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REVIEW

The role of the epithelial-to-mesenchymal transition (EMT) in diseases of the salivary glands

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Abstract

The link between inflammatory microenvironment and cancer emerged in the last years as a decisive factor in the induction of the pathological epithelial–mesenchymal transition (EMT). The EMT induces changes of cell states converting the epithelial cells to mesenchymal cells when this program is fully executed and EMT has emerged as a central driver of tumor malignancy. Cellular pathways activated by chronic inflammation brought about by chronic infections, by immune-mediated diseases, or by dysregulated wound healing at sites of repetitive tissue injury, constitute risk factors or initial cell transformation and for cancer progression. EMT and its intermediate states have recently been identified as crucial inducers of organ fibrosis, inflammation and tumor progression. In this review, we discuss the current state-of-the-art and latest findings regarding the link between EMT, inflammation, fibrosis and cancer, highlighting the most recent data on EMT-dependent tissue fibrosis during chronic inflammatory salivary glands conditions and salivary glands tumors.

Keywords Epithelial–mesenchymal transition · Fibrosis · Inflammation · Salivary glands · Cancer

Introduction

The process known as epithelial–mesenchymal transition (EMT), essential for the accurate development during embryogenesis and also for wound healing, is involved in many pathological processes such as degenerative fibrosis and cancer (Thiery and Sleeman 2006; Thiery et al. 2009; Kalluri 2009; Chapman 2011). Initially described as the "epithelial-to-mesenchymal transformation", this trans-differentiation process is now commonly termed EMT to emphasize the transient nature of the transformation of epithelial cells into motile mesenchymal cells (Kalluri 2009). During EMT, distinct molecular processes are activated: loss of junctions and apical-basal polarity by epithelial cells, activation of transcription factors, downregulation of epithelial cell-surface proteins and up-regulation of mesenchymal markers, reorganization and expression of cytoskeletal proteins, production of extra cellular matrix (ECM)-degrading enzymes, modification of the cell shape from cuboidal to fibroblastoid and re-programming of gene expression by specific micro-RNAs (Thiery and Sleeman 2006; Kalluri 2009; Thiery et al. 2009) (Fig. 1). All these processes increase the motility of individual cells and enable the development of an invasive phenotype characterized by the capacity to degrade the basement membrane and migrate through the ECM to populate different territories during embryonic development but also in cancer progression (Acloque et al. 2009; Kalluri and Neilson 2003; Kalluri and Weinberg 2009).

EMT was classified in three different biological subtypes based on the biological context and different functional consequences (Fig. 2). The results of studies conducted since 2007 have suggested several characteristics for the classification of EMT: type 1 EMT affects embryo formation, gastrulation, neurulation, and neural crest formation (Thiery et al. 2009; Zeisberg and Neilson 2009; Kalluri and Weinberg 2009). The second EMT subtype, type 2 EMT, is linked to wound healing, tissue regeneration, and organ fibrosis. During the course of organ fibrosis, type 2 EMT can lead to organ failure following the persistent release of a variety of

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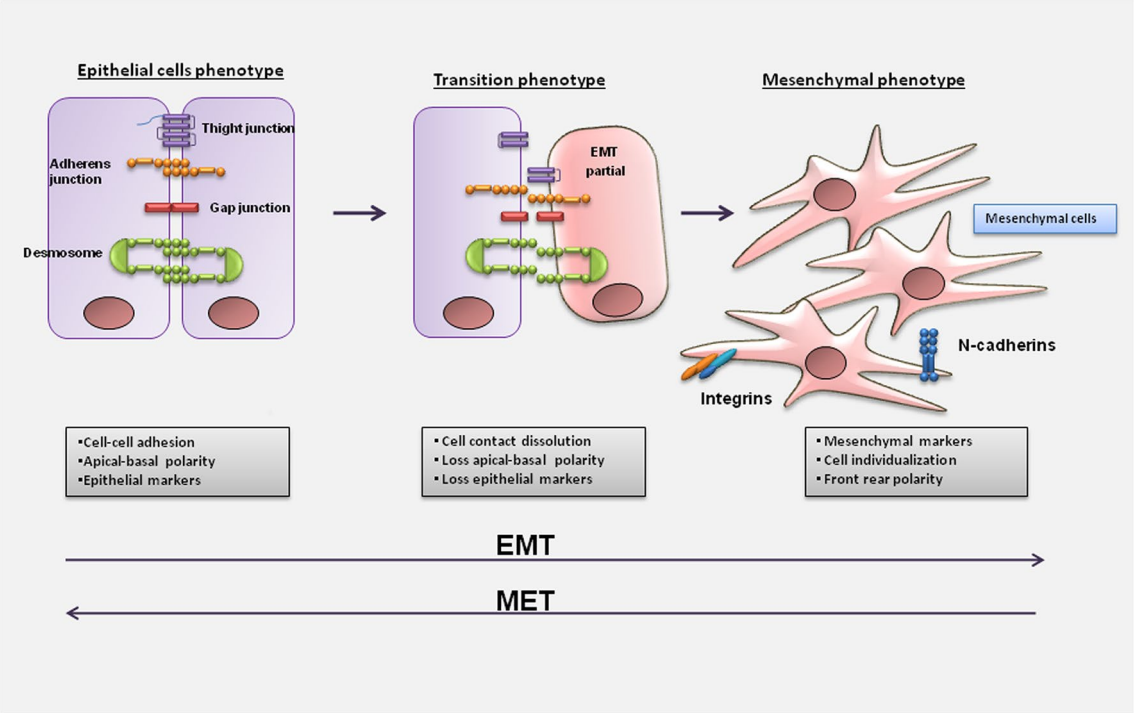

Fig. 1 Schematic cellular processes during epithelial–mesenchymal transition (EMT). The first steps of the EMT program are the dissolution of cell–cell contacts, the loss of the apical-basal polarity and of epithelial markers expression; concomitantly, the activation of mesenchymal genes expression and acquisition of the mesenchymal phenotype with front-rear polarity take place. The reversion of cells that have undergone EMT to the epithelial phenotype occurs through the mesenchymal–epithelial transition (MET)

inflammatory signals (Kalluri 2009; Zeisberg and Neilson 2009; Kalluri and Weinberg 2009) (Fig. 2). Type 3 EMT is involved in cancer progression and metastasis (Balkwill et al. 2005; Kalluri and Zeisberg 2006; De Visser et al. 2006; Mantovani et al. 2008; Wu and Zhou 2009).

The primary mesenchyme can be re-induced to form secondary epithelia by a mesenchymal–epithelial transition (MET) program (Figs. 1, 2) (Thiery et al. 2009). MET is a reversible biological process that involves the transition from mesenchymal cells to polarized epithelial cells. MET takes place during normal development (Ouyang 1998); moreover, MET occurs in cancer metastasis, induced pluripotent stem cell reprogramming and mucosal healing (Thiery et al. 2009). The induction and regulation of this complex, reversible biological program are not fully understood. MET during carcinogenesis has been shown to be induced by the c-met proto-oncogene (c-MET) (Tsarfaty et al. 1994), because through its increased expression leads to epithelial differentiation. In addition, other factors such as Frizzled-7, a receptor for the canonical Wnt signalling pathway (Vincan et al. 2007), 5-azacytidine, a DNA methyltransferase inhibitor (Darmon et al. 1984) and a stable RNA interference-mediated inhibition of Snail expression in carcinoma cell lines was demonstrated to induce a complete MET program (Chen et al. 2013). The induction of MET is also of major clinical importance. In the case of severe mucosal damage, the time for complete epithelial regeneration may be reduced by enhancing the MET program.

Since the EMT is now considered a converging point among inflammation, fibrotic diseases and cancer (Arnoux et al. 2008; Futterman et al. 2011; Huang et al. 2012; Tam and Weinberg 2013; Grigore et al. 2016; Nieto et al. 2016; Suarez-Carmona et al. 2017), here we review the relationship between inflammation, EMT, fibrosis and cancer progression. Fibrosis results from a repair or reactive process; under chronic inflammatory conditions, fibrosis progresses to advanced states that lead to the destruction of organ architecture and the impairment of organ function (Kalluri and Neilson 2003). Fibroblasts/myofibroblasts are the primary "effector" cells in the pathogenesis of fibrosis. Both EMT and myofibroblastic differentiation are common cellular events during wound healing, tissue regeneration, development, but also in inflammation, fibrosis and tumor progression. It is now clear that the same cell types, as well as soluble and matrix elements that drive wound healing, also fuel chronic fibrosis and tumour progression via distinct signaling pathways (Fig. 2). Since salivary glands (SGs) provide an excellent model facilitating the study of epithelial–mesenchymal interactions, this review also focuses on the most recent studies that have offered better insights into

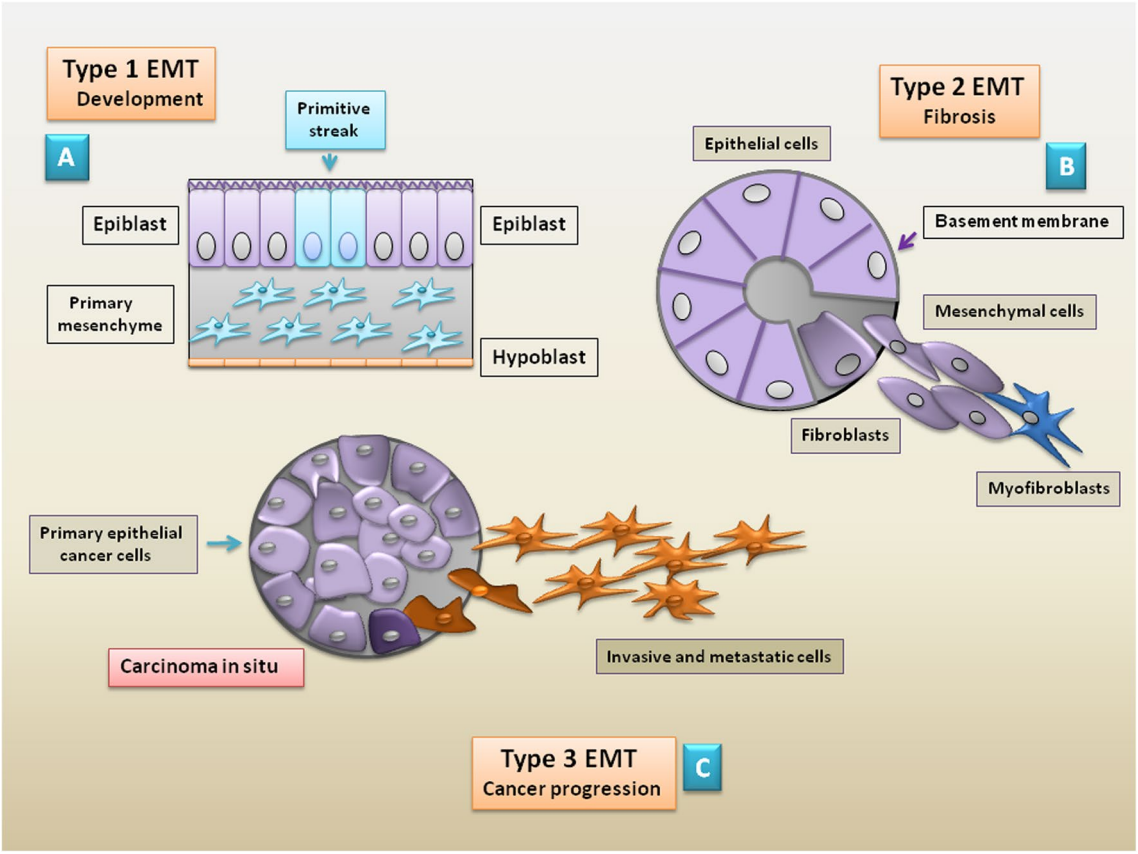

Fig. 2 Different EMT program subtypes. **a** Type 1 EMT occurs during embryogenesis and organ development. Epithelial cells of the epiblast give rise to mesenchyme organization by EMT program. **b** Type 2 EMT is important in the context of inflammation and organ fibrosis. **c** Type 3 EMT is linked with cancer progression and metastasis

the mechanisms of EMT-dependent tissue fibrosis during SGs' diseases and SGs' tumors.

Multiple molecular signals driving the EMT program

Multiple paracrine signaling factors can induce the EMT process by activating a corresponding set of several intracellular signaling pathways. An elevated and forced expression of EMT-inducing transcription factors (Scheel et al. 2011) in epithelial cells has been well documented in metastatic cancers (Yang et al. 2004; Peinado et al. 2007; Gregory et al. 2008; Mani et al. 2008; Guo et al. 2012; Wellner et al. 2009). During disease, activation of the EMT process can occur in an uncoordinated and cell-independent fashion, leading to the disruption of epithelial integrity that sequentially determines a shift in cytoskeletal dynamics and thereby to a disorganization of epithelial tissue as well as the production of new mesenchymal cells, which can perpetuate the disease process. Regulation of the EMT includes key components of epithelial junctions for transcriptional suppression such as E-cadherin (E-cad), one of the major components of adherent junctions and the hallmark of epithelial integrity (Larue et al. 1994; Berx et al. 1995; Thiery and Sleeman 2006; Perez-Moreno and Fuchs 2006; Onder et al. 2008; Yang and Weinberg 2008; LaBarge et al. 2009; Kalluri and Weinberg 2009; Thiery et al. 2009; Derksen et al. 2011; Lamouille et al. 2014; Zhou et al. 2017).

EMT is induced by a series of specific transcription factors that include members of the Snail, ZEB, and Twist families; these factors are known to regulate the expression of the cadherin family and in particular, E-cad. Nevertheless, transcriptional repression of E-cad by Twist1 remains a central event in cancer metastasis (Peinado et al. 2007; Yang and Weinberg 2008). Searching for genes involved in mouse mammary tumor metastasis, the currently accepted role of Twist1 was first described (Yang et al. 2004). Elevated levels of Twist1 expression associated with loss of E-cad expression were demonstrated in human breast cancers and correlated with high-grade invasive lobular carcinoma (Bill and Christofori 2015). These results demonstrate a link among Twist, EMT, and cancer progression (Yang et al. 2004; Mironchik et al. 2005). Among transcriptional repressors

of E-cad, the Snail family members of zinc finger proteins (Snail1/Snail, Snail2/Slug and Snail3/Smuc) are prominent examples of a common downstream target of various signaling pathways that regulate EMT (Barrallo-Gimeno and Nieto 2005; Peinado et al. 2007; Lamouille et al. 2014). Snail transcription factors induce EMT, contributing to the generation of many tissues during embryonic development and to the acquisition of metastatic properties (Rowe et al. 2009; Hotz et al. 2010).

Epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), transforming growth factor β 1 (TGF-β1), bone morphogenetic proteins (BMPs), WNTs and Notch are also able to activate the EMT program. These multiple signaling pathways seem to converge leading to Snail expression in all processes of EMT studied, inducing Snail genes in normal development and during tumor progression (De Craene et al. 2005). Many recent reports have suggested alternative mechanisms for tumor dissemination. Interestingly, many metastases, examined histologically, express epithelial markers and it has been hypothesized that cells transition back to an epithelial state through MET to form secondary metastases (Yang and Weinberg 2008; Kalluri 2009). Indeed, the tumor cells that have undergone EMT, becoming circulating tumor cells (CTC), leave the primary tumor site, migrate through the stroma to reach blood capillaries, and revert back to the epithelial phenotype. In this way they become able to grow in the secondary site, through the dissemination of cancer cells that gives rise to clinically detectable distant metastatic lesions (Banyard and Bielenberg 2005). These CTC referred to as circulating tumor microemboli, were observed in patients with invasive melanoma-derived lung metastases, inflammatory breast cancer, renal cancer and colon-derived liver metastases (Hong et al. 2016).

A wealth of literature in recent years, has highlighted the importance of the post-translational regulators of EMT progression. Micro-RNA (miRNAs) that are able to target the expression of key proteins that in turn modulate these processes, have been reported as new potent regulators and repressors of the EMT program (Warzecha and Carstens 2012; Lamouille et al. 2013). Therefore, miRNAs have emerged as key effector molecules of most physiological and pathological processes, including metastatic cancer progression (Park et al. 2008; O'Day and Lal 2010).

Multiple miRNAs modulate EMT machinery (Díaz-López et al. 2014), establishing a negative feedback that under normal conditions is thought to maintain epithelial homeostasis (Puisieux et al. 2014). Indeed, various epithelial markers are downstream targets of this regulatory loop, including E-cad, claudins, and occludins (Jordan et al. 2011; Lamouille et al. 2014; Bedi et al. 2014). Therefore, the consequences of the epigenetic changes triggered by multiple signals during EMT confer dynamic control over nuclear organization during the transcription of EMT effector genes (Korpal and Kang 2008; Abell et al. 2011; Jordan et al. 2011; Wu et al. 2012; Enkhbaatar et al. 2013; Ding 2014; Chung et al. 2016).

Moreover, like epithelial cells, endothelial cells can also shift to a mesenchymal phenotype, a process known as endothelial–mesenchymal transition (EndMT), evident during cardiac, renal and pulmonary fibrosis (Zeisberg et al. 2007b; Medici and Kalluri 2012; van Meeteren and ten Dijike 2012; von Gise and Pu 2012). EndMT is an important source of fibroblasts known to promote the invasiveness of cancer (Zeisberg et al. 2007a; Potenta et al. 2008; Medici and Olsen 2012). A schematic overview of the major signaling pathways involved in the EMT program is reported in Fig. 3.

Type 2 EMT as biomarker in fibrosis

Fibrosis is usually the end result of many chronic inflammatory diseases and may lead to loss of function and organ failure (Campanholle et al. 2013; Xue et al. 2013). Damaged tissues show an increased number of resident fibroblasts in response to a multifactorial network of chemical signals which migrate, proliferate (Schaeffer et al. 2014) and proceed toward differentiated myofibroblasts (Micallef et al. 2012), passing through an intermediate phenotype or proto-myofibroblastic stage (Desmouliere et al. 2005). Myofibroblasts play an important role in organogenesis and oncogenesis (De Wever and Mareel 2003), inflammation, repair, and fibrosis in most organs and tissues (Hinz et al. 2007). Myofibroblasts upregulate ECM deposition and produce ECM molecules such as collagen type I, glycosaminoglycans, tenascin, and fibronectin, involved in their growth, differentiation and wound healing function (Hinz et al. 2012). Epithelial cells that undergo type 2 EMT contribute, in a direct way, to the pool of fibroblasts and myofibroblasts during fibrogenesis (Kalluri and Weinberg 2009). Type 2 EMT is characterized by a change from the apical-basolateral polarity of the epithelial cells to the front-rear polarity of the mesenchymal cells. These changes are characterized by the decreased cellular expression of epithelial markers and the acquisition of new mesenchymal markers, such as fibroblast-specific protein-1 (FSP1), vimentin, N-cadherin, and α-SMA gaining a fully fibroblastic phenotype (Zavadil and Bottinger 2005; Lorusso and Ruegg 2008; Kalluri and Weinberg 2009; Nakamura and Tokura 2011; Carew et al. 2012; Lekkerkerker et al. 2012). The expression of α-SMA in microfilament bundles or stress fibers leads these cells to exhibit a motile and invasive phenotype. Indeed, persistent myofibroblast activation is a shared feature of fibrotic diseases and the dysregulation of injury-triggered EMT is

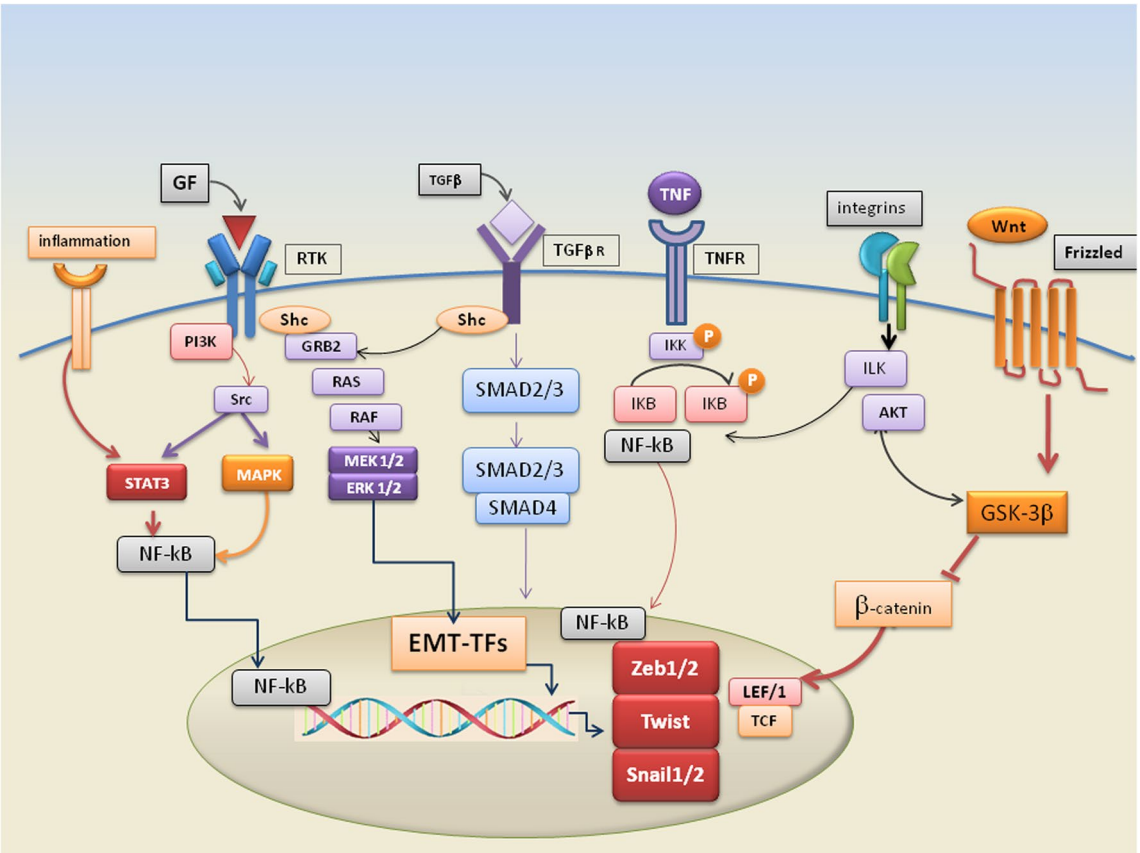

Fig. 3 Overview of the major signaling pathways involved in the EMT program. EMT progression is regulated by several signaling pathways that cooperate to trigger the EMT program. Transforming growth factor-β (TGF-β), by interacting with SMAD protein and TGF-β receptors activates the EMT program, inducing the phosphorylation of the adaptor protein homology 2 domain-containing-transforming A (Shc), which creates a site for growth factor receptor-bound protein 2 (GRB2) and son of sevenless (SOS); these events lead to the activation of the RAS/RAF/MEK/ERK/MAPK pathway. Several growth factors (GF) that act through receptor tyrosine kinases (RTKs), including epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF), activate the EMT program. The RAS/RAF/MEK/ERK/MAPK signaling cascade is the major pathway activated by RTKs in response to these growth factors. The WNT signaling activation pathway initiates by binding to Frizzled receptors; this determines the inhibition of β-catenin-negative regulator, glycogen synthase kinase-3β (GSK3β), and the stabilization of β-catenin, which translocates to the nucleus to engage the T-cell factor (TCF) and the lymphoid enhancer factor1 (LEF1) that are the major end point mediators of the EMT program. The cellular microenvironment also regulates the EMT process. During inflammation, the cytokines promote the EMT process through the activator of transcription 3 (STAT3)-induced SNAIL1 expression. All these signaling cascades are able to induce the activation of transcription factors (TFs) that, through binding to EMT-inducing transcription factors genes promoters, determine the synthesis of Snail1/2, ZEB1/2 and Twist, which induce EMT by repressing the expression of genes encoding cell adhesion molecules. ILK, integrin-linked kinase

believed to contribute to fibrosis of multiple organs (Terao et al. 2011).

In vitro and in vivo evidence of EMT-dependent fibrosis

Studies conducted on cultured cells in vitro have shown that the presence of pro-fibrogenic factors determines the transformation of epithelial cells derived from the kidney, lung, and liver into mesenchymal cells (Iwano et al. 2002; Chilosi et al. 2003; Kalluri and Neilson 2003; Li et al. 2016). TGF-β1, a pro-fibrotic factor, plays a key role in the induction of the EMT in various epithelial cells (Farris and Colvin 2012). In addition to gathering data on pro-fibrogenic factors, there are a number of molecules that can promote EMT, inducing the loss of the epithelial phenotype, and the acquisition of a spindle-like fibroblastic morphology, more amenable to cell migration. Hypoxia (Du et al. 2012), high levels of glucose, angiotensin II, and albumin (Ibrini et al. 2012; Lee et al. 2013), and also inflammatory mediators (Lopez-Novoa and Nieto 2009) and matricellular proteins can promote EMT (DeMaio et al. 2012; Schneider et al. 2012). These results have been confirmed by in vivo studies. Progressive chronic kidney disease characterized by interstitial fibrosis can lead

to tubular atrophy, loss of kidney function and end-stage renal failure (Liu 2010). Several studies have provided evidence that EMT-derived myofibroblasts originating from tubular epithelia contribute to renal fibrosis (Fragiadaki and Mason 2011). Different experimental procedures based on animal models, human kidney biopsies, staining techniques for epithelial and fibroblast cell lineage markers, lineage tags and activation of various transcriptional signals known to activate the EMT program, demonstrated the correlation of EMT with the severity of various chronic kidney diseases such as glomerulonephritis, diabetic nephropathy and chronic allograft nephropathy (Iwano et al. 2002; Rastaldi et al. 2002; Strutz et al. 2002; Zeisberg et al. 2003; Nishitani et al. 2005; Higgins et al. 2007; Inoue et al. 2009; Humphreys et al. 2010; Macary et al. 2010; Duan et al. 2012; Xu et al. 2013). In addition, in patients with fibrosis-inducing obstructive nephropathy, obstructed tubular epithelial cells expressed FSP1 (Okada et al. 1997), and acquired an EMT-like fibroblast morphology (Inoue et al. 2009; Nishitani et al. 2005). Furthermore, tubular epithelia cells are also able to release ECM proteins, that are clinically positively correlated with elevated levels of serum creatinine and markers of renal dysfunction and interstitial fibrotic damage (Rastaldi et al. 2002). The expression of FSP1 in transitioning tubular epithelium is induced by TGF-β1 (Fan et al. 1999; Okada et al. 2000; Strutz et al. 2002; Strutz and Neilson 2003); in fact, tubular basement membrane disintegration leads to TGF-β1 up-regulation by mouse proximal tubular epithelial cells, contributing to EMT during renal fibrosis (Zeisberg et al. 2001).

The contribution of EMT during single-walled carbon nanotube-induced pulmonary fibrosis was investigated in a mouse model by Chang et al. (2012), who demonstrated the downregulation of E-cadherin balanced by the increased occurrence of epithelial cell-derived fibroblasts expressing vimentin and neural cadherin (N-cadherin). Similarly, lung epithelial cells expressing vimentin were reported by Kim et al. in an established pulmonary fibrosis model used a cell fate-reporter mouse (Iwano et al. 2002) with overexpressing active TGF-β1 (Kim and Kim 2013) and FSP1-positive mesenchymal cells derived from the lung epithelium in bleomycin-induced pulmonary fibrosis were detected in the same experimental mouse model (Tanjore et al. 2009).

Evidence clarifying the role of EMT in liver fibrosis is still under still debate. Hepatocytes do not seem to undergo EMT in vivo, and they do not seem to be transformed into collagen-producing cells in liver fibrosis (Taura et al. 2010). In fact, the principal source of the myofibroblast population in transgenic mice seems to be the hepatic stellate cells (Mederacke et al. 2013), as neither hepatocytes nor cholangiocytes seem to undergo EMT (Scholten et al. 2010; Chu et al. 2011). In contrast, earlier studies suggested that fibroblasts were derived from hepatocytes that underwent EMT (Zeisberg et al. 2007b) and, interestingly, miRNAs can modulate EMT in cultured hepatocytes through TGF-β inhibition (Zhao et al. 2014; Brockhausen et al. 2015). Using a carbon tetrachloride (CCl4)-induced model of liver fibrosis, several authors demonstrated the transdifferentiation of hepatocytes into FSP1-positive fibroblasts that lost albumin and had an activated Laz gene which drives the EMT, in a similar process to the one occurring in the kidney (Iwano et al. 2002; Zeisberg et al. 2007a). In the light of these studies, the new data deriving from renal fibrosis (Grande et al. 2015; Lovisa et al. 2015), have led many researchers to speculate on the exact role of type 2 EMT in contributing to the development of liver fibrosis. In parallel with what has been observed in the kidney, damaged hepatocytes could secrete signals after undergoing a partial EMT, which promotes stellate cell transdifferentiation and enhances inflammation. The demonstration that parenchymal cells express multiple mesenchymal markers in patients with advanced chronic liver disease supports the in vivo role for TGF-β1-induced EMT in human hepatic fibrosis (Diaz et al. 2008; Rygiel et al. 2008).

Morphogenesis and physiology of SGs

The human SGs' system comprises the major salivary glands [submandibular (SMG), parotid (PG), and sublingual glands (LSG)] and also, additionally, hundreds of minor glands located in the mucosa of the upper aerodigestive tract, including the buccal, labial, palatoglossal, palatal and lingual glands (Martinez-Madrigal and Micheau 1989). SGs secrete saliva, that is essential for digestion, vocalization, taste, remineralization, as well as for immunity, and the overall maintenance of homeostasis within the human body (Pedersen et al. 2002).

Early works suggested that development of the SGs is initiated by the presence of a primordial anlage that invaginates into a condensed mesenchyme containing an endothelial plexus. This single epithelial bud undergoes rounds of branching morphogenesis, defined by multiple cycles of cleft formation, expansion of end buds (pre-acini), and duct tubulogenesis (Redman 1987). Subsequently, the formation of lobules and duct canalization arises and ciliated epithelial cells cover the inner part of the lumen, while external surfaces are lined by ectodermal myoepithelial cells. Then, the maturation of the acini and intercalated ducts occurs, and finally, the branches of the salivary glands terminate in saliva-producing acini (Redman 1987). The major salivary glands contribute approximately 90% of saliva production. Therefore, SMG and LSG secrete saliva under resting conditions, while PG secretes saliva upon stimulation. The endocrine, paracrine and autonomic nervous systems control salivary secretion (Redman 1987).

In general, parasympathetic and sympathetic nerves regulate salivary secretion (Proctor and Carpenter 2007). Parasympathetic nerves primarily stimulate water secretion, in part through transmembrane water channels, including aquaporin 5 (AQP5) (Ma et al. 1999) as well as paracellular pathways (Nakahari et al. 1998; Murakami et al. 2001); this occurs in response to acetylcholine, that activates M3 and M1 receptors in both acinar and ductal cells of the acini (Gautam et al. 2004; Nakamura et al. 2004). Sympathetic nerves, on the other hand, control the enzyme secretion from acinar cells and fluid and electrolyte transport in ductal cells (Anderson et al. 1988). Once secreted, saliva flows through a series of water-impermeable ducts (intercalated, striated, and excretory) that create as first step, an isotonic-like fluid and subsequently modify the composition of the fluid by reabsorbing most ions for delivery to the oral cavity (Baum 1993).

Salivary glands provide an excellent model for the study of the EMT program, since it is a key mechanism for appropriate embryonic development, and furthermore, EMT events could be best investigated in oral tissues, owing to the greater epithelial presence in the development of organs of the oral cavity. Likewise, this program switches on again in adults during repair the injured tissue, organ fibrosis, and tumor progression. The fibrotic process that occurs in the SGs can also be considered as the end result of chronic inflammatory reactions induced by a variety of stimuli including persistent infections and autoimmune reactions; these pathological conditions lead to glandular failure and constitute risk factors for initial cell transformation and for cancer progression.

Role of EMT in SGs' fibrosis

The concept that injury triggers the inflammatory wound healing cascade, and pathologically sustained inflammation is tightly associated with fibrogenesis was recently associated with atrophy and fibrosis of SGs, but the underlying mechanism is not clear. In the SGs, fibrosis specifically causes constriction of secretory components, leading to hyposalivation and xerostomia (Ficarra 1996). SGs' fibrosis typically occurs after repeated episodes of inflammation following chronic infections in the glands or the autoimmune disease Sjögren's syndrome (SS) (Koski et al. 1995, 2001; Skopouli et al. 1998). Fibrosis of the glands also occurs due to tissue damage from radiation, particularly during radiotherapy treatment for head-and-neck cancer (Cooper et al. 1995), that has been shown to induce TGF-β1 expression (Martin et al. 2000). This was experimentally confirmed using a transgenic mouse that conditionally over-expresses the active TGF-β1; in this context, the overexpression of active TGF-β1 leads to an excessive accumulation of ECM proteins, thus affecting, the capacity of the mutated mice to secrete saliva (Hall et al. 2010). Interestingly, most of the normal glandular parenchyma was replaced with fibrotic tissue and this most likely caused the lack of saliva secretion in the adult mice. ECM proteins and other indicators of fibrosis like connective tissue growth factor and α-SMA were upregulated in response to the transgenic expression of TGF-β. Aberrant active TGF-β1-overexpression in mice causes salivary gland hypofunction and submandibular gland atrophy in animal models (Bhaskar et al. 1956; Teymoortash et al. 2003). Obstruction of the SGs in these cases often leads to the degeneration of acinar cells, dilation of the ducts and increased fibrotic tissue (Fig. 4). In addition, many patients with SS develop progressive fibrosis in their SGs (Koski et al. 1995, 2001; Skopouli et al. 1998), although clinical studies on TGF-β production in SS has yielded conflicting results (Cauli et al. 1995; Kizu et al. 1996; Mason et al. 2003; Nandula et al. 2007). High-radiation dose for head-and-neck cancer can also cause fibrosis of the submandibular gland associated with a higher frequency of small-dilated ducts (Cooper et al. 1995); in addition, following radiotherapy SGs can lead to the excessive production of ECM induced by TGF-β, contributing to radiation-induced salivary gland fibrosis (Martin et al. 2000; Hall et al. 2010; Woods et al. 2015). Extensive SGs' fibrosis results in diminished saliva production which, in turn, leads to dysphagia, dysgeusia, oral pain, dental caries, oral infection and periodontal disease (Sroussi et al. 2017). Irradiated rat submandibular glands show a downregulation of AQP5 expression that could be one of the mechanisms of radiation-induced xerostomia; a similar reductions in AQP5 staining was detected in SGs of the transgenic mouse beta1(glo) that conditionally overexpresses active TGF-β1 (Li et al. 2006). β1glo/MC mice had reduced salivation caused by salivary gland fibrosis and, in addition, an altered TGF-β1 overexpression determined salivary gland hypofunction in this mouse experimental model (Hall et al. 2010). Overall, changes in the expression levels of TGF-β1 could have a profound impact on the SGs' physiology. TGF-β1 defective signaling may be one of the triggering factors behind autoimmunity in the SGs (Kizu et al. 1996; Nandula et al. 2007). On the contrary, when an excess of TGF-β1 was produced, the replacement of the normal SGs' parenchyma with connective tissue was well documented (Hall et al. 2010) (Fig. 4). Altogether, these observations indicate that TGF-β1 could be implicated in pathological cases of SGs' inflammation and fibrosis occurring during chronic infection conditions in the glands or the autoimmune disease SS or following radiation therapy given to head-and-neck cancer patients. Therefore, a balanced TGF-β1 expression and signaling is required for normal SGs' homeostasis.

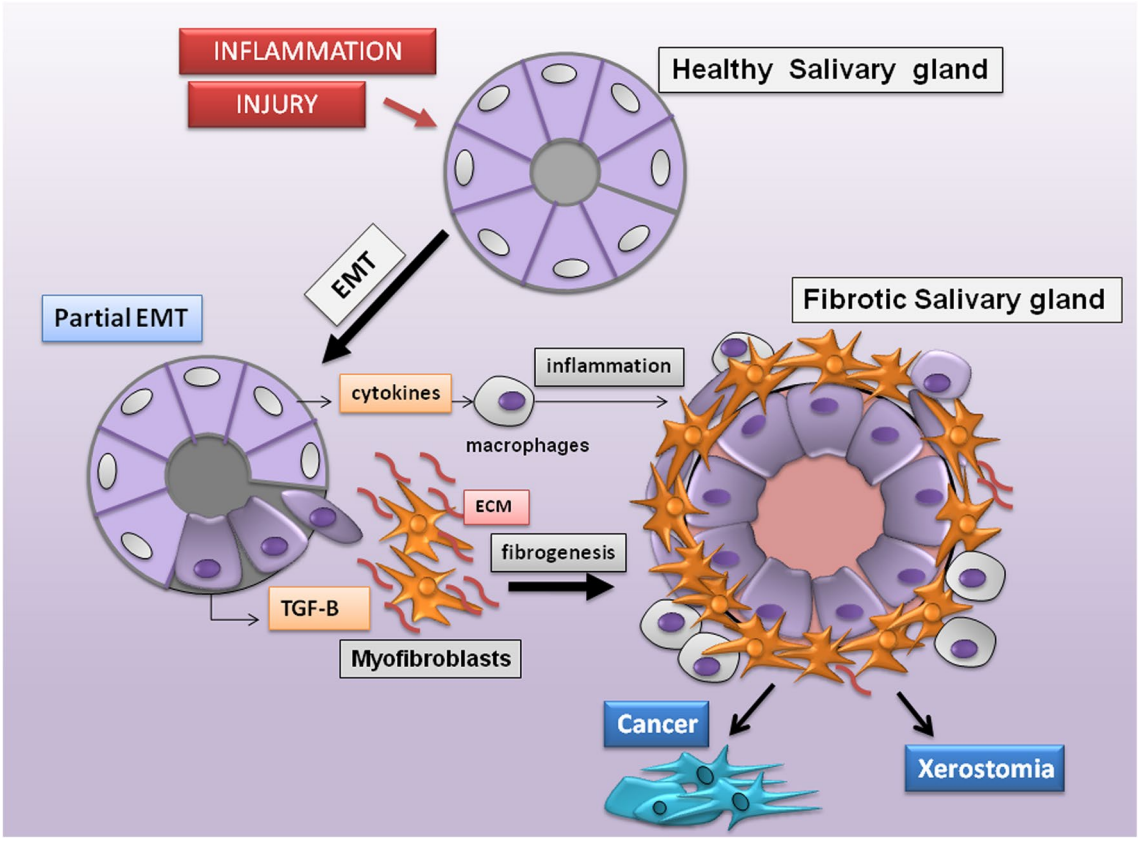

Fig. 4 Schematic representation of the type 2 EMT induced by injury or inflammation in healthy SGs. The type 2 EMT program begins following injury or inflammation-associated events; healthy salivary epithelial cells undergo a partial EMT characterized by the loss of epithelial and specific differentiation markers and of the apical-basal polarity. These damaged salivary epithelial cells acquire mesenchymal markers, leave the epithelial layer through the basement membrane, accumulating in the tissue interstitium, where they gain a fibroblastic phenotype. In fibrotic salivary tissue, fibroblasts convert to myofibroblasts, secreting an excessive amount of extracellular matrix (ECM) components that compromise organ function, leading to organ failure. Therefore, up-regulation of TGF-β by damaged epithelial salivary cells, during chronic inflammation, stimulates fibrogenic processes and tumor promotion

Prognostic relevance of EMT in SGs' malignancies

Cancer of the major salivary glands comprises a morphologically diverse group of rare deadly tumours of largely unknown cause accounting for 2–6.5% of all head-and-neck tumors (Bell and Hanna 2012). Salivary adenoid cystic carcinoma (SACC) and mucoepidermoid carcinoma (MEC) are among the most common malignancies of the major and minor SGs (Ellington et al. 2012) that account for approximately 15–25% of all malignant salivary gland carcinomas (Khan et al. 2001; Persson et al. 2009). SACC and MEC present metastasis into adjacent tissue and distant organs (lung, bone and liver) (Adams et al. 2013) and are characterized by a poor long-term outcome. Furthermore, SGs' cancers pose a highly significant public health issue due to the lack of progress in finding effective treatments.

Increasing literature data show that EMT has a pivotal role in invasion and metastasis of these salivary tumors, driving the conversion of the polarized, epithelial phenotype to a motile fibroblastoid or mesenchymal phenotype (Thiery et al. 2006). Snail1 and Slug genes, biomarkers of EMT, have also resulted linked to an increased tumor invasiveness and are considered as both diagnostic markers and therapeutic targets for diagnosis of salivary gland cancers (Jiang et al. 2010; Tang et al. 2010). Transcription factor Snail1 is reported to repress E-cad expression and allows epithelial cells to acquire enhanced migratory and invasive properties (Jiang et al. 2010). Elevated levels of Snail1 expression were significantly associated with perineural invasion, local regional recurrence, and distant metastasis of SACC, and the patients with positive Snail1 had a poorer prognosis (Jiang et al. 2010).

Slug (Snail2) is an important mediator of EMT and is involved in tumor growth, invasion and metastasis; recently, some researchers have established that the c-kit signaling pathway mediated by elevated levels of Slug expression promotes invasion and metastasis in SACC

patients (Tang et al. 2010). c-kit was demonstrated to be able to activate the EMT process in SACC cells and to generate cancer stem cells (CSC) thus contributing to a dramatic increase in metastases formation (Tang et al. 2014). Some studies have demonstrated that CSC are resistant to standard chemotherapy and radiation treatments; in fact emerging evidence also suggests that the surrounding tumor microenvironment allows CSC to survive chemo and radiation therapies as well as to sustain the self-renew capacity and metastatic cancer progression (Morrison and Spradling 2008; Tang et al. 2014). For such reasons, the detection and enrichment of CSC are intriguing elements in the context of salivary gland tumors, which are not responsive to chemotherapy treatments. Initial emerging research has highlighted that aldehyde dehydrogenase (ALDH) activity is a potential CSC marker and SACC cells with an elevated ALDH level have a strong self-renewal capacity and acquire invasive, and metastatic tumor properties (Zhou et al. 2013; Sun and Wang 2010).

Recent evidence has highlighted the critical functions and potential role of pro-oncogenic protein AGR2 (anterior gradient protein 2) in modulating the EMT process during carcinogenesis and progression of SACC. Indeed, elevated levels of AGR2 in SACC cells trigger EMT program activation in combination with TGF-β1 that leads to a further metastasis, thus demonstrating the potential pro-metastatic role of AGR2 in SACC (Ma et al. 2017). Accumulating data show that tumor cells, after undergoing EMT, acquire better survival and stronger metastatic capabilities. Recent emerging research has shown that TGF-β1 protein is potently able to induce the migration and invasion of SACC cells (Ma et al. 2017). Yet, a recent study has demonstrated that brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (TrkB) play a key role in the induction of the EMT process in head-and-neck squamous cell carcinoma. This recent study highlighted that an altered BDNF/TrkB pathway associated to a downregulated expression of E-cad triggers the migration and invasion of SACC cells, and is a mark of poor prognosis in these patients (Jia et al. 2015).

It has long been known that aforementioned Twist, is an oncogene that plays a crucial role in the EMT program inducing tumor progression in malignant cells. One study, recently, reported that Twist expression contributed to the invasiveness of salivary SACC (Shen et al. 2010) and Twist may also be linked to perineural tumor invasiveness (Zhou et al. 2012). High levels of Twist were shown also in MEC, confirming the emerging role of this protein in carcinogenesis of the salivary glands and also in malignant transformation and tumor invasiveness (Pardis et al. 2016).

Strategies for anti-EMT-dependent SGs' fibrosis therapies

Targeting the EMT-like phenotypes would seem to offer potential strategies for the development of novel anticancer therapeutics and current research is aimed at evaluating the use of this approach in specific SGs' tumors. Recently, treatment with Nimotuzumab, an anti-EGFR monoclonal antibody, showed therapeutic benefit by reverting the EMT program of tumor cells to a more normal state with an advantageous anti-tumor effect in patients affected by SACC associated with a poor long-term outcome (Jiang et al. 2014; Jang et al. 2017). In addition, integrin-linked kinase (ILK) has been reported to play a key role in cell–extracellular matrix interactions mediated by integrins and several growth factors, and has been identified as a novel EMT regulator, attracting widespread attention as a potential therapeutic molecular target for patients with SACC (Zhao et al. 2013). Interestingly, Notch inhibitors have been proposed to work by targeting stemness or the EMT, and various trials testing the efficacy of drugs are currently ongoing, with secondary endpoints evaluating changes in EMT markers in patients with head-and-neck tumors (Chaffer et al. 2016; Espinoza and Miele 2013). In human samples of SACC, c-kit, a tyrosine kinase receptor, resulted overexpressed and linked with poor prognosis in SACC. The overexpression of c-kit in SACC cell lines allows the acquisition of the mesenchymal phenotype and contributes to cellular invasiveness. Therefore, c-kit is able to positively modulate the expression of EMT factors, also activating TGF-β to contribute to the EMT process (Tang et al. 2014). Recently, Yi et al. studied the expression of BMI-1, one of the main components of the polycomb group complex 1 and a potential stem cell marker, together with SNAI1/2 EMT-TF, and E-cad in a cohort of SACC patients (Yi et al. 2016). They demonstrated a positive correlation between high BMI-1 levels and SNAI1 and SNAI2 overexpression in these patients, identifying BMI-1 as a regulator for both EMT and cancer stem cells characteristics, based on the observation that BMI-1 knockdown resulted in simultaneous loss of the stem cell markers and EMT markers contributing to the migration and the invasion abilities of SACC (Yi et al. 2016). Elevated expression of the brain-derived neurotrophic factor (BDNF) and its receptor Tropomyosin-related kinase B (TrkB), together with reduced E-cad expression, is also a common feature of SACC. TrkB activation mediated by BDNF induces EMT progression and poor prognosis. In fact, the BDNF/TrkB signalling pathway leads to migration and SACC cells invasiveness through the EMT process, and therefore, targeting the inactivation of the BDNF/TrkB axis may be a potential therapy in the care of SACC patients (Jia et al. 2015).

The availability of immune checkpoint inhibitors, such as antibodies against PD-L1 (programmed cell death ligand-1), provides a unique opportunity to revolutionize the treatment of head-and-neck squamous cell carcinoma (HNSCC) (Baum et al. 2017). Interestingly, several studies have discovered a link between EMT and high levels of expression of PD-L1 in distinct cancers, including HNSCC (Lee et al. 2016). In the context of HNSCC, recent research has demonstrated that silencing of kallikrein-related peptidase 6 (KLK6) gene expression, involved in tissue remodeling, induces the EMT program accompanied by a mesenchymal-like cell phenotype as well as increased cell migration and cancer progression (Schrader et al. 2015). In addition, it has been shown that not only the loss of KLK6, but also the loss of the transcription factor sex determining region (Y SRY)-box 2 (SOX2), play a crucial role in the induction of cell motility via vimentin up-regulation and are unfavorable risk factors for the survival of patients with HNSCC (Bayo et al. 2015).

Conclusion

These recent results strongly encouraged the development of new potential therapeutic molecular targets for anti-EMT drug discovery, but unfortunately, the results of EMT targeted agents in salivary gland tumors have been disappointing: there has been some disease stabilization but no objective responses. It is possible that the observed discrepancies may be due to the following problems. Firstly, there is a lack of specific markers for evaluating EMT and most of commonly used mesenchymal markers are expressed both in the fibroblast and in other cell types, such as inflammatory cells and endothelial cells. Thus, the combination of various mesenchymal markers is widely used to evaluate the EMT program. Secondly, EMT is a highly dynamic molecular mechanism. Most of the studies involving EMT primarily depend on identifying the cells at the transitional stage, when they express both epithelial and mesenchymal markers; thirdly, animal models cannot fully represent the pathophysiology of human SGs' diseases, but the research resulting from animal models may provide some useful reference information. Thus, it is important to control the reproducibility of a fibrotic model. There is a pressing need for well-designed prospective clinical studies to improve the management of SGs' tumors. Unraveling molecular principles that drive the EMT provides new concepts to better understand tumor cell plasticity and the response to established as well as new treatment modalities, and has the potential to identify new drug targets promising a more effective, less toxic, and individualized therapy for SGs' tumors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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