaction is the formation of either *N*-mono(γ-glutamyl)- or *N*,*N*-bis(γ-glutamyl)-PUT, -SPD or -SPM. It has been suggested that "polyamination" reactions are physiologically relevant. In particular, it has been speculated that polyamine binding to a specific glutamine residue may naturally occur in vivo to modify the structural and/or catalytic properties of a protein. Additionally, the TG-catalyzed reaction of a protein-bound polyamine with a second glutamine residue may lead to the

formation of a covalent crosslink between two polypeptide chains (Schrode and Folk 1978). Various important functions have been ascribed to the enzyme in both the intra- and extracellular environment (Griffin et al. 2002), suggesting a potential role in the various stages of the metastatic cascade.

Adhesion to the extracellular matrix

The interactions between cells and the ECM represent a quite complex phenomenon which provides stromal and tumor cells with mechanical support for adhesion. The tumor microenvironment is able to activate stromal cells, mostly fibroblasts, largely responsible for tumor-associated changes in the ECM (Elenbaas and Weinberg 2001; Kalluri and Zeisberg 2006). These changes include upregulated ECM synthesis, post-translational modification of ECM, and extensive remodeling of ECM proteins by proteinases, e.g. MMPs) (Kessenbrock et al. 2010). The altered ECM then influences tumor progression by architectural and signaling interactions. As cancer cells acquire the metastatic phenotype, they detach from the primary tumor and migrate towards the circulation for their dissemination. Specific adhesion of circulating cancer cells to the capillary endothelial cells (EC) and subsequent interaction with the basement membrane underneath the endothelium represent necessary steps for metastatic tumor cells to extravasate and form secondary foci into the target tissue. One of the most documented functions of TG family proteins in cancer spreading is their involvement in tumor cell–ECM interaction. TG2 present in the ECM also aids the adhesion of cancer cells to the matrix. Moreover, cell-surface TG2 is associated with integrins and mediates cell–matrix adhesion. Several major classes of adhesion receptors present on various cell types include integrins, selectins, cell adhesion molecules of immunoglobulin superfamily (CAMs) and heparan sulphate proteoglycans (HSPGs), which together define the specific patterns of cellular interactions with ECM glycoproteins such as fibronectin (FN), collagens, laminins and matrix proteoglycans via TG2 action (Zemskov et al. 2006). The ability of TG2 to function as a cell adhesion protein has been well documented, promoting increased attachment, as well as cell growth and spreading (Verderio et al. 1998, 2000; Colligan and Griffin 2009). Many evidences suggest that TG2 overexpression is responsible for increased tumor cell adhesion to the ECM and motility, whereas its reduced expression leads to impairment of these functions (Jones et al. 1997; Verderio et al. 1998). High expression of TG2 by breast cancer cells has been reported to increase their metastatic activity. In these cells, TG2 was demonstrated to be associated with β1, β4 and β5 integrins. Furthermore, downregulation of endogenous TG2 by siRNA inhibited fibronectin-mediated cell adhesion and invasion, whereas TG2 overexpression improved those functions (Herman et al. 2006; Mangala et al. 2007). In addition, it has been suggested that the regulation of cancer cell attachment and motility may be ascribed to the digestion of cell-surface TG2 by membrane-type matrix metalloproteinases (MT-MMPs). This event was shown to suppress cell adhesion and locomotion on fibronectin (Belkin et al. 2001). In addition, the proteolytic degradation of glioma and fibrosarcoma cell-surface TG2 following overexpression of MT1-MMP suppresses cell adhesion and locomotion of the tumor cells on FN, yet stimulates cell motility on collagen matrices (Belkin et al. 2001). Post-translational modification of ECM proteins by TG2 is a key step for the regulation of tumor cell metastaticity, conferring resistance to MMPs and promoting cell–matrix interactions, particularly via cross-linking of FN and collagen (Aeschlimann and Thomazy 2000; Chau et al. 2005). In fact, it has been shown that the crosslinking of collagen by TG2 results in increases cell adhesion and spreading on the modified collagen (Chau et al. 2005). In addition, cell-surface TG2 is involved in cell adhesion via its tight interaction with FN (Gaudry et al. 1999a, b), (Fig. 2) whose binding site is located in the N-terminal domain, with peptide ^{88}WTAT VVDQQDCTLSLQLTT^{106} being directly involved in this interaction (Hang et al. 2005).The resultant intracellular signalling effects are reported to be mediated by various β1 and β3 integrins (Gaudry et al. 1999a, b; Isobe et al. 1999; Akimov et al. 2000; Takahashi et al. 2000; Tanaka et al. 2007). The transamidating activity of TG2 is not required (Isobe et al. 1999; Akimov and Belkin 2001a, b) and TG2 is thought to remain associated with the assembled FN fibres (Akimov and Belkin 2001a, b). Once deposited into the matrix and in complex with FN, TG2 can also bind to the heparan sulphate chains of syndecan 4 on the cell surface (Verderio et al. 2003), an abundant constituent of

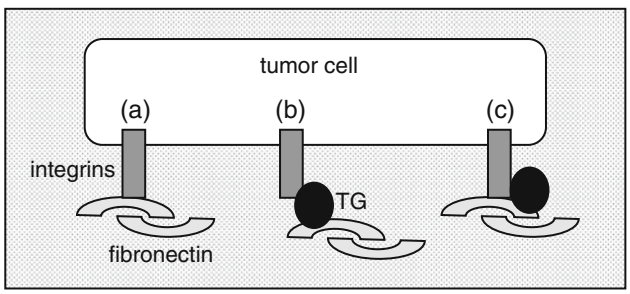

Fig. 2 Possible role of transglutaminase (TG) in tumor cell adhesion. **a** Integrin-mediated adhesion to fibronectin in the absence of TG; **b** TG improves adhesion acting as a bridge between integrins and fibronectin; **c** association of integrins with TG promotes cell adhesion and spreading due to formation of ternary adhesion complexes with fibronectin (from Akimov et al. 2000, with modifications)

the cell surface/ECM (Scarpellini et al. 2009). An important role for TG2 in the extravasation of metastatic tumor cells has been also documented. In fact, specific interaction of cancer cells to EC and to their basement membrane is required for the following invasion process and TG2 seems to be involved in both events. As described above, TG present in EC plays a pivotal role in the interaction between circulating tumor cells and the endothelium. Furthermore, others found that prostate cancer cells with over-expressed prostate TG (TG4) had a significantly increased capacity to adhere to EC and to disrupt the barrier function of EC (Jiang et al. 2009). The major constituents of the basement membranes are represented by laminin, collagen type IV and heparan sulfate proteoglycans. Laminin, the most abundant noncollagenous protein, is present in the tissue as an equimolar complex with the protein nidogen (entactin) (Timpl et al. 1979; Paulsson et al. 1987). Nidogen is a dumbbell-shaped molecule of about 150 kDa, composed of one single polypeptide chain (Paulsson et al. 1986), associated with one of the short arms of laminin with its carboxyl-terminal globular domain (Mann et al. 1989). As demonstrated for heparan sulphate proteoglycan, also the laminin-nidogen complex serves as a TG2 substrate. The specific incorporation of [^{3}H] putrescine and monodansylcadaverine into nidogen by guinea pig liver TG was detected in the isolated, as well as in the complexed form, but not in laminin. Electron microscopy of the reaction products showed that the laminin-nidogen complexes become stabilized in a head-to-head arrangement, characteristic of Ca^{2+}-induced self-aggregation (Aeschlimann and Paulsson 1991). Interestingly, the post-translational modification with polyamines of laminin or Matrigel, a reconstituted basement membrane, catalyzed by TG2, is able to impair the adhesiveness of a murine melanoma cell line. The inhibitory effect due to the formation of γ-glutamyl-polyamine derivatives into the substrate protein suggests a possible polyamine-mediated modulation of TG2 cross-linking action in the adhesion process (Lentini et al. 2008).

Migration and invasion activities

Cancer cell interactions with ECM, migration and invasion activities involve the function of adhesion receptors of the integrin family, a dynamic cytoskeleton, as well as proteolytic mechanisms, to overcome tissue barriers. The migratory machinery executes several interdependent cyclic steps. First, pseudopod protrusion and polarization initiate by actin polymerization. Next, these protrusions adhere to ECM via adhesion molecules, thereby forming several focal adhesion sites. Matrix barriers are cleaved by proteolysis by MMPs, released in the attachment sites (Sabeh et al. 2004). The involvement of TG in cancer cell motility and invasion appears controversial, in fact different effects have been observed after protein overexpression or enhancement of the enzyme activity through specific activators. Jiang et al. (2010) have shown that human TG4 overexpression in CAHPV10 and PC3 cells was associated with significantly increased cell motility. Then, the increased expression of TG2 in breast cancer cells contributes to their increased survival, invasion and motility. In fact, downregulation of endogenous TG2 by siRNA inhibited fibronectin-mediated cell attachment, survival and invasion (Mangala et al. 2005). In contrast, it has been recently observed that cancer cell morphology and the actin fibers reorganization was drastically modulated under treatment with inducers of TG activity, leading to the increase of the adhesion and decrease of migration and invasion of tumor cells (Tabolacci et al. 2010). These data might depend on the activation of the transamidating form of TG2 leading to a Ca^{2+}–dependent polymerization of actin and FN to integrins (Akimov et al. 2000), and other cytoskeleton proteins, well-known substrates for the enzyme (Takashi 1988). The modulation of tumor cell plasticity may likely affect tumor cell metastatic potential. It can be likely influenced also by the degree of the TG-mediated post-translational modification of protein with polyamines. Evidences for the formation and intracellular localization of γ-glutamyl-polyamine derivatives in two murine melanoma cell lines with different metastatic potential have been provided (Beninati et al. 1993). Although the results demonstrated the presence of protein-bound polyamines in these cancer cells, pronounced differences were observed in the two cell lines investigated. Whereas few polyamine conjugates were found in highly metastatic B16-F10 cells, many of those were identified in the lowly metastatic counterparts, B16-F10^{Lr6}. The finding of augmented levels of *N*1,*N*8-bis(γ-glutamyl)SPD in the proteolytic digest from the less metastatic cell line (B16-F10^{Lr6}), suggests a role for this cross-link in the modulation of the cellular plasticity of melanoma cells (Fig. 3). The role of the post-translational modification of ECM and basement membrane proteins with polyamines in the invasion process, catalyzed by an activated TG2, has been extensively investigated in B16-F10 murine melanoma cell line (Lentini et al. 2008). Commonly, TG activity in tumor cells is quite low and the levels of free polyamines are higher compared to the normal counterpart. Therefore, the possibility of increasing intracellular TG activity, and consequently the amount of protein-polyamine conjugates, has been considered a promising approach for cancer research.

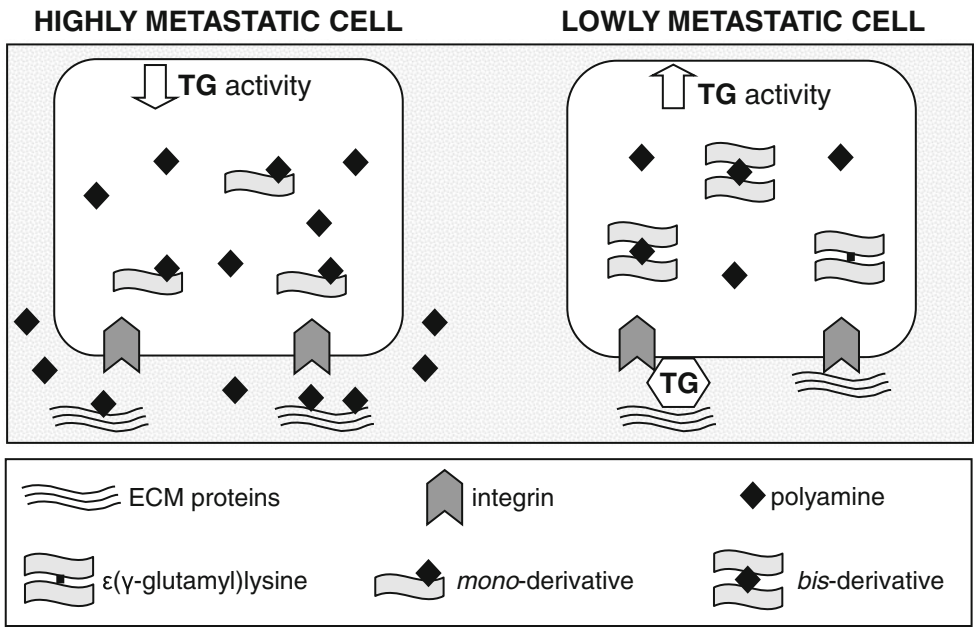

Fig. 3 Scheme of the potential involvement of transglutaminase (TG) cross-linking activity in the regulation of the metastatic potential of cancer cells. Highly metastatic cells possess low TG activity, high levels of intracellular polyamines, associated to their enhanced secretion into the extracellular environment. The preferential formation of mono-(γ-glutamyl)derivatives of polyamines reduces the intracellular protein polymerization, maintaining the cellular plasticity, and interferes with cell–cell or cell–matrix interactions, favoring the cell detachment and/or cellular motility. In contrast, in lowly metastatic cells, TG activity is higher and polyamine synthesis/secretion is slowed down. Here, the rate of the intracellular protein polymerization increases, through the formation of ε-(γ-glutamyl)lysine and bis-(γ-glutamyl)polyamine derivatives, reducing the cellular plasticity. In parallel, the integrin- and TG-mediated cell–matrix interactions contribute to a stronger adhesion of cells with ECM

Angiogenesis

Angiogenesis is defined as a vascular neoformation usually of capillary origin. This phenomenon is important during development and under several physiological and or pathological conditions. Moreover, the process of new blood vessel formation is dependent on the proliferation, migration, and differentiation of EC into tubular structures. The tumor microenvironment contains excessive amounts of pro-angiogenic factors derived from neoplastic, stromal, and infiltrating immune cells. The imbalance of pro-angiogenic and anti-angiogenic factors promotes abnormal angiogenesis, creating numerous blood vessels with structural abnormalities and functional defects (Hall and Ran 2010). EC are a rich source of TG2 (Korner et al. 1989) and this enzyme plays an important role at the surface of those cells. In fact, it has been demonstrated that celiac disease-specific IgA class autoantibodies targeting TG disturb angiogenesis (Myrsky et al. 2008). Moreover, TG2 plays a essential role in the remodeling of small arteries (Bakker et al. 2005). In cells undergoing attachment and cell spreading, TG2 appears to be concentrated at cell adhesion points, which are rich in β1 integrin, suggesting that these areas may be the initial focal points for enzyme externalization (Gaudry et al. 1999a, b). Conflicting in vivo studies have proposed that TG overexpression both stimulates and inhibits angiogenesis. In fact, on one side, TG is an important tissue stabilizing enzyme that is active during wound healing and can function to promote angiogenesis (Haroon et al. 1999a). On the other hand, TG can also enhance stability and strength of the ECM by its ability to facilitate the activation of transforming growth factor-beta (TGF-β), playing an important role in the host response mechanism against tumor growth (Haroon et al. 1999b). In particular, TGF-β is secreted in a biologically inactive form, known as large latent TGF-β complex, which consists of latent TGF-β binding protein (LTBP). Increased TG2 expression led to an increased rate of LTBP-1 deposition in the matrix (Verderio et al. 1999).

However, in an in vitro angiogenesis assay, application of exogenous TG2 blocks angiogenesis in a dose-dependent manner, without causing cell death, via a mechanism that involves increased accumulation of ECM proteins (Jones et al. 2006). Interestingly, TG2, which is also referred to as G-protein, is downregulated during EC morphogenesis in 3D collagen matrices (Bell et al. 2001). Recently, Faye et al. (2010) have demonstrated that endostatin binds to TG2 with an affinity in the nanomolar range in a calcium-dependent manner. Both endostatin and TG2 are involved in the regulation of angiogenesis, due to

their direct interaction for the modulation of EC migration and/or proliferation. Endostatin is a C-terminal fragment of the α1 chain of collagen XVIII, which inhibits angiogenesis and tumor growth (Folkman 2006). TG2 inhibitory effect on angiogenesis is demonstrated also by Dardik and Inbal (2006). These authors show that the formation of a complex between TG2 and vascular endothelial growth factor receptor 2 (VEGFR-2) has been proposed as a mechanism for the modulation of EC response to VEGF. In fact, stimulation of EC with VEGF resulted in translocation of the TG2–VEGFR-2 complex from the cytoplasm to the nucleus. Moreover, TG2–VEGFR-2 association was inhibited by a specific VEGFR-2 protein tyrosine kinase inhibitor, as well as by cystamine, inhibitor of the transamidating activity of TG2, but not by bacitracin, which inhibits the protein-disulfide isomerase activity of TG2. Furthermore, cystamine completely abolished the VEGF-induced nuclear translocation of the TG2–VEGFR-2 complex. Blockade of the crosslinking activity of TG2 by cystamine enhanced VEGF-induced migration of EC. On the contrary, Factor XIII (FXIII), a plasma TG that participates in the final stage of the coagulation cascade, shows pro-angiogenic activity. In fact, thrombin-activated FXIII (FXIIIa) catalyzes the formation of covalent cross-links between γ-glutamyl and ε-lysyl residues on adjacent fibrin chains in polymerized fibrin to yield the mature clot (Dardik et al. 2006).

Conclusive remarks

From the evidences presented in this review, TGs appear implicated in a variety of cellular functions, most of which are crucial in tumor cell proliferation and spread. The wide range of mechanisms involved include, from one side, the growth, death and survival of tumor cells. On the other side, other TG functions are closely related to the dissemination of tumor cells, such as its role as a cell-surface receptor, which can mediate tumor cell-ECM interactions, or modulate tumor angiogenesis. One of the most intriguing evidence, which emerges from the literature is the different pattern of TG expression and activity in cells of the primary tumor body or in those cells, which undergo dissemination. In particular, it seems that TG expression is maintained quite low to favor the initial tumor mass growth. As a confirmation, it is noteworthy that successful induction of TG activity by powerful inducers (e.g. retinoids) causes an effective switch to tumor cell differentiation and apoptotic death. Conversely, TG expression must be augmented when cells detach form the primary tumor, move into the ECM, intravasate and then extravasate to form metastases. Nevertheless, in other cases, the use of inducers of TG transamidating activity seems to contrast tumor cell plasticity, migration and invasion. Therefore, it is reasonable to hypothesize that TGs affect selectively the tumor-associated events by modulating their properties, enzymatic (transamidating or G-protein activities) or structural (surface receptor). In this view, the precise definition of the complex interplay between TG activation or overexpression during the initial tumor growth phase and the following metastatic progression, should likely provide a tool for designing successful TG-based anti-tumor strategies.

Conflict of interest The authors declare that they have no conflict of interest.

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