TUMOUR SUPPRESSORS

Notch blocks bladder tumorigenesis

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The Notch pathway has been shown to have both oncogenic and tumour-suppressive roles in cancer, depending on the tissue type and cellular context. Following an initial observation that mice lacking urothelial γ -secretase activity (which results in loss of Notch signalling) develop urothelial carcinomas, Rampias *et al.* found that Notch signalling is frequently inactivated in human bladder cancers and delineated a mechanism that could explain why its loss promotes proliferation.

Full-exon sequencing of Notch genes and those encoding other components of the Notch pathway in 72 patients with bladder transitional cell carcinoma (TCC) revealed that 31 patients (43%) had somatic mutations in this pathway, which were not confined to a particular grade or stage of tumour. The majority of these mutations were confirmed to inhibit Notch activity when exogenously expressed in cell culture. *NOTCH1* copy number loss was observed in half of the patients; combining this observation with the mutation data

from Notch pathway proteins resulted in an overall number of pathway alterations in 44 of 72 tumours (61%). Furthermore, patients whose tumours had Notch pathway alterations had significantly worse overall survival compared with patients whose tumours lacked these changes.

Mutually exclusive, activating mutations in fibroblast growth factor receptor 3 (FGFR3) and RAS (HRAS and to a lesser extent KRAS) have previously been associated with bladder cancers, primarily through their ability to promote phosphorylation of ERK1 and ERK2 (ERK1/2). The authors found that Notch pathway alterations occurred in the absence of FGFR3 and RAS mutations in 18 of 72 tumours (25%), and loss of function Notch mutations alone also increased ERK1/2 phosphorylation. Exogenous expression of the active NOTCH1 intracellular domain or the Notch ligand Jagged 1 (JAG1) in TCC cells reduced both ERK1/2 phosphorylation and cell proliferation. Several members of

the dual-specificity phosphatase (DUSP) family can dephosphorylate ERK1/2, and the authors found that the expression of several DUSPs was increased following Notch pathway activation. Notch signalling leads to activation of the transcription factor CSL (also known as recombining binding protein suppressor of hairless (RBP)), and promoter analyses and chromatin immunoprecipitation showed that CSL binds to several DUSP genes. This indicates that Notch signalling in normal bladder cells keeps ERK1/2 signalling and proliferation low by promoting the transcription of DUSPs.

Mice with global inactivation of Notch signalling through knockout of the γ -secretase component Nicastrin (*Ncstn*) developed invasive urothelial carcinomas that had high levels of ERK1/2 phosphorylation. Tumorigenesis and ERK1/2 activation were then suppressed in *Ncstn*-null mice that also overexpressed the NOTCH1 intracellular domain. Urothelial-specific deletion of *Ncstn* also caused tumour formation, but these tumours were non-invasive. The reasons for this difference are unclear, but could indicate different cells of origin.

The authors conclude that Notch pathway abrogation is a driver of bladder tumorigenesis, and that further analysis of this pathway in mouse models and human tumours is warranted. Notch agonists could have therapeutic potential in bladder cancers, but this would have to take into account the oncogenic roles of Notch signalling in other contexts.

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A new tumor suppressor role for the Notch pathway in bladder cancer. *Nature Med.*
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