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INVITED REVIEW

Tissue transglutaminase, inflammation, and cancer: how intimate is the relationship?

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Abstract Despite significant advances in surgery and biology, cancer remains a major health problem. It is now well accepted that metastasis and cancer cells' acquired or inherent resistance to conventional therapies are major roadblocks to successful treatment. Chronic inflammation is an important driving force that provides a favorable platform for cancer's progression and development and suggests a link between inflammation and metastatic transformation. However, how chronic inflammation contributes to metastatic cell transformation is not well understood. According to the current theory of cancer progression, a small subpopulation of cancer stem cells (CSCs) in tumors is responsible for their metastasis, resistance, and sustenance. Whether CSCs originate from normal stem cells or from dedifferentiation of terminally differentiated cells remains unknown. Recent evidence indicates that stem cells are not unique; malignant or nonmalignant cells can reprogram and de-differentiate to acquire a stemness phenotype. Thus, phenotypic plasticity may exist between stem cells and non-stem cells, and a dynamic equilibrium may exist between the two phenotypes. Moreover, this equilibrium may shift in one direction or another on the basis of contextual signals in the microenvironment that influence the interconversion between stem and non-stem cell compartments. Whether the inflammatory microenvironment influences this interconversion and shifts the dynamic equilibrium towards stem cell compartments remains unknown. We recently found that aberrant tissue transglutaminase (TG2) expression induces the mesenchymal transition (EMT) and stem cell characteristics in epithelial cells. This finding, in conjunction with the observation that inflammatory signals (e.g., TGFβ, TNFα, and NF-κB) which induce EMT, also induce TG2 expression, suggests a possible link between TG2, inflammation, and cancer progression. In this review, we summarize TG2-driven processes in inflammation and their implications in cancer progression.

Keywords Chemoresistance · Metastasis · Cancer stem cells · EMT · Inflammation · Transglutaminase 2

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Introduction

Transglutaminase (TGase) activity was first described by Clarke et al. in 1957. Since then, many proteins with TGase activity have been identified (Mehta and Eckert 2005). In mammals, eight distinct TGases have been identified at the genomic level (Grenard et al. 2001), six of which have been isolated and characterized at the protein level. TGase 2 (TG2, also known as tissue TGase) is probably the most diverse and most studied member of this family. It is a multifunctional protein and a bifunctional enzyme with both protein cross-linking and GTP-hydrolyzing activities (Lee et al. 1989). TG2 is widely distributed in many biologic systems for tissue stabilization and immediate defense against injury or infection. Aberrant TG2 activity in tissues contributes to a variety of disease processes, including neurodegenerative diseases (Lesort et al. 2000), autoimmune diseases such as celiac disease (Dieterich et al. 1997), rheumatoid arthritis (Johnson et al. 2001), and tissue fibrosis (Griffin et al. 2002).

Human TG2 is composed of an N-terminal β-sandwich domain, a catalytic core, and two C-terminally located

β-barrels. These domains comprise amino acids from 1–139, 140–454, 479–585, and 586–687, respectively (Fig. 1a), with different secondary structures in which domains 1, 3, and 4 are folded in β-barrels and domain 2 contains an α-helical secondary structure (Pinkas et al. 2007). The C-terminal domain 4 of TG2 is responsible for the transamidation-inactive GTP-bound state and is crucial to the enzyme's role as a GTP-binding effector protein in transducing extracellular α-adrenergic signals, coupled with phosphatidylinositide metabolism (Nakaoka et al. 1994). TG2's catalytic active site is located in the terminal a-helix (H_4) in domain 2, hidden from contact with peptidylglutamine substrates due to overlayering of domains 3 and 4 in a resting or compact conformation (Fig. 1b). During activation, the interaction between domain 2 and domains 3 and 4 breaks down after the binding of Ca^{2+}, an essential activator of transamidating activity. Its catalytic activity requires high calcium ($\geq$1 mM) and low GTP ($\leq$9 μM), implying that under physiologic conditions, intracellular TG2 exists as a cryptic enzyme and thus functions as a G-protein (Grenard et al. 2001) (Fig. 1b).

TG2 and Inflammation

Wound healing is a complex and dynamic process that is characterized by three interconnected and overlapping phases: inflammation, tissue formation, and tissue remodeling (Verderio et al. 2004). The results of several studies have supported the involvement of TG2 during the initial phase of wound healing and inflammation (Iismaa et al. 2009; Verderio et al. 2005). Factor XIIIa, another member of the TGase family, is known to participate in controlling blood loss after blood vessel injury. Factor XIIIa stabilizes fibrin by intra-molecularly cross-linking fibrin and activating platelets and results in the deposition of granulation tissues, which represents the first stable repair of the local lesion. In response to cutaneous injury, TG2 expression and activity is increased at sites of neovascularization and in endothelial cells, skeletal muscle cells, and macrophages that infiltrate wounds at the border between healthy and injured tissue (Kuncio et al. 1998).

In addition, TG2's involvement in the pathogenesis of chronic inflammatory diseases, such as liver cirrhosis, liver fibrosis, alcoholic hepatopathy, lung fibrosis, rheumatoid arthritis, and osteoarthritis has been suggested (Grenard et al. 2001; Richards et al. 1991; Johnson et al. 1997, 2001). Interestingly, many cytokines and growth factors that are secreted during early phases of cell injury are also known regulators of TG2 expression. For example, TGF-β1 induces TG2 expression in keratinocytes and dermal fibroblasts via the TGF-β1 response element, which is located in the *TGM2* gene promoter (Quan et al. 2005). Tumor necrosis factor (TNF)-α induces TG2 synthesis in liver cells by activating IκBα phosphorylation. This causes IκB to dissociate from the nuclear factor (NF-κB),

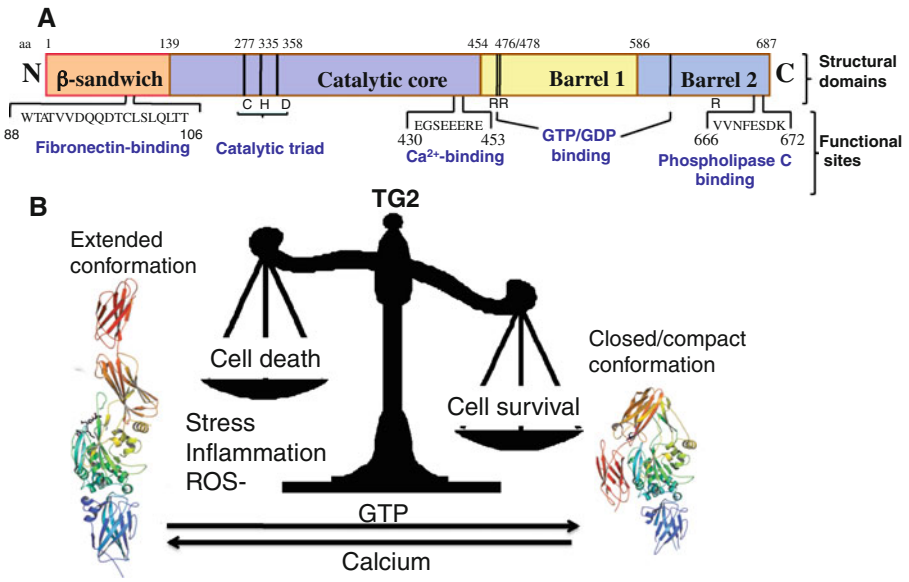

Fig. 1 Schematic representation of TG2's structure and functions. **a** The four structural domains of TG2 and their associated activities. **b** GTP and calcium are two well-known regulators of TG2's catalytic function. Under physiologic conditions, low calcium and high GTP levels make the intracellular environment conducive for TG2 to maintain a catalytically inactive, compact conformation. In this form, TG2 acts as a scaffold protein, interacting with various cell-signaling proteins to modify their structure, activity, function, or stability. In the compact or closed conformation, TG2 promotes cell survival and other oncogenic functions due to constitutive activation of pathways such as NF-κB, Akt, and PTEN downregulation. However, under extreme stressful conditions, TG2 can acquire the catalytically active extended conformation, resulting in cell death due to massive cross-linking of cellular proteins

allowing nuclear translocation of NF-κB; NF-κB then binds to the *TGM2* promoter and induces its expression (Kuncio et al. 1998). TG2 can also activate NF-κB via the non-canonical pathway by cross-linking or polymerizing the NF-κB inhibitory protein, IκBα (Kim 2006). This effect was confirmed when TG2 inhibition was found to reverse NF-κB activation. TG2 inhibition also reversed inflammation in conjunctivitis models (Lee et al. 2004).

TG2 can also induce inflammation by aggregating and functionally sequestering the anti-inflammatory factor peroxisome proliferator-activated receptor γ (PPARγ), as demonstrated in a model of cystic fibrosis (CF). Thus, in vitro TG2 inhibition was able to reinstate PPARγ and inflammatory cytokine levels (Maiuri et al. 2008). Cystic fibrosis, the most common life-threatening inherited disease, is mainly due to mutations in the CF transmembrane conductance regulator (*CFTR*) gene and is characterized by chronic airway inflammation and pulmonary infections. Defects in the *CFTR* gene are also associated with a marked increase in proinflammatory cytokines, such as TNF-α, IL-6, IL-1β, and IL-17 (Osika et al. 1999; Dubin et al. 2007; Maiuri et al. 2008). The inflammatory response is not secondary to pulmonary infections. Indeed, several studies have shown that inflammation and proinflammatory activity in CF tissue is present in sterile conditions. Recent reports indicate that TG2 levels are remarkably upregulated in *CFTR*-defective CS patients and bronchial epithelial cells (Maiuri et al. 2008).

Moreover, aberrant TG2 expression has been implicated in renal fibrosis, which is characterized by renal tubule and interstitial capillary destruction and extracellular matrix protein accumulation. The severity of tubulointerstitial fibrosis has long been considered a crucial determinant in progressive renal injury in both human and experimental glomerulonephritis. In humans, a strong association between renal fibrosis, TG2 expression, and its cross-link product has been observed (Johnson et al. 1997, 2003). Thus, in TG2-knockout mice, renal inflammation is significantly reduced and fewer myofibroblasts accumulate compared with in wild-type mice. Similarly, active TGF-β, total fibrillar collagen, and collagen are significantly lower in TG2-KO animals than in wild-type mice (Shweke et al. 2008).

Liver fibrogenesis is mainly driven by activated hepatic stellate cells and perivascular or portal fibroblasts that transform to excess extracellular matrix (ECM), producing myofibroblasts that resemble dermal or intestinal myofibroblasts in scar or stricture formation, respectively (Elli et al. 2009). Because various ECM component proteins (such as procollagens, fibronectin, and laminins) are known TG2 substrates, important wound healing regulators, and fibrogenesis inducers (TGFβ, TNFα, and IL-6) are also known TG2 expression inducers, TG2 has been implicated in liver fibrogenesis (Facchiano et al. 2006). This was demonstrated in fibrotic liver specimens from patients with chronic hepatitis B or C and alcoholic hepatitis, in whom high TG2 levels are detected extracellularly and are associated with the formation of *N*-γ-glutaminyl-ε-lysyl cross-links as a measure of TG2 activation (Grenard et al. 2001). Thus, TG2 is considered profibrogenic because its cross-linking activity stabilizes the ECM network, conferring resistance to proteolytic breakdown.

TG2 and cancer

After heart disease, cancer is the second leading cause of mortality worldwide. Despite an increasing understanding of the biologic processes involved in cancer initiation and progression, incidence and mortality due to cancer has continued to rise. The use of surgery, radiotherapy, chemotherapy, and more recently, gene therapy regimens are only marginally effective in metastatic disease or are limited to specific tumor types. Cancer progression shares many similarities with inflammatory response, tissue injury, and remodeling (Grivennikov et al. 2010; Mantovani et al. 2008). Increased TG2 expression and transamidation activity is a common feature of many inflammatory diseases (Verderio et al. 2004, 2005). As discussed in the preceding section and depicted in Fig. 2, various cytokines and growth factors (such as TGF-β1, TNF-α, IL-1, and IL-6) secreted during tissue injury or wound healing are potent inducers of TG2 gene expression (Mehta et al. 2010). It is becoming evident that inflammatory responses play a critical role in tumor initiation, promotion, invasion, and metastasis. Immune cells that infiltrate tumors can engage in cross talk with cancer cells and modulate their growth, survival, and progression (Grivennikov et al. 2010; Mantovani et al. 2008).

Multiple studies have shown elevated TG2 expression in many cancer cell types, including pancreatic carcinoma (Verma et al. 2006), breast carcinoma (Mehta et al. 2004), malignant melanoma (Fok et al. 2006), ovarian carcinoma (Hwang et al. 2008), lung carcinoma (Park et al. 2010), and glioblastoma (Yuan et al. 2007). For example, an analysis of more than 30,000 genes from tumor samples revealed that TG2 is one of the highly expressed genes in pancreatic adenocarcinoma (Iacobuzio-Donahue et al. 2003). Similarly, a proteomic analysis of metastasis-associated proteins revealed that TG2 is one of the 11 proteins that are selectively amplified in metastatic human lung carcinoma (Jiang et al. 2003). TG2 expression in cancer cells has been implicated in disease progression, drug resistance, metastasis, and poor patient survival (Verma and Mehta 2007a, b; Mangala et al. 2007; Verma et al. 2006; Mehta et al. 2004; Fok et al. 2006; Hwang et al. 2008; Park et al. 2010;

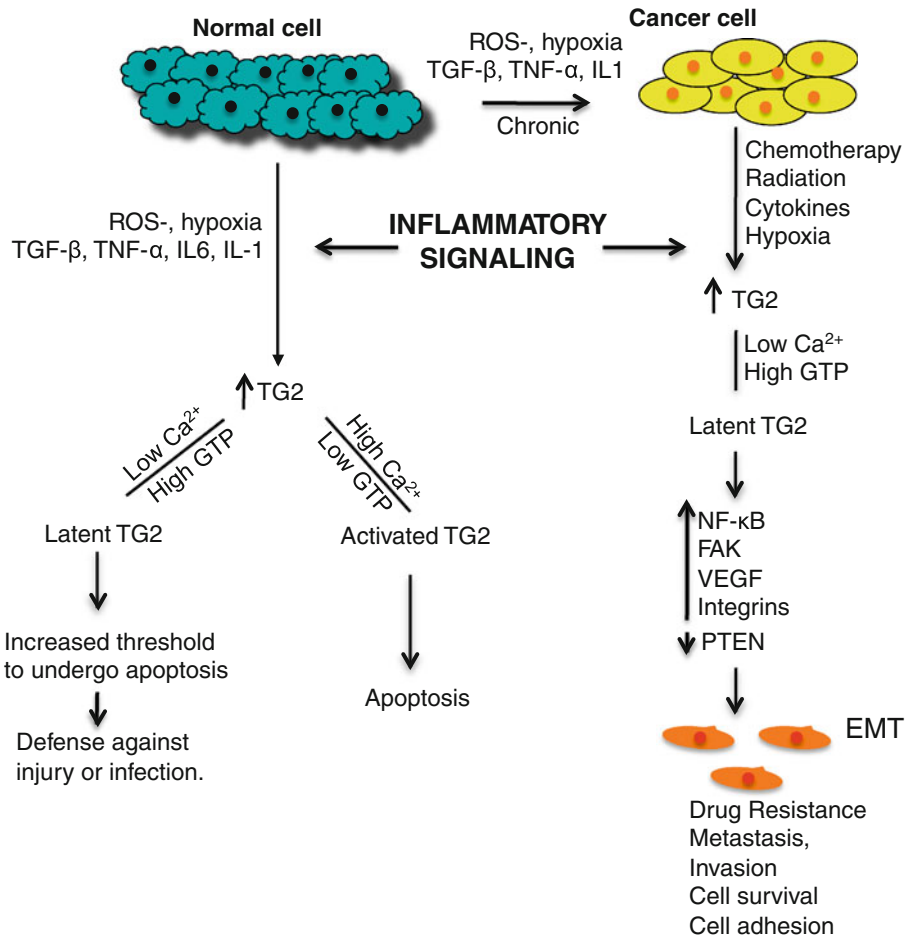

Fig. 2 Implications of TG2 expression in normal and transformed cells. Stress- and inflammation-related signals can induce TG2 in normal cells, which may be related to TG2's ability to confer transient protection to cells after injury or infection. In addition, TG2's ability to promote EMT may play a role in wound healing and tissue repair by promoting matrix synthesis and stabilization. Acute stress or physical damage to cells in this environment could result in elevated calcium levels, resulting in the activation of TG2's catalytic function and apoptotic cell death due to massive cross-linking of cellular proteins. Chronic infection or inflammation may divert TG2's initial protective functions to pathologic events such as fibrosis and cancer due to sustained TG2 expression. Once the infection or inflammation is resolved, TG2 expression is silenced by a not yet well understood mechanism. In cancer cells, in contrast, TG2's expression is deregulated, and its aberrant expression leads to the constitutive activation of various oncogenic signaling pathways that promote EMT and stem cell-like characteristics and confer an invasive and drug-resistant phenotype

Yuan et al. 2007). These findings suggest a possible link between inflammation, TG2, and cancer progression.

Most anticancer drugs kill tumor cells initially by activating apoptotic pathways; however, some tumor cells may escape because of deregulated apoptotic pathways or drug resistance protein expression (e.g., Pgp and MRP). Indeed, numerous alterations that confer resistance to apoptosis in cancer cells have been identified. For example, activation of pro-survival signal transduction pathways such as those mediated by Ras, PI3K/Akt, and NF-κB; inactivation of apoptotic pathways due to mutation or silencing of p53, pRb, Bax, Bad, Apaf-1, and caspase-8 genes; and overexpression of pro-survival proteins such as Bcl-2, IAP, and FLIP are frequently observed in advanced-stage cancer (Fesik 2005).

An important property of highly malignant tumor cells is their ability to survive in hostile host environments as they pass through the lymphatic system or bloodstream in an attempt to colonize distant sites. TG2 expression has been shown to be positively correlated with tumors' metastasis propensity. The results of one proteomic analysis indicated that TG2 expression was significantly higher in metastatic lung cancer cell lines than in those with lower metastatic potential (Levental et al. 2009). Most solid tumors start out with epithelial phenotype and progressively acquire mesenchymal traits. The epithelial-to-mesenchymal transition (EMT) causes the fatal progression from benign epithelial cells to malignant, highly motile fibroblastoid-like cells. The metastases of these predominantly secondary tumors to distant sites occur at the cost of proliferative potential,

but allow for a more fatal prognosis. The EMT, characterized by increased drug resistance and metastatic potentiation, embodies cancer for pathological shift from benign to malignant. It is marked by the loss of intracellular cohesion, disruption of the extracellular matrix, increased cell motility, cadherin shift. Recent studies have indicated that the aberrant expression of TG2 can lead to the constitutive activation of signaling pathways intimately involved in EMT regulation (Kumar et al. 2010; Shao et al. 2009) (Fig. 2).

EMT, cancer, and TG2

Epithelial–mesenchymal transition (EMT) is a dynamic and essential process for reprogramming epithelial cells during embryonic development. Reactivation of EMT during adulthood has been associated with various pathologic conditions. For example, EMT has been implicated to play a role in wound healing, tissue regeneration, and organ fibrosis and initiate epithelial cancer cell invasion and metastasis (Kiemer et al. 2001; Janda et al. 2002; Vincent-Salomon and Thiery 2003). Inflammation is a crucial conspirator in the emergence of EMT in adults but is absent during embryonic development. Body cells are derived from a single cell into morphologically and functionally distinct cell types. A phenotypic variant of cells in tissues and organs is due to the specific expression of a defined transcriptome that facilitates further functional diversity. During embryogenesis, epithelia are considered highly plastic and able to switch between epithelia and mesenchyme via EMT and mesenchymal–epithelial transition, respectively (Thiery 2002; Kalluri and Neilson 2003). Mesenchymal cells are unique spindle-shaped cells that exhibit end-to-end polarity. Fibroblasts are prototypical mesenchymal cells that exist in many tissues and are activated during repair processes (Kalluri and Zeisberg 2006). EMT during embryogenesis occurs in an immunologically privileged setting, driven by internal molecular programs. Immune privilege may be necessary for EMT associated with embryo development, whereas inflammation and epigenetics are likely the key inducers of EMT in pathologic settings of organ fibrosis and cancer progression (Kalluri 2009).

Cancer progression shares many similarities with inflammatory response and tissue injury. Rudolph Virchow first identified a possible link between inflammation and cancer in 1863 (Balkwill and Mantovani 2001). He hypothesized that cancer originates at the sites of chronic inflammation and suggested that some classes of irritants, together with tissue injury and ensuing inflammation, enhance cell proliferation and cancer progression. Several years of studies have shown that chronic inflammation predisposes individuals to various cancer types. Ulcerative colitis, chronic gastritis, hepatitis, and chronic pancreatitis and their respective associations with colon, gastric, liver, and pancreatic carcinomas are a few examples of the relationship between inflammation and tumor progression. Moreover, anti-inflammatory drugs are known to reduce the risk of cancer development. It is estimated that underlying infections and inflammatory responses are linked to 15–20% of all cancer deaths worldwide (Bertout and Thomas-Tikhonenko 2006).

Recent evidence suggests that EMT plays a critical role in cancer progression by promoting drug resistance and invasion and localized carcinoma metastasis (Jeanes et al. 2008). Cells with EMT acquire the ability to degrade the basement membrane as a result of increased activity of matrix metalloproteases (such as MMP2, MMP3, and MMP9); these cells migrate through the ECM to populate different areas during cancer progression or behave like profibrotic myofibroblasts in the interstitial spaces between tissues. Certain cytokines and transcriptional factors, such as TGF-β1, IL-1, TNF-α, NF-κB, and HIF-1, which are known for their role in controlling inflammation and inducing tumor cell death, can act as inducers of the EMT through a complex network of effectors (Singh and Settleman 2010). For example, TGF-β proteins can activate both Smad and non-Smad signals, which can then cross talk with other signaling pathways to provide context-dependent outcomes. Although our understanding of the molecular mechanism of EMT has significantly advanced during the past decade, much work is needed to define the transcriptional regulatory networks and key target genes that drive EMT in a context-specific manner. In this regard, our recent findings that TGF-β-induced EMT in mammary epithelial cells depends on TG2 expression is significant (Kumar et al. 2010). MCF10A cells harboring TG2-specific shRNA failed to undergo mesenchymal transition after treatment with TGFβ. In contrast, cells transfected with control shRNA and treated with TGFβ under identical conditions showed morphologic and molecular alterations that were typical of mesenchymal cells.

TG2 expression in cancer cells that exhibit chemotherapy resistance or isolated from metastatic sites has been associated with constitutive activation of FAK, Akt, and NF-κB and downregulation of the tumor suppressor protein PTEN (Verma et al. 2008). TG2-mediated activation of these oncogenic pathways probably contributes to increased invasiveness and chemotherapy resistance in these cancer cells. Using gain- and loss-of-function strategies, we and others observed that TG2 expression in mammary epithelial and ovarian cancer cells induces EMT, as revealed by a cadherin switch and increased invasive behavior (Fig. 3). The TG2-induced EMT in these cells was mediated at the transcriptional level by altered

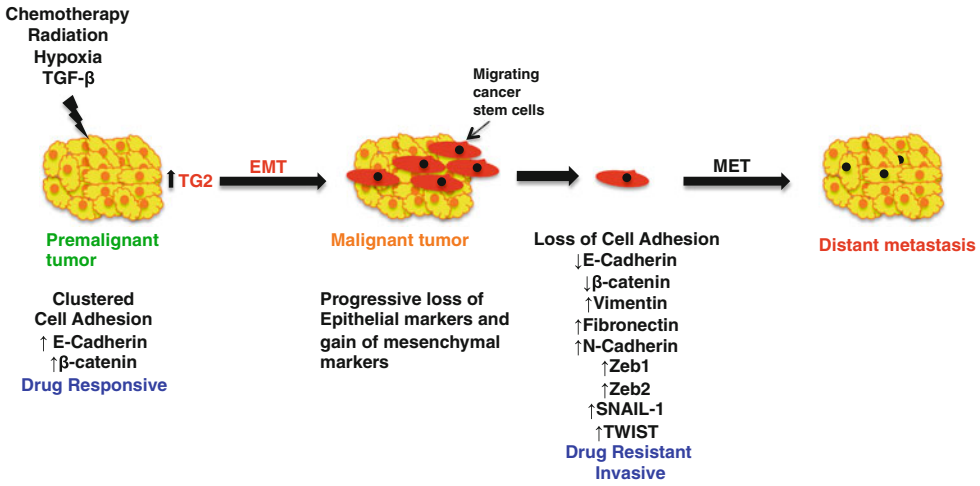

Fig. 3 Aberrant TG2 expression in epithelial cancer cells promotes an aggressive phenotype by inducing EMT and stem cell traits

expression of transcriptional repressors such as *Snail*, *Slug*, *Zeb1*, *Zeb2*, and *Twist* (Kumar et al. 2010; Shao et al. 2009). One possible mechanism through which TG2 could induce these repressors is by constitutively activating the proinflammatory transcription factor, NF-κB (Mann et al. 2006; Verma and Mehta 2007a, b).

Recently, it was proposed that EMT enables cancer cells not only to disseminate but also to acquire a self-renewal ability by inducing a stem cell-like state. Cancer stem cells may also be responsible for the formation of macroscopic metastases. In line with these observations, our recent findings suggested that sustained TG2 expression confers stem cell-like properties in non-transformed and transformed mammary epithelial cells (Kumar et al. 2011). Thus, TG2 expression is associated with an increased $CD44^{high}/CD24^{low/-}$ subpopulation, an increased mammosphere-formation ability in cells, and the acquisition of self-renewal ability. Mammospheres derived from TG2-transfected mammary epithelial cells (MCF10A) differentiated into complex secondary structures when grown in Matrigel cultures (Kumar et al. 2011). These observations imply that constitutive TG2 expression not only induces the EMT that enables cancer cells to disseminate, but also leads them to acquire self-renewal ability by inducing a stem cell state (Fig. 3). Further studies are needed to characterize the complex molecular network through which TG2 modulates EMT and stem cell characteristics in epithelial cells.

Consistent with aberrant TG2 expression's promotion of EMT and the stem cell state in cancer cells, TG2 inhibition resulted in drug resistance reversal and attenuated pancreatic cancer (Verma et al. 2008), ovarian cancer (Hwang et al. 2008), lung cancer (Frese-Schaper et al. 2010), malignant melanoma (Fok et al. 2006), and glioblastoma (Yuan et al. 2005) cell invasion. These findings clearly imply that aberrant TG2 expression is an important step in the acquisition of EMT and plasticity and hence is an excellent therapeutic target for treating advanced-stage aggressive cancer. Indeed, as a proof-of-concept, we showed that TG2 downregulation by liposomal siRNA is highly effective at blocking the dissemination and reversing the sensitivity of orthotopically growing ovarian (Hwang et al. 2008) and pancreatic (Verma et al. 2008) tumors to chemotherapeutic drugs. A thorough investigation of the structure-based design and identification of small molecule inhibitors that block TG2-regulated signaling and pathways may offer therapeutic modalities for chemoresistant and metastatic cancer, which account for more than 90% cancer-related deaths.

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