MOUSE MODELS

Brain-gain

Mutations in members of the RB tumour-suppressor pathway are commonly detected in human gliomas, but are they sufficient to cause cancer? By inactivating the Rb pathway in the astrocytes of mice, Terry Van Dyke and colleagues have developed a much-needed model of the most common primary human brain tumour.

Mutations in the RB signalling pathway occur in 70–80% of human grade III and IV gliomas, which are tumours that originate from glial cells — most often astrocytes. The authors used an inducible form of the truncated SV40 T antigen (T_{121}) that is expressed specifically in astrocytes. T_{121} dominantly inactivates Rb, along with its family members p107 and p130, but not p53. The transgenic mice developed hypercellularity in the periventricular region by 7 days after birth, and they died by 5–8 months of age from malignant anaplastic astrocytomas.

The long latency between T_{121} expression and the development of astrocytomas (over 100 days) indicated that additional events might be required after Rb inactivation for transformation to occur. In human glioma cells, the activity of the anti-apoptotic protein kinase AKT is frequently upregulated, and is correlated with tumour progression. Andrew Xiao *et al.* report that in the transgenic mice, Akt was activated (phosphorylated) in 72% of astrocytomas, and apoptosis levels were greatly reduced in regions of Akt activation. This indicates that astrocytes in which the Rb pathway is inactivated might be under selective pressure for dysregulation of Akt.

The lipid phosphatase Pten negatively regulates Akt, and inactivating *PTEN* mutations occur in 50% of high-grade human astrocytomas — frequently co-existing with *RB* mutations. The authors found that astrocytoma development was accelerated when transgenic mice were created in a *Pten*^{+/-}, but not a *Trp53*^{+/-} background. So, defects in *PTEN*-specific pathways of apoptosis induction seem to be important for astrocyte transformation. This highly penetrant mouse model of astrocytoma, which has similar characteristics to the human disease, will be useful for studying pathogenesis and therapeutics.

Kristine Novak

References and links

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WEB SITE

Terry Van Dyke's lab: http://www.unc.edu/depts/van_dyke/

TUMOUR SUPPRESSORS

Hard to stomach

We know a lot about the environmental risk factors for stomach cancer — the world's second most common cause of cancer death — but what about its molecular genetics? Although several chromosomal aberrations have been implicated, the significance of these changes, and the specific genes that are involved, are poorly understood. But a knockout study has now serendipitously identified a candidate tumour-suppressor gene that is inactivated in a high proportion of advanced human stomach cancers.

The runt family of transcription factors associate with SMADS to transmit signals from the transforming factor- β (TGF- β) receptor. RUNX1 is required for haematopoiesis, and individuals who inherit heterozygous mutations in this gene develop acute myeloid leukaemia. RUNX2 is required for osteogenesis. Qing-Lin Li *et al.* set out to investigate the function of Runx3 by analysing knockout mice.

Their first observation was that the stomach mucosa of *Runx3*-null mice, which die soon after birth, was twice as thick as that of wild-type animals, indicating gastric hyperplasia. The gastric epithelial cells of these mice proliferated more rapidly in culture than those from wild-type mice and could not respond to the apoptosis-inducing effects of TGF- β . Loss of the gene that encodes the TGF- β receptor has been observed in human gastric cancer cells, so could RUNX3 loss also be associated with this cancer?

RUNX3 was expressed by normal gastric epithelial cells, but expression was reduced or not detectable in all gastric cell lines tested and was reduced in primary gastric cancer samples. *RUNX3* expression was reduced in 40% of early-stage carcinomas, but this level increased to nearly 90% in advanced cases. Loss of expression was found to be a result of *RUNX3* hypermethylation in both cancer cell lines and primary tumour samples. But *RUNX3* point

mutations were rare, so it might be possible to slow gastric tumour growth by re-expressing the protein in cancer cells.

Is RUNX3 a tumour suppressor? Stable re-expression of *RUNX3* in gastric cancer cells reduced their tumorigenicity *in vitro* and *in vivo*, whereas expression of a mutant form of the protein did not, indicating that this protein has anti-oncogenic activity. *Runx3*-null gastric epithelial cells also induced adenocarcinoma formation in mice.

So RUNX3 seems to be a new tumour suppressor, the inactivation of which is involved in gastric carcinogenesis. Whether inactivation of the TGF- β –RUNX3 pathway is a prerequisite for gastric cancer progression, and whether RUNX3 inactivation contributes to the development of other tumours, are important avenues for investigation.

Kristine Novak

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