Spotlight

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Pancreatic Cancer: Rites of Passage

Zhao *et al*.
10.1002/ijc.25412 (Resolve a DOI—http://dx.doi.org)

The development of all human cancers can be divided into a series of obstacles to tumorigenesis that cells need to overcome before they can start proliferating in an uncontrolled fashion, and pancreatic cancer is no exception. In this type of cancer, activating *KRAS* mutations is typically an early event and seems to be a virtual rite of passage to malignancy. They are closely followed by inactivation of *SMAD4*/*DPC4*, which compromises TGF-β tumor suppressor activity. These two events lead to a remarkable array of cellular effects, including the activation of EGFR, erbB2, IGF-1R and Ron receptors, but whether, and if so, how TGF-β and Ras pathways collaborate to accelerate tumor progression was not clear.

Using immortalized human pancreas ductal cells (HPNE), Zhao *et al*. asked whether activating mutations of *KRAS* and loss of *SMAD4*/*DPC4* play a role in causing the aberrant expression of phosphotyrosine kinase receptors (PTKRs). Expression of K-Ras^{GD12} upregulated the expression of EGFR and erbB2 and induced an invasive phenotype but did not change the expression of Ron or IGF-1R. Knock-down of Smad4 had more or less the same effect, just to a lesser extent. Interestingly, decreasing Smad4 activity in K-Ras^{GD12}-expressing HPNE cells boosted the activity of EGFR and erbB2 and their downstream signaling targets ERK and AKT even higher. These findings suggest that Smad4 normally suppresses Ras-induced upregulation of EGFR and erbB2 and that a loss of Smad4 signaling gives Ras free rein to activate these PTKRs.

Many other pathways are likely to contribute to the pathogenic role of activated K-Ras, and a deeper understanding of what each one brings to the table will be vital for the development of new treatment approaches towards this disease.