Inflammation and EMT: an alliance towards organ fibrosis and cancer progression

Jose Miguel López-Novoa1 & M. Angela Nieto2*

Keywords: inflammation; epithelial–mesenchymal transition; TGF-β; TNF-α; NF-kB

DOI 10.1002/emmm.200900043

Received June 18, 2009 / Revised August 17, 2009 / Accepted August 26, 2009

Introduction—EMT in cancer and fibrosis

Although inflammation has been associated with the progression of chronic kidney disease and cancer for decades, the molecular mechanisms involved have remained elusive until recently (Cordon-Cardo & Prives, 1999; Kalluri & Neilson, 2003; Mantovani et al, 2008). The epithelial to mesenchymal transition (EMT) now takes centre stage as the convergence point between inflammation and the progression of degenerative fibrotic diseases and cancer. This cellular process is characterized by the loss in cell polarity and a change in cell shape from cuboidal to fibroblastoid, the downregulation of epithelial markers and the upregulation of mesenchymal markers. The cell acquires the capacity to degrade the basement membrane and migrate through the extracellular matrix to populate different territories either during embryonic development or cancer progression, or to adopt a profibrotic myofibroblast nature in the renal interstitial space (Acloque et al, 2009; Kalluri & Neilson, 2003; Kalluri & Weinberg, 2009). Betty Hay was the first to coin the term ‘epithelial to mesenchymal transformation’ in embryos (Hay, 1968), as well as later describing this cellular behaviour during migration (Hay, 1990) and the importance of the transient nature of this process (Hay, 1991; Fig 1A). Ironically, important elements in the control of the inflammatory response and in the induction of tumour cell death such as TGF-β1 and hypoxia can also act as potent inducers of EMT in an inflammatory microenvironment.

EMT events have been very well defined during embryonic development for many years (reviewed in Acloque et al, 2009). However, the significance of the EMT in cancer progression has been debated until recently. The main discussion regarding the role of EMT in cancer came from the difficulty in finding morphological evidence from clinical samples, due to the lack of specific markers for many years and the sometimes focal nature of the event. Nevertheless, more than 100 years ago, both Santiago Ramón y Cajal and Hugo Apolant noticed what we would definitely consider an EMT in both human and mouse breast cancer (Fig 1B,C). Indeed, the description of the breast tumours by Cajal in his ‘Manual of Anatomopathology’ is premonitory of the implication of the EMT as the first step in the metastatic cascade. He referred to undifferentiated breast carcinomas as follows: ‘The epithelial islands are not surrounded by a basement membrane… We shall mention the fusiform, pear-like and star-like forms… The cells are not attached to each other… This explains their invasive ability, since free of intercellular cement, they can migrate through the connective tissue’ (Ramon y Cajal, 1890). When we read...
cement’ in Cajal’s words we immediately think of E-cadherin, the molecule that maintains epithelial cells together and that we now know is the main target repressed by the EMT inducers. Figure 1B and C shows fragments of Cajal’s and Apolant’s drawings illustrating human and mouse breast carcinomas. The reversibility of the EMT process has been well described in the context of embryonic development, where mesenchymal to epithelial processes (MET) are fundamental for the differentiation of tissues and organs once the embryonic migratory cells have reached their destination. Indeed, the MET events certainly take place during metastasis formation as suggested by cell morphology and the re-expression of E-cadherin expression (Buholm et al, 2000). This EMT–MET double switch for metastasis formation has been discussed by Brabletz et al (2001) while providing a convincing illustration of an EMT process at metastasis formation has been discussed by Brabletz et al (2001) while providing a convincing illustration of an EMT process at metastasis formation as suggested by cell morphology and the re-expression of E-cadherin expression (Buholm et al, 2000). This EMT–MET double switch for metastasis formation has been discussed by Brabletz et al (2001) while providing a convincing illustration of an EMT process at the invasive front of human colon carcinoma (Fig 2A).

Fibrosis is characterized by the presence of an excess of fibrous connective tissue in an organ, and in particular by an excessive deposition of collagen I. It can be the result of a reparative or reactive process that can occur in the lung, the liver, the heart and the kidney among other organs. Under chronic pathological situations, fibrosis progresses to advanced states that lead to defective organ function and final organ failure. In this review we will focus on renal fibrosis as it has been very well studied at the cellular level and the mechanisms leading to the development of fibrosis are thought to be very similar in different organs. Renal fibrosis is the link between the progressive loss of renal function and primary diseases such as glomerulonephritis, diabetes, toxic injury, congenital abnormalities, urinary tract obstruction and chronic rejection of transplanted kidneys (Kalluri & Neilson, 2003; Liu, 2006; Vongwiwatana et al, 2005). Renal fibrosis has been associated with the activation of interstitial fibroblasts to give rise to collagen secreting myofibroblasts. However, different studies have shown that in addition, myofibroblasts can also originate from renal tubular epithelial and endothelial cells that undergo EMT in mouse models of renal fibrosis (Iwano et al, 2002; Zeisberg et al, 2008). Furthermore, the aberrant activation of Snail1, a well-known EMT inducer leads to the appearance of renal fibrosis and renal failure in transgenic mice (Boutet et al, 2006). Interestingly, high Snail1 expression and evidence of EMT has also been found in the kidneys of patients with renal fibrosis (Boutet et al, 2006; Jinde et al, 2001; Rastaldi et al, 2002).

In this review, we will discuss the dual role of TGF-β1 and hypoxia in fibrotic tissues and in the tumour microenvironment. We propose that in the context of a chronic inflammatory
condition, TGF-β1 and hypoxia reactivate EMT developmental programmes that converge in the activation of NF-κB also induced by the inflammatory cytokines and oxidative stress. These EMT programmes, in an unsuccessful attempt to repair the injured tissue, turn to a sinister role and lead to the destruction of epithelial homeostasis and accumulation of extracellular matrix in fibrosis, and to the progression of carcinomas towards the metastatic state.

Inflammation as an inducer of fibrosis and cancer

Inflammation and cancer

The link between cancer and inflammation has been recognized for decades, as strong associations have been established between chronic inflammatory conditions and tumourigenesis (Cordon-Cardo & Prives, 1999). As such, ulcerative colitis, chronic gastritis, hepatitis and chronic pancreatitis, and their respective relationships with colon, gastric, liver and pancreatic carcinomas exemplify the close connection between inflammation and tumour appearance. Furthermore, non-steroidal anti-inflammatory drugs reduce both the risk of cancer development and its mortality (Mantovani et al, 2008).

Renal fibrosis as an inflammatory disease

Renal fibrosis is a paradigmatic example of organ fibrosis towards degenerative organ disease and final stage kidney damage leading to the destruction of the tissue and death from renal failure. Obstructive nephropathy (ON) in humans, either due to congenital or acquired obstruction of the urinary tract, is the first primary cause of chronic renal failure (CRF) in children and a major cause of kidney failure in adults (Klahr & Morrissey, 2002; Smith et al, 2007). In ON, the evolution of renal disease is similar to that occurring in polycystic kidney disease or renal transplant rejection. Moreover, in its final fibrotic phase, ON is also very similar to the fibrosis secondary to glomerulonephritis, diabetes or hypertension (Chevalier, 2006; Chevalier et al, 2009). Indeed, long-term ON is characterized by tubular atrophy and the appearance of fibrosis (Fig 2B). Studies of ON have benefited from the existence of a recognized experimental model, the unilateral ureteral obstruction (UUO), in mice. UUO does not compromise the life of the animal, as the contralateral kidney maintains or even augments its function offering functional compensation (Klahr & Morrissey, 2002). Since UUO reproduces all the hallmarks of ON and it generates progressive renal fibrosis, it has become the standard experimental model to study the causes and mechanisms underlying tubulointerstitial fibrosis (Chevalier et al, 2009). Even though ON is not an immune disease, it has a major inflammatory component, characterized by the overexpression of inflammatory genes, the release of pro-inflammatory cytokines, the activation of NF-κB and the infiltration of macrophages and lymphocytes (Diamond, 1995; Esteban et al, 2004; Misseri et al, 2005; Silverstein et al, 2003). Similarly, fibrosis can also be considered as the end result of chronic inflammatory reactions induced by a variety of stimuli including persistent infections, autoimmune reactions, allergic responses, chemical insults,
radiation, tissue injury and normal ageing (Kalluri & Neilson, 2003). Therefore, ON and UUO can be used as a reference for the development of fibrosis, in part because inflammatory responses have been analysed in depth in this model.

**NF-κB activation in fibrosis and cancer**

After renal obstruction, an increase in the expression of the prototypical pro-inflammatory cytokines tumour necrosis factor (TNF-α) and interleukin-1 (IL-1) is crucial for the induction of NF-κB, the major inflammatory response pathway, and for recruitment of inflammatory cells to the obstructed kidney (Meldrum et al, 2006; Metcalfe et al, 2008; Misseri et al, 2005; Silverstein et al, 2003; Yamagishi et al, 2001). An increase in leukocyte infiltration, especially macrophages and T lymphocytes, is detected as early as 4–12 h after ureteral obstruction, and it continues to increase over the following days (Diamond, 1995). These cells play a central role in the renal inflammatory response to UUO as the progression of renal injury is closely associated with their accumulation and blocking their recruitment protects against interstitial fibrosis (Lange-Sperandio et al, 2007). The recruitment of circulatory leukocytes is mediated by several mechanisms including the expression of pro-inflammatory, profibrotic and chemoattractant cytokines in the kidney and the corresponding leukocyte chemotactic response to those chemokines (Ferenbach et al, 2007).

Once activated, NF-κB generates a loop that maintains the inflammatory signals as it controls the expression of genes encoding pro-inflammatory cytokines (e.g. IL-1, IL2, IL-6, TNF-α, etc.), chemokines (e.g. IL-8, MIP-1α, MCP-1, RANTES, eotaxin, etc.), adhesion molecules (e.g. ICAM, VCAM, E-selectin), inducible enzymes (COX-2 and iNOS), growth factors, some of the acute phase proteins and immune receptors, all of which play critical roles in controlling most inflammatory processes (Blackwell & Christman, 1997; Fig 3). As inflammation plays an important role in fibrosis, inhibition of NF-κB has a big impact on the development of chronic kidney disease. Indeed, NF-κB inactivation prevents inflammatory injury and diminishes the expression of inflammatory genes after UUO (Esteban et al, 2004; Miyajima et al, 2003). Similarly, increasing the levels of the endogenous inhibitor of NF-κB, I-κB, or inhibiting the pathway by the administration of curcumin, reduces renal fibrosis and macrophage influx following UUO or protects against interstitial inflammation in ON, respectively (Kuwabara et al, 2006; Tashiro et al, 2003).

Like the injured kidney, inflammation or infection in the context of a neoplasia can trigger the activation of NF-κB, the main transducer of inflammatory responses, which in turn induces the secretion of a plethora of inflammatory cytokines (Fig 3). These cytokines recruit inflammatory cells and, at the tumour–stroma interface, tumour cells together with tumour-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs) again converge in producing NF-κB and the hypoxia-inducible factor (HIF1-α), generating a microenvironment capable of driving tumour progression (Mantovani et al, 2008). HIF-1α is a potent inducer of EMT in the kidney and also in cancer cells in general (see Box 1 and Fig 3) and the inflammation-mediated increase in NF-κB expression has been associated with several aspects of cancer development, mainly resistance to apoptosis and increased angiogenesis, with some connections to invasiveness (Karim, 2006).

NF-κB can also directly activate the expression of potent EMT inducers, including Snail1 and Zeb factors (Bachelder et al, 2005; Barberà et al, 2004; Chua et al, 2007; Julien et al, 2007; Kim et al, 2007) (Fig 3). Thus, there seems to be an important connection between cancer, inflammation and EMT. This connection has been reinforced recently by the finding that TNF-α induces Snail1 promoter activity and EMT in cancer cells (Dong et al, 2007) and that it can also stabilize Snail1 protein (Wu et al, 2009). Snail1 is a highly unstable protein, targeted for degradation by phosphorylation and ubiquitylation mediated by GSK-3β and SCFβ-Trcp, respectively (Zhou et al, 2004). TNF-α induces Snail1 protein stabilization by activating the expression of the COP9 signalosome 2 (CNS2), which in turn inhibits the binding of Snail1 to GSK-3β and β-Trans (Wu et al, 2009; Fig 3).
Interestingly, both transcriptional and post-transcriptional mechanisms act through the induction of the main target of TNF-α in the inflammatory response, NF-κB.

The link between TNF-α and Snail factors points to the EMT as the molecular and cellular explanation for the association between inflammation, fibrosis and tumour progression. As mentioned above, EMT events are now directly associated with invasion and metastasis in cancer progression. Elegant in vivo imaging studies have shown that carcinoma cells migrate from mouse primary tumours through a process of EMT and that this process is dependent on an inflammatory microenvironment provided by the TAMs and other stromal cells such as the CAFs (Condeelis & Segall, 2003) (Fig 3). TAMs and stromal cells in general are essential for angiogenesis, extracellular matrix remodelling and the inflammatory response associated with cancer (Condeelis & Pollard, 2006). Stromal cells secrete TNF-α which, as in renal cells in the obstructed kidney, induces NF-κB in the tumour cells. The significance of NF-κB activation in cancer cells is evident from the results obtained in inflammation-associated models of cancer (Karin & Greten, 2005; Pikarsky et al., 2004). Selective inactivation of NF-κB in these tumours led to deficient tumour development. Importantly, at least in the liver, activation of NF-κB was not important in the early stages of tumour development, but was crucial for malignant conversion and for the survival of tumour cells. This combined effect is very reminiscent of that produced by the EMT inducers and Snail in particular as, in addition of triggering EMT, Snail-expressing cells are resistant to the cell death induced by the removal of survival factors, by genotoxic stress, chemotherapy and immunotherapy and even by TNF-α (reviewed in Barrallo-Gimeno & Nieto, 2005; see also Kudo-Saito et al., 2009; Vega et al., 2004). In addition to the activation of Snail1 by NF-κB, it should be noted that angiotensin...
**Box 1: The dual role of hypoxia in fibrosis and cancer**

As TGF-β1, hypoxia has an early beneficial role in fibrosis and cancer, but as if both were Dr Jekyll and Mr Hyde they can take a sinister role that favours the progression of the disease (Bottaro & Liotta, 2003; Massague, 2008). Indeed, TGF-β1 can act as a tumour suppressor or as a promoter of invasion and metastasis, and in the injured kidney, it can behave either as a healing anti-inflammatory cytokine or as a profibrotic agent (see main text). Similarly, while cutting off the oxygen supply seemed a good strategy to kill cancer cells since they massively die at low oxygen concentrations, hypoxia increases the aggressiveness in tumours and promotes renal fibrosis. Interestingly, they share a common mechanism to fulfil their deleterious role, the induction of the EMT.

Hypoxia is an important factor in the development of tissue fibrosis. The obstructed kidney suffers from chronic hypoxia due to a reduced renal blood flow (Hegarty et al, 2001). Hypoxia regulates the expression of a variety of growth factors and cytokines through the activation of the HIF-1α, a potent transcriptional regulator of oxygen-dependent genes, including VEGF and TGF-β1 (Baan et al, 2003) (Fig 3). In accordance with the induction of TGF-β1 by HIF-1α, hypoxia also enhances EMT in vitro, and genetic ablation of epithelial HIF-1α in a mouse model of renal fibrosis was associated with reduced ECM accumulation. Interestingly, in addition to inducing TGF-β1, HIF-1α can also directly activate the expression of EMT inducers Snail, Twist and the members of the Zeb family (Evans et al, 2007; Krishnamachary et al, 2006; Sun et al, 2009; Yang et al, 2008) (Fig 3). This activation can occur in renal cells subjected to hypoxia or that constitutively express HIF-1α, as found in those defective in the von Hippel–Lindau (VHL) tumour suppressor. Furthermore, hypoxia also enhances Snail1 activity by activating the expression of its partners lysyl-oxidases (LOX) both in the kidney after UUO and in cancer cells, thereby promoting fibrogenesis and tumour progression through the reinforcement of the EMT programme (Higgins et al, 2007; Sahlgren et al, 2008) (Fig 3). Importantly, there is a reciprocal activation of HIF-1α and NF-κB (Rius et al, 2008), reinforcing the EMT programme (Fig 3). Thus, rather than dying, many cells in tumours and in the damaged kidney can benefit from a lack of oxygen through the induction of EMT, favouring the progression of cancer and fibrosis.

In summary, while some steps of the pathways involved may be tissue or disease specific, it is clear that in both cancer and fibrosis the concerted action of several cytokines as IL-1β and TNF-α plus Ang II together with oxidative stress and hypoxia converge on the activation of NF-κB, a major inducer of the inflammatory response.

**Yin and Yang of TGF-β1**

In addition to the secretion of inflammatory cytokines, many organs and tissues release TGF-β1 after an injury, as seen in the lung, liver, heart, kidney and bone (Devescovi et al, 2008; Frangogiannis, 2008; Kaneto et al, 1993; Kisseleva & Brenner, 2008; Gharaei-Kermani et al, 2009; Gressner et al, 2008). TGF-β1 is considered a major anti-inflammatory cytokine, as TGF-β1 knockout mice suffer from a lethal multifocal inflammatory disease (Kulkarni et al, 1993; Letterio & Roberts, 1998) and the blockage of TGF-β1 signalling in T cells or in bone marrow results in similar multifocal inflammatory responses (Gorelik & Flavell, 2000; Shull et al, 1992). However, TGF-β1 has been known for many years to display a schizophrenic behaviour in cancer. While it can act as a tumour suppressor at early tumour stages, it can later contribute to the malignant progression by promoting invasion and metastasis (Massague, 2008). In the kidney too, although TGF-β1 acts as an anti-inflammatory cytokine to heal the injured kidney, it also has negative effects on the development of chronic renal disease as it is an important fibrogenic agent. Indeed, the role of TGF-β1 as a promoter of tumour progression and profibrotic agent is associated with its ability to act as a potent activator of EMT inducers (Aloque et al, 2009). The Yin and Yang of TGF-β1 in both cases are explored below.
TGF-β1 in cancer: tumour suppressor and promoter of invasion and metastasis

There are paradigmatic examples illustrating how TGF-β1 can impair tumourigenesis while promoting metastasis (Siegel et al., 2003, reviewed in Massague, 2008). In normal cells, TGF-β1 can maintain tissue homeostasis by suppressing cell proliferation and by inducing apoptosis. Tumour cells evade this response by losing the ability to respond to the cytostatic and apoptotic effects through different mechanisms (Shi & Massague, 2003). In addition, TGF-β1 helps cancer cells to acquire the ability to invade and disseminate by inducing the EMT process. Thus, TGF-β1 is a potent EMT inducer in tumours albeit it is also initially secreted to control pathological proliferation and inflammation.

The study of the molecular pathways that drive the differential response to TGF-β1 continues to be a very active field of research and recent findings indicate that both genetic and epigenetic mechanisms are involved. On one hand, the methylation state of the platelet-derived growth factor (PDGF) gene limits the proliferative or cytotastic effect of TGF-β1 in gliomas (Bruna et al., 2007) and the concerted action of TGF-β1 with oncogenic Ras and mutant p53 sequester p63 in a complex that inactivates its tumour suppressor effects (Adorno et al., 2009). This indicates that two molecules frequently mutated in cancer, p53 and Ras, can divert the response to TGF-β1 towards the promotion of metastasis. Indeed, TGF-β1 and oncogenic Ras cooperate in the induction of Snail1 expression and EMT in epithelial cells (Peinado et al., 2003). Interestingly, NF-κB is required for the induction and maintenance of the EMT by TGF-β1 in mammary epithelial cells overexpressing the Ras oncogene (Huber et al., 2004), explaining the role of NF-κB as a modulator of TGF-β1-induced EMT in addition to its role as a direct activator of the EMT inducers.

But what are the sources of TGF-β1 in the tumours? Again, as in the injured organs, TGF-β1 is produced by cancer cells and, particularly, by stromal cells in an attempt to control inflammation. TNF-α can induce TGF-β1 in lung fibroblasts (Sullivan et al., 2009) and TGF-β1 can also activate the resident fibroblasts to convert them into myofibroblasts, called cancer-associated fibroblasts in the contexts of tumours (CAF) and associated with tumour invasion (Micke & Ostman, 2005). Some of these ‘myofibroblastic’ CAFs are surely the result of the EMT undergone by carcinoma cells, as EMT is now recognized as an important event in carcinoma progression.

TGF-β1 in fibrosis: anti-inflammatory and healing factor versus profibrotic factor

The release of TGF-β1 by renal or by infiltrating cells in the damaged kidney moderates the inflammatory reaction and helps to heal the damaged tissue. Among its anti-inflammatory functions, TGF-β1 antagonizes the pro-inflammatory cytokines IL-1 and TNF-α in glomerular disease, and it is a prominent macrophage deactivator during kidney injury (Kitamura & Suto, 1997). Renal TGF-β1 mRNA expression increases considerably after the onset of obstruction (Kaneto et al., 1993), and its concentration increases in the plasma of patients with obstruction due to ureteral calcui and renal fibrosis (Liu, 2006; Vuruskan et al., 2005). TGF-β1 expression is induced by Ang II (Wolf, 2006), upon increased stretch of tubular epithelial cells (Quinlan et al., 2008), and it is also produced by interstitial fibroblasts and infiltrating macrophages (Diamond et al., 1998; Ding et al., 1993). As already mentioned, in addition to its anti-inflammatory effects, TGF-β1 also acts as a profibrotic agent. The profibrotic effect of TGF-β1 is achieved by increasing the synthesis of matrix proteins and the expression of proteinase inhibitors, including plasminogen activator inhibitor-1 (PAI-1), and by decreasing that of ECM-degrading proteins such as collagenase (Chevalier, 2006). Therefore, sustained aberrant expression of TGF-β1 results in the pathological accumulation of extracellular matrix material in both the glomerulus and interstitial compartments (Bottinger, 2007). TGF-β1 also has some pro-inflammatory properties, as it functions as a chemo-attractant for leukocytes (Wahl et al., 1987) and induces COX-2 in mesangial cells (Rodríguez-Barbero et al., 2006). This profibrotic activity of TGF-β1 reflects its behaviour as a potent inducer of EMT, which contributes to the conversion of renal epithelial cells into myofibroblasts in the context of the injured kidney. In addition, part of the TGF-β1-induced EMT programme promotes the remodelling of the cell contacts with the basal membrane by activating the matrix metalloproteases MMP2 and MMP9 (Li et al., 2003; Strutz et al., 2002), leading to the degradation of the collagen type IV component of basement membrane. Thus, the molecule secreted to control inflammation has an alter ego and it promotes the development of fibrosis.

TGF-β1, myofibroblasts and EMT

Myofibroblasts play a major role in interstitial fibrosis as they are the main source of matrix proteins. They originate from several sources, including bone marrow cells, resident interstitial fibroblasts, vascular pericytes, as well as endothelial and tubular epithelial cells (reviewed in Grande & López-Novoa, 2009). As mentioned above, TGF-β1 contributes to the formation of myofibroblasts through the activation of resident fibroblasts and by inducing the transition to mesenchyme of epithelial and endothelial cells via EMT or EndMT, respectively (Zavadil & Bottinger, 2005; Zeisberg & Kalluri, 2008; Zeisberg et al., 2008). Indeed, the transformation of tubular and endothelial cells to mesenchymal cells contributes to more than 60% of the myofibroblast population in the obstructed kidney after UUO (Iwano et al., 2002; Zeisberg et al., 2008), and this process plays a major role in tubulo-interstitial fibrosis (Kalluri & Neilson 2003). The induction of EMT by TGF-β1 also explains the fibrotic effect of Ang II, as this anti-inflammatory factor also induces the synthesis of TGF-β1 and its receptors in tubular epithelial cells (Wolf, 2006). Accordingly, the infusion of Ang II into mice subjected to UUO (Iwano et al., 2002; Zeisberg et al., 2008), and by decreasing that of ECM-degrading proteins such as collagenase (Chevalier, 2006). Therefore, sustained aberrant expression of TGF-β1 results in the pathological accumulation of extracellular matrix material in both the glomerulus and interstitial compartments (Bottinger, 2007). TGF-β1 also has some pro-inflammatory properties, as it functions as a chemo-attractant for leukocytes (Wahl et al., 1987) and induces COX-2 in mesangial cells (Rodríguez-Barbero et al., 2006). This profibrotic activity of TGF-β1 reflects its behaviour as a potent inducer of EMT, which contributes to the conversion of renal epithelial cells into myofibroblasts in the context of the injured kidney. In addition, part of the TGF-β1-induced EMT programme promotes the remodelling of the cell contacts with the basal membrane by activating the matrix metalloproteases MMP2 and MMP9 (Li et al., 2003; Strutz et al., 2002), leading to the degradation of the collagen type IV component of basement membrane. Thus, the molecule secreted to control inflammation has an alter ego and it promotes the development of fibrosis.
activating the α-smooth muscle actin (αSMA) gene and protein expression (Masszi et al., 2004). The processes triggered by TGF-β1 converge in the activation of the so-called EMT inducers, which are transcription factors capable of eliciting this dramatic phenotypic change that converts epithelial cells into activated ‘myofibroblast-like’ cells. As in cancer, among the transcription factors involved in the induction of EMT, Snail factors have been associated with renal fibrosis and significantly, TGF-β1 is the most potent inducer of Snail transcription (Fig. 3). The expression of these genes increases in the obstructed kidney after UUO (Sato et al., 2003; Tan et al., 2006; Yoshino et al., 2007) and Snail1 activation is sufficient to induce EMT and all the hallmarks of kidney fibrosis in adult mice (Boutet et al., 2006). Snail1 directly represses E-cadherin transcription and that of the renal-specific Cadherin16 gene through the direct repression of HNF-1β gene expression. Snail also activates, albeit indirectly, the transcription of mesenchymal genes, such as vimentin and αSMA, and it promotes collagen I synthesis and deposition (Boutet et al., 2006). Interestingly, Snail factors are strongly upregulated in fibrotic kidneys from patients subjected to nephrectomy due to urinary obstruction and kidney failure (Boutet et al., 2006). Altogether, data from many laboratories indicate that Snail factors are crucial mediators of TGF-β1-induced EMT.

Concluding remarks and perspectives

From all the work carried out in the context of organ fibrosis and cancer we can conclude that the pathways and players identified that lead to pathological EMTs are basically the same. Both in cancer and fibrosis TGF-β1, TNF-α and hypoxia cooperate in the triggering of EMT, converging in the induction of Snail activity through different mechanisms among which the activation of NF-κB seems to play a central role. This can be regarded as the reactivation of a developmental programme designed to endow cells with migratory and invasive properties and with amazing survival properties, crucial for migratory cells to reach their sometimes far destinations within the embryo (Acloque et al., 2009). This developmental programme, firstly reactivated to control the inflammatory response and to heal the injured tissue, is corrupted in the context of chronic inflammation and cancer, favouring the survival of injured or malignant cells and stimulating the production of pro-inflammatory cytokines in the tumour mass or in the organ interstitial space. The cooperation between TGF-β1 and the pro-inflammatory cytokines generates a microenvironment that favours the generation of autoregulatory loops to reinforce the EMT programme (Fig 3). Not only Ang II, TNF-α, ROS and hypoxia converge in the induction of Snail, but also Ang II and TNF-α can induce TGF-β1 at the transcriptional level (Sullivan et al., 2009), the most potent Snail inducer. In addition, Snail1 itself also seems to upregulate the expression of pro-inflammatory mediators such as several ILs (IL-1, IL-6, IL-8; Lyons et al., 2008). It will be interesting to determine whether other EMT inducers are also activated in the context of this inflammatory microenvironment, which seems to be very likely, given that both TGF-β1 and hypoxia can induce the expression of Twist and Zeb transcription factors.

The relationship between inflammation and Snail activity has been established in cancer cells from different origins, indicating that this is a general mechanism in carcinoma progression. While the majority of studies on fibrosis have been carried out in the kidney, the same pathways are likely to operate during other fibrotic processes, including those in the liver and the lung, especially since there is evidence of EMT in hepatic fibrosis (Kim et al., 2006; Zeisberg et al., 2007a). A similar process also occurs when endothelial cells undergo an EMT during cardiac or renal fibrosis (EndMT; Zeisberg et al., 2007b, 2008) as well as during mesothelial fibrosis in patients subjected to peritoneal dialysis where the NF-κB/Snail1 axis has already been described (Strippoli et al., 2008).

In summary, the relationship between inflammation and EMT seems to be a conserved feature in the progression of organ fibrotic diseases and cancer, suggesting that specific anti-EMT drugs should be considered to treat these conditions in combination with anti-inflammatory therapies. With respect to therapies targeting the EMT programme, small molecule inhibitors or antibodies directed against TGFβR have been effective in preclinical and clinical trials, and neutralizing antibodies against TGF-β1 are in Phase 1 clinical trials for renal cell carcinoma and pulmonary fibrosis (Chua et al., 2008). Treatment with BMP7, an inhibitor of TGF-β1 signalling, is a promising strategy to treat fibrosis as it can reverse TGF-β1-induced renal fibrosis in mice (Zeisberg et al., 2003). It should be noted that since signalling molecules such as TGF-β1 or hypoxia trigger complex transduction cascades with deleterious but also beneficial outcomes, inhibiting the EMT inducers rather than the extracellular signalling molecules or their receptors could provide a more specific way to fight both fibrosis and cancer progression. However, EMT inducers are transcription factors, and thus very difficult to target. While RNA interference approaches are promising specific reagents, these are still early days for their wide use due to their low stability and, more importantly, due to the current low efficiency in their cell targeting and intracellular delivery. Finally, as the same signalling pathways can act as promoters or suppressors of fibrosis and cancer, better understanding of the cellular response that depends on the context and stage of the disease is crucial to design more advanced therapies.
Acknowledgements
Work in our laboratories is supported by grants from the Spanish Ministry of Education and Science (SAF2007-63893), from Instituto Carlos III (Red Cooperativa de Investigación Renal, RedinRen Retic 06/0016) and Junta de Castilla y León (SA029/A05 and Excellence Group GR-100), to J. M. L.-N. and from the Spanish Ministry of Education and Science (BFU2008-01042; CONSOLIDER-INGENIO 2010 CSD2007-00017 and CSD2007-00023) and the Generalitat Valenciana (Prometeo 2008/049) to M. A. N. We are very grateful to the Cajal Institute (CSIC) where Cajal’s original drawing and slides are kept, to Robert Cardiff for providing Apolant’s drawing and to Robert Cardiff and Thomas Brabletz for providing micrographs.

References
Acloque H, Adams M, Fishwick K, Bronner-Fraser M, Nieto MA (2009) Epithelial-mesenchymal transitions: the importance of changing cells’ state in development and disease. J Clin Invest 119:1438-1449
Acloque H, Thiery JP, Nieto MA (2008) The physiology and pathology of the epithelium to mesenchymal transition. EMBO Rep 9:322-326
Adorno M, Cordenonsi M, Montagner M, Dupont S, Wong C, Hann B, Solaria A, Bobisse S, Rondina MB, Guzzardo V, et al (2009) A mutnat-p53/Smad complex opposes p63 to empower TGF-β-induced metastasis. Cell 177:87-98
Apolant H (1906) Die epithelialen Geschwülste der Maus. Arb Königl Inst Exp Ther 1:7-62
Baan C, van Gelder T, Peeters A, Mol W, Niesters H, Weimar W, IJzermans J (2008) Apolant H (1906) Die epithelialen Geschwülste der Maus. Arb Königl Inst Exp Ther 1:7-62
Bruna A, Darken RS, Rojo F, Ocanà A, Penuelas S, Arias A, Paris P, Tortosa A, Mora J, Baselga J, et al (2007) High TGFβeta-Smad activity confers poor prognosis in glioma patients and promotes cell proliferation depending on the methylation of the PDGF-B gene. Cancer Cell 11:147-160
Bukholm IK, Nesland JM, Berresen-Dale AL (2000) Re-expression of E-cadherin, alpha-catenin and beta-catenin, but not of gamma-catenin, in metastatic tissue from breast cancer patients. J Pathol 190:15-19
Chevalier RL, Forbes MS, Thornhill BA (2009) Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. Kidney Int 75:1145-1152
Chevalier RL (2006) Obstructive nephropathy: towards biomarker discovery and gene therapy. Nat Clin Pract Nephrol 2:157-168
Chua HI, Bhat-Nakshatri P, Clare SE, Morimya A, Badve S, Nakshatri H (2007) NF-kappaB represses E-cadherin expression and enhances epithelial to mesenchymal transition of mammmary epithelial cells: potential involvement of ZEB-1 and ZEB-2. Oncogene 26:711-724
Chua KN, Ma J, Thiery JP (2008) Targeted therapies in control of EMT in carcinoma and fibrosis. Drug Discov Today 4:261-267
Condeelis J, Pollard JW (2006) Macrophages: obligate partners for tumor cell migration, invasion and metastasis. Cell 124:263-266
Condeelis J, Segall JE (2003) Intravital imaging of cell movement in tumours. Nat Rev Cancer 3:921-930
Cordon-Cardo C, Prives C (1999) At the crossroads of inflammation and tumorigenesis. J Exp Med 190:1367-1370
Dehayes F, Nahmias C (2005) Angiotensin receptors: a new role in cancer? Trends Endocrinol Metab 16:293-299
Devescovi V, Leonardi E, Ciapetti G, Cenni E (2008) Growth factors in bone repair. Chir Organi Mov 92:161-168
Diamond JR (1995) Macrophages and progressive renal disease in experimental hydropneumorrhesis. Am J Kidney Dis 26:133-140
Diamond JR, Ricardo SD, Klahr S (1998) Mechanisms of interstitial fibrosis in obstructive nephropathy. Semin Nephrol 18:594-602
Ding G, Pesek-Diamond I, Diamond JR (1993) Cholesterol, macrophages, and gene expression of TGF-β1 and fibronectin during nephrosis. Am J Physiol Renal Fluid Electrolyte Physiol 264:F577-F584
Dong R, Wang Q, He X, Chu YK, Lu JG, Ma QJ (2007) Role of nuclear factor kappa B and reactive oxygen species in the tumor necrosis factor-alpha-induced epithelial-mesenchymal transition of MCF-7 cells. Braz J Med Biol Res 40:1071-1078
Esteban V, Ruperez M, Vitoria J, Lopez ES, Mezzano S, Plaza J, Egido J, Ruiz-Ortega M (2003) Effect of simultaneous blockade of AT1 and AT2 receptors on the NFκB pathway and renal inflammatory response. Kidney Int Suppl S33-S38
Esteban V, Lorenzo O, Ruperez M, Suzuki Y, Mezzano S, Blanco J, Kretzler M, Sugaya T, Egido J, Ruiz-Ortega M (2004) Angiotensin II, via AT1 and AT2 receptors and NF-κβ pathway, regulates the inflammatory response in unilateral ureteral obstruction. J Am Soc Nephrol 15:1514-1529
Evans AJ, Russell RC, Roche O, Burry TN, Fish JE, Chow VW, Kim WY, Saravanan A, Maynard MA, Gervais ML, et al (2007) VHL promotes E2 box-dependent E-cadherin transcription by HIF-mediated regulation of SIP1 and snail. Mol Cell Biol 27:157-169
Ferenbach D, Kluth DC, Hughes J (2007) Inflammatory cells in renal injury and repair. Semin Nephrol 27:250-259
Frangogiannis NG (2008) The immune system and cardiac repair. Pharmacol Res 58:88-111
Charaee-Kermani M, Hu B, Phan SH, Gyetko MR (2009) Recent advances in molecular targets and treatment of idiopathic pulmonary fibrosis: focus on TGFβeta signaling and the myofibroblast. Curr Med Chem 16:1400-1417
Gloire C, Legrand-Poels S, Piette J (2006) NF-κB/pp65 activation by reactive oxygen species: fifteen years later. Biochem Pharmacol 72:1493-1505
Corellk L, Flavell RA (2000) Abrogation of TGF-β signaling in T cells leads to spontaneous T cell differentiation and autoimmune disease. Immunity 12:171-183
Grande MT, Lopez-Novoa JM (2009) Fibroblast activation and myofibroblast generation in obstructive nephropathy. Nat Rev Nephrol 5:319-328
Gressner OA, Rizk MS, Kovalenko E, Weiskirchen R, Gressner AM (2008) Where will it go Changing the pathogenetic roadmap of liver fibrosis? Where did it start, depending on the methylation of the PDGF-B gene. Cancer Cell 11:147-160
Hay ED (1968) Organization and fine structure of epithelium and mesenchyme in the developing chick embryo. In: Epithelial-Mesenchymal Interactions, Fleischmajer R and Billingham RE (eds), Baltimore, MD, USA: Williams & Wilkins Co: pp 31-55

Hay ED (1990) Role of cell-matrix contacts in cell migration and epithelial-mesenchymal transformation. Cell Differ Dev 32: 367-375

Hay ED (1991) Collagen and other matrix glycoproteins in embryogenesis. In: Cell Biology of Extracellular Matrix, Hay ED (ed), New York: Plenum Press: pp 419-462

Hegarty NJ, Young LS, Kirwan CN, O'Neill AJ, Bouchier-Hayes DM, Sweeney P, Watson RW, Fitzpatrick JM (2001) Nitric oxide in unilateral ureteral obstruction: effect on regional renal blood flow. Kidney Int 59: 1059-1065

Higgins DF, Kimura K, Bernhardt WM, Shrimanker N, Akai Y, Hohenstein B, Saito Y, Johnson RS, Kretzler M, Cohen CD, et al (2007) Hypoxia promotes fibrogenesis in vivo via HIF-1 stimulation of epithelial-to-mesenchymal transition. J Clin Invest 117: 3810-3820

Huber MA, Azulet N, Baumann B, Grünert S, Sommer A, Pehamberger H, Kraut N, Beug H, Wirth T (2004) NF-κappaB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. J Clin Invest 114: 569-581

Iwano M, Plieth D, Danoff TM, et al (2002) Evidence that fibroblasts derive from epithelium during tissue fibrosis. J Clin Invest 110: 341-350

Jinde K, Nikolic-Paterson DJ, Huang XR, Sakai H, Kurokawa K, Atkins RC, Lan HY et al (1997) Tubular phenotypic change in progressive tubulointerstitial fibrosis in human glomerulonephritis. Am J Kidney Dis 38: 761-769

Julien S, Puig I, Caretti E, Bonaventure J, Nelles L, van Roy F, Dargent M, de Herreros AG, Bellacosa A, Larue L (2007) Activation of NF-κappaB by Akt upregulates Snail expression and induces epithelial mesenchyme transition. Oncogene 26: 7445-7456

Kalluri R, Neilson EG (2003) Epithelial-mesenchymal transition and its implications for fibrosis. J Clin Invest 112: 1776-1784

Kalluri R, Weinberg R (2009) The basics of epithelial-mesenchymal transition. Annu Rev Cell Dev Biol 25: 209-233

Kaneto H, Morrissey J, Klahr S (1993) Increased expression of TGF-beta 1 mRNA in the obstructed kidney of rats with unilateral ureteral ligation. Kidney Int 44: 313-321

Kawada N, Moriyama T, Ando A, Fukunaga M, Miyata T, Kurokawa K, Imai E, Hori M (1999) Increased oxidative stress in mouse kidneys with unilateral renal obstruction: effect on regional renal blood flow. Kidney Int 56: 1004-1013

Karim M (2006) Nuclear factor-kappaB in cancer development and progression. Nature 441: 431-436

Karim M, Greten FR (2005) NF-kappaB: Linking inflammation and immunity to cancer development and progression Nat Rev Immunol 5: 749-759

Kim KK, Kugler MC, Wolters PJ, Robillard L, Galvez MC, Brunwell AN, Sheppard D, Chapman HA (2006) Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix. Proc Natl Acad Sci USA 103: 13180-13185

Kim HJ, Litzenburger BC, Cui X, Delgado DA, Grabiner BC, Lin X, Lewis MT, Gottardis MM, Wong TW, et al (2007) Constitutively active type I insulin-like growth factor receptor causes transformation and xenograft growth of immortalized mammary epithelial cells and is accompanied by an epithelial-to-mesenchymal transition mediated by NF-kappaB and snail. Mol Cell Biol 27: 3165-3175

Kisseleva T, Brenner DA (2008) Fibrogenesis of parenchymal organs. Proc Am Thorac Soc 5: 338-342

Kitamura M, Suto TS (1997) TGF-beta and glomerulonephritis: anti-inflammatory versus prosclerotic actions. Nephrol Dial Transplant 12: 669-679

Klahr S, Morrissey J (2002) Obstructive nephropathy and renal fibrosis. Am J Physiol Renal Physiol 283: F861-F875

Krishnamachary B, Zagzag D, Nagasawa H, Rainey K, Okyuma H, Baek JH, Semenza CL (2006) Hypoxia-inducible factor-1-dependent repression of E-cadherin in von Hippel-Lindau tumor suppressor-null renal cell carcinoma mediated by TCF3, ZFHX1A, and ZFHX1B. Cancer Res 66: 2725-2731

Kudo-Saito C, Shirako H, Takeuchi T, Kawakami Y (2009) Cancer metastasis is accelerated through immunosuppression during Snail-induced EMT of cancer cells. Cancer Cell 15: 195-206

Kulkarni AR, Huh CG, Becker D, Geiser A, Lught M, Flanders KC, Roberts AB, Sporn MB, Ward JM, Karlsson S (1993) Transforming growth factor β1 null mutation in mice causes excessive inflammatory response and early death. Proc Natl Acad Sci USA 90: 770-774

Kuwabara N, Tamada S, Iwai T, Teramoto K, Kaneda N, Yokimura T, Nakatani T, Miura K (2006) Attenuation of renal fibrosis by curcumin in rat obstructive nephropathy. Urology 67: 440-446

Lange-Sperandio B, Trautmann A, Eickelberg O, Jayachandran A, Oberle S, Schmidtuz F, Rodenbeck B, Hömme M, Horuk R, Schaefer F (2007) Leukocytes induce epithelial to mesenchymal transition after unilateral ureteral obstruction in neonatal mice. Am J Pathol 171: 861-871

Lettiero JJ, Roberts AB (1998) Regulation of immune responses by TGF-β. Annu Rev Immunol 16: 137-161

Li JH, Zhu HJ, Huang XR, Lai KN, Johnson RJ, Lan HY (2002) Smad7 inhibits fibrotic effect of TGF-beta on renal tubular epithelial cells by blocking smad2 activation. J Am Soc Nephrol 13: 1464-1472

Li Y, Yang J, Dai C, Wu C, Liu Y (2003) Role for integrin-linked kinase in mediating tubulointerstitial fibrosis to epithelial mesenchymal transition and renal interstitial fibrosis. J Clin Invest 112: 503-516

Liu Y (2006) Renal fibrosis: new insights into the pathogenesis and therapeutics. Kidney Int 69: 213-217

Lyons JC, Patel V, Rowe NC, Fok SY, Soon LL, Halliday GM, Gutkind JS (2008) Snail up-regulates proinflammatory mediators and inhibits differentiation in oral keratinocytes. Cancer Res 68: 4525-4530

Ma LJ, Yang H, Gaspert A, et al (2003) Transforming growth factor-beta-dependent and -independent pathways of induction of tubulointerstitial fibrosis in beta(7/7) mice. Am J Pathol 163: 1261-1273

Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454: 436-444

Massague J (2008) TGFβ in cancer. Cell 134: 215-230

Masszi A, Di Ciano C, Sirokmany G, Arthur WT, Rotstein OD, Wang J, McCulloch CA, Rosivall L, Muci I, Kapus A (2003) Central role for Rho in TGF-beta1-induced alpha-smooth muscle actin expression during epithelial-mesenchymal transition. Am J Physiol 284: F911-F924

Masszi A, Fan L, Rosivall L, McCulloch CA, Rotstein OD, Muci I, Kapus A (2004) Integrity of cell-cell contacts is a critical regulator of TGF-beta 1-induced epithelial-to-mesenchymal transition: role for beta-catenin. Am J Pathol 165: 1955-1967

Meldrum KK, Metcalfe P, Leslie JA, Misseri R, Hile KL, Meldrum DR (2006) TNF-alpha neutralization decreases nuclear factor-kappaB activation and apoptosis during renal obstruction. J Surg Res 131: 182-188

Metcalfe PD, Leslie JA, Campbell MT, Meldrum DR, Hile KL, Meldrum KK (2008) Testosterone exacerbates obstructive renal injury by stimulating TGF-α production and increasing proapoptotic and profibrotic signaling. Am J Physiol Endocrinol Metab 294: E435-E443

Misseri R, Meldrum DR, Dinarello CA, Dagher P, Hile KL, Rink RC, Meldrum KK (2005) TNF-alpha mediates obstruction-induced renal tubular cell apoptosis and proapoptotic signaling. Am J Physiol Renal Physiol 288: F406-F411

Micie P, Ostman A (2005) Exploring the tumour environment: cancer-associated fibroblasts as targets in cancer therapy. Expert Opin Ther Targets 9: 1217-1233

Miyajima A, Kosaka T, Seta K, Asano T, Umezawa K, Hayakawa M (2003) Novel nuclear factor kappa B activation inhibitor prevents inflammatory injury in unilateral ureteral obstruction. J Urol 169: 1559-1563

Miyarayama T, Kawada N, Nagatoya K, Takeji M, Horio M, Ando A, Imai E, Hori M (2003) Fluvastatin suppresses oxidative stress and fibrosis in the interstitium of mouse kidneys with unilateral ureteral obstruction. Kidney Int 59: 2095-2103

Morrissey JJ, Klahr S (1997) Eselectin decreases nuclear factor kappa B activation in the kidney with ureteral obstruction. Kidney Int 52: 926-933
Peinado H, Quintanilla M, Cano A (2003) Transforming growth factor beta-1 induces snail transcription factor in epithelial cells: mechanisms for epithelial mesenchymal transitions. J Biol Chem 278: 21113-21123

Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, Gutfkovich-Pyest E, Ureli-Shoval S, Galun E, Ben-Neriah Y (2004) NF-kappaB functions as a tumour promoter in inflammation-associated cancer. Nature 431: 461-466

Quinlan MR, Docherty NG, Watson RW, Fitzpatrick JM (2008) Exploring mechanisms involved in renal tubular sensing of mechanical stretch following ureteric obstruction. Am J Physiol Renal Physiol 295: F1-F11

Radiczy DC, Levy DD, Littlepage LE, Liu H, Nelson CM, Fata JE, Leake D, Godden EL, Albertsson DG, Nieto MA, et al (2005) Rac1b and reactive oxygen species mediate MMP-3-induced EMT and genomic instability. Nature 436: 123-127

Ramón y Cajal S (1890) Manual de Anatomía Patológica General. Barcelona: Imprenta de la Casa Provincial de la Caridad

Rastaldi MP, Ferrario F, Giardino L, Dell'Antonio G, Grillo C, Grillo P, Strutz F, Muller GA, Colasanti G, D'Amico G (2002) Epithelial-mesenchymal transition of tubular epithelial cells in human renal biopsies. Kidney Int 62: 137-146

Ricardo SD, Ding G, Eufemio M, Diamond JR (1997) Antioxidant expression in www.embomolmed.org

Siegel PM, Shu W, Cardiff RD, Muller WJ, Massague J (2003) Transforming growth factor-beta1 expression in lung fibroblasts at the transcriptional level via AP-1 activation. J Cell Mol Med, DOI: 10.1111/j.1582-4934.2008.00647.x

Sun S, Ning X, Zhang Y, Lu Y, Nie Y, Han S, Liu S, Du R, Xia L, He L, et al (2009) Hypoxia-inducible factor-1alpha induces Twist expression in tubular epithelial cells subjected to hypoxia, leading to epithelial-to-mesenchymal transition. Kidney Int 75: 1278-1287

Tan R, Zhang J, Tan X, Zhang X, Yang J, Liu Y (2006) Downregulation of Snail expression in obstructive nephropathy is mediated by an enhanced ubiquitin-dependent degradation. J Am Soc Nephrol 17: 2781-2791

Tashiro K, Tamada S, Kuwabara N, Komiya T, Takekida K, Asai T, Iwao H, Sugimura K, Matsumura Y, Takaoka M, et al (2003) Attenuation of renal fibrosis by proteasome inhibition in rat obstructive nephropathy: possible role of nuclear factor kappaB. Int J Mol Med 12: 587-592

Uemura H, Ishiguro H, Ishiguro Y, Hoshino K, Takahashi S, Kubota Y (2008) Angiotensin II induces oxidative stress in prostate cancer. Mol Cancer Res 6: 250-258

Vega S, Morales AV, Ocana OH, Valdes F, Fabregat I, Nieto MA (2004) Snail blocks the cell cycle and confers resistance to cell death. Genes Dev 18: 1113-1143

Vongviwatanat A, Tasanarong A, Rayner DC, Melk A, Halloran PF (2005) Epithelial to mesenchymal transition during late deterioration of human kidney transplants: the role of tubular cells in fibrogenesis. Am J Transplant 5: 1367-1374

Vuruskun H, Caliskan Z, Kordan Y, Ozakin C, Yavascaoglu I, Oktay B (2005) Elevated plasma concentrations of transforming growth factor-beta 1 in patients with unilateral ureteral obstruction. Urol Res 33: 465-469

Wahl SM, Hunt DA, Wakefield LM, McCartney-Francis N, Wahl LM, Roberts AB, Sporn MB (1987) Transforming growth factor type beta induces monocoyte chemotaxis and growth factor production. Proc Natl Acad Sci USA 84: 5788-5792

Wolf G (2006) Renal injury due to renin-angiotensin-aldosterone system activation of the transforming growth factor-beta pathway. Kidney Int 70: 1914-1919

Wolf G, Ziyadeh FN, Thaiss F, Tomaszewski J, Caron RJ, Wenzel U, Zahner G, Helmchen U, Stahl RA (1997) Angiotensin II stimulates expression of the chemokine RANTES in rat glomerular endothelial cells. Role of the angiotensin type 2 receptor. J Clin Invest 100: 1047-1058

Wu Y, Deng J, Rychahou PG, Qiu S, Evers BM, Zhou BP (2009) Stabilization of Snail by NF-kappaB is required for inflammation-induced cell migration and invasion. Cancer Cell 15: 416-428

Yamagishi H, Yokoyama T, Kishida M, Kojima S, Tashiro K, Tamada S, Kuwabara N, Komiya T, Takekida K, Asai T, Iwao H, Sugimura K, Matsumura Y, Takaoka M, et al (2003) Attenuation of renal fibrosis by proteasome inhibition in rat obstructive nephropathy: possible role of nuclear factor kappaB. Int J Mol Med 12: 587-592

Yang MH, Wu MZ, Chiou SH, Chen PM, Chang SY, Liu CJ, Teng SC, Wu KJ (2008) Direct regulation of Twist by HIF-1alpha promotes metastasis. Nat Cell Biol 10: 295-305

Zeisberg M, Hanai J, Sugimoto H, Mamamoto T, Chaytan D, Strutz F, Kalluri R (2003) BMP-2 counteracts TGF-beta-induced epithelial-to-mesenchymal transition and reverses chronic renal injury. Nat Med 9: 964-968
Zeisberg M, Kalluri R (2008) Fibroblasts emerge via epithelial-mesenchymal transition in chronic kidney fibrosis. Front Biosci 13: 6991-6998
Zeisberg EM, Potenta SE, Sugimoto H, Zeisberg M, Kalluri R (2008) Fibroblasts in kidney fibrosis emerge via endothelial-to-mesenchymal transition. J Am Soc Nephrol 19: 2282-2287
Zeisberg M, Yang C, Martino M, Duncan MB, Rieder F, Tanjore H, Kalluri R (2007a) Fibroblasts derive from hepatocytes in liver fibrosis via epithelial to mesenchymal transition. J Biol Chem 282: 23337-23347
Zeisberg EM, Tarnavski O, Zeisberg M, Dorfman AL, McMullen JR, Gustafsson E, Chandraker A, Yuan X, Pu WT, Roberts AB, et al (2007b) Endothelial-to-mesenchymal transition contributes to cardiac fibrosis. Nat Med 13: 952-961
Zhou BP, Deng J, Xia W, Xu J, Li YM, Gunduz M, Hung MC (2004) Dual regulation of Snail by GSK-3beta-mediated phosphorylation in control of epithelial-mesenchymal transition Nat Cell Biol. 6: 931-940