Mastering matriptase

Similar to MMPs, matriptase, a transmembrane serine protease, is commonly overexpressed in epithelial tumors[9]. Elevated levels of matriptase correlate with the grade of malignancy and predict a poor prognosis in human cancers, but a formal *in vivo* demonstration that matriptase is causally involved in tumor development was still lacking.

Now, List *et al.* have generated transgenic mice with increased expression of matriptase in the epidermis[4]. They found that even a modest increase of matriptase activity was sufficient for the induction of spontaneous squamous cell carcinomas and strongly potentiated chemical skin carcinogenesis, possibly through activation of the tumor-promoting PI3K-Akt pathway (**Fig. 1**); in contrast, double-transgenic mice coexpressing matriptase and its cognate inhibitor hepatocyte growth factor activator inhibitor 1 (HAI-1) did not develop spontaneous skin cancers and did not show increased susceptibility to chemical carcinogenesis.

Again, the major finding of this study is that a tumor-associated proteolytic enzyme is causally involved in cancer initiation. The challenge now is to identify the molecular mechanisms underlying the tumorigenic activity of matriptase. An indirect role can be easily envisaged: indeed, matriptase is an efficient activator of hepatocyte growth factor (HGF)[10], a mesenchymal cytokine that stimulates proliferation, migration and survival of epithelial cells and whose deregulated activity has a crucial role in cancer onset and progression[11].

Interestingly, transgenic expression of HGF in the epidermis increases the incidence of spontaneous and UV-induced squamous cell carcinomas[12], suggesting a linear molecular flowchart along which augmented matriptase activity would lead to enhanced production of mature HGF, which in turn might stimulate keratinocyte transformation. Demonstration of a direct oncogenic role for matriptase awaits development of purified and cell-based systems in which to test whether and how matriptase can affect cellular behavior in the absence of coexisting environmental biases.

Tumor tension

The different molecular composition of the tumor microenvironment compared with the stromal compartment of normal organs not only influences the activity of some extracellular proteases, but also regulates stiffness of the ECM and, therefore, the overall rigidity of the neoplastic mass; in particular, the tumor stroma is much more fibrotic, that is, much stiffer, than normal connective tissues as a result of a massive deposition of collagen fibers. It has long been known that the physical properties of the ECM can affect cellular responses. Variations in the compliance of the ECM are interpreted by surface receptors called integrins, which connect to the cytoskeleton and translate the external mechanical information into modification of cell contractility, mainly by controlling the activity of Rho GTPases[13].

The role of integrins as mechanotransducers has been extensively investigated at the morphological and biochemical levels, but little data are available on how their ability to transduce tensional forces can affect biological parameters such as differentiation and neoplastic transformation.

Paszek *et al.* now report that increasing matrix rigidity results in integrin clustering, which in turn enhances activation of Rho, with consequent modification of cytoskeletal tension[5] (**Fig. 1**). They showed that this effect was sufficient to induce some phenotypic traits of neoplastic transformation: when cultured on rigid substrates, normal mammary epithelial cells disrupted cell-cell contacts, underwent depolarization, produced a higher number of well-organized focal

Anchors aweigh

Normal cells will commit suicide if they lose strong attachments to neighboring cells or extracellular matrix. Cancer cells overcome this checkpoint and grow in an anchorage-independent manner. A recent study shows that the p600 protein may connect external cellular signals and the decision to die (*Proc. Natl. Acad. Sci. USA* **102**, 15093–15098).

Yoshihiro Nakatani *et al.* found that p600 was expressed throughout the cell, overlapping with cytoskeletal proteins in the cytoplasm and nucleus (shown here: p600 in green, microtubules in red, and actin in blue). Loss of p600 resulted in reduced membrane ruffling and cellular adhesion and increased cell death, suggesting the involvement of p600 in survival pathways possibly related to membrane attachments.

p600 may have additional functions in the nucleus, where it interacted with the tumor suppressor protein retinoblastoma. Other recent studies have shown that p600 binds the human papilloma virus protein E7—which also interacts with retinoblastoma and triggers its degradation. Knockdown of p600 diminishes anchorage-independent growth in human papilloma virus–infected cells, suggesting that p600 may have a vital role in antitumor defense (*Proc. Natl. Acad. Sci. USA* **102**, 11486–11491; 11492–11497).

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