BMP7 stabilizes differentiation and branching during development of renal tubules[8]. In several models of kidney injury, the administration of BMP7 in pharmacological doses attenuates the process of renal fibrosis and in some cases restores the structure of epithelial tubules[7,9,10].

Although TGF-β and BMP7 signaling create a balanced paradigm, other signaling pathways and transcription factors undoubtedly come in play[2]. Nevertheless, the reciprocity between these two cytokines provides a useful framework for building more complex models of epithelial-mesenchymal transition.

Another emerging feature of epithelial-mesenchymal transition is the potential role of ligand-trap proteins in the regulation of epithelial transitions leading to fibrosis (**Fig. 1**). Trap proteins are attached to cell membranes and act as accessory coreceptors, or circulate in interstitial spaces as soluble moieties to block receptor activation by free ligand[4]. They are increasingly understood as important modulators of body plan development during embryogenesis[11]. Whereas TGF-β and the BMPs share some soluble trap proteins, most ligand-trap proteins have subfamily specificity; within a subfamily, however, there is promiscuity.

Many trap proteins are negative regulators of receptor binding. The TGF-β trap protein decorin, for instance, prevents renal fibrosis after inflammation of renal glomeruli[12]. Negative trap proteins for TGF-β also include LAP and α2-macroglobulin, and for BMP7 include noggin, chordin and follistatin[4,11]. Connective tissue growth factor (CTGF) is both a positive trap that facilitates the binding of TGF-β to its receptor and a negative trap for BMP7 (ref. 13). There have been no reports until now of trap proteins that facilitate receptor binding to BMP7. Enter KCP.

KCP is a secreted protein containing multiple cysteine-rich signaling domains[14]. Lin *et al.* found that KCP enhanced receptor binding of BMP7 (and BMP4) and elevated intracellular levels of phosphorylated Smad1 (ref. 3). Whether there is an effect on Smad2 and Smad3 mediating TGF-β was not addressed in the current study.

Lin *et al.*[3] showed that KCP-null mice were born normal and matured as adults without incident until they were stressed. The authors next challenged the mice by inducing acute tubular necrosis along their kidney tubules and found that the mice developed a renal fibrosis not seen in wild-type controls.

In a second model, after obstruction of one kidney, the scarring in that kidney was more intense than in wild-type controls and occurred earlier. Unexpectedly, in these experiments fibrosis also appeared in the contralateral, erstwhile normal, kidney. This was probably the result of profibrotic cytokines leaking from the obstructed kidney that re-entered the circulation—although no one knows for sure. An implication of this result is that KCP might normally rescue local epithelia under collateral assault by drivers of epithelial-mesenchymal transition.

Lin *et al.*[3] also showed that KCP is expressed in embryonic tissues, but not routinely in the adult. Curiously, embryos do not form scars when wounded[15]. Perhaps the embryonic expression of KCP or other trap proteins partly explains this observation. In adult injury, KCP is probably expressed in response to stress.

There are no effective treatments for established tissue fibrosis, which has led to an emphasis on understanding the molecular processes behind it. The study of Lin *et al.*[3] offers up a more sophisticated view of the role of cytokine balance in epithelial-mesenchymal transition that results in scarification. Regulation at two levels of competition can now be imagined; one level depends on the extracellular equilibrium of rival ligand-trap proteins, whereas the second level operates intracellularly by modulating the balance of various Smad proteins in the nucleus. This dual control favors a state of terminal differentiation in normal epithelia that preserves organ structure and function.

BMP7 has shown promise as an avenue of therapy in mouse models of fibrosis, although human clinical studies have yet to get underway. If KCP can be produced recombinantly, it may serve a combined role with BMP7 in attenuating new like tissue scars therapeutically.

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Skin contact

A potential therapeutic target for skin cancer emerges from a study in the 18 March issue of *Science* on a rare blistering disorder.

The disorder results from defects in type VII collagen, which helps glue the outer and inner layers of the skin together. The slightest abrasion can cause painful skin blistering in individuals with the disorder, called recessive dystrophic epidermolysis bullosa (RDEB). More than half of RDEB patients also die by age 40 of a more common affliction, squamous cell carcinoma—the second most common cancer in the United States.

Susana Ortiz-Urda *et al.* asked why some RDEB patients succumb to skin cancer whereas others are spared. Some RDEB patients, they found, retain a small region of the type VII collagen gene that encodes NC1 (the amino-terminal noncollagenous domain). The investigators provide evidence that NC1—through binding to laminin-5—acts as a conduit to promote the invasion of cancerous skin cells into surrounding tissue. Such invasion could be stopped by antibodies to NC1 in animal models.

Shown is skin from a RDEB patient with NC1: NC1 is in red, epithelial cells in green and nuclei in blue.

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