An early stage therapeutic target for bile duct cancer

Notch-3 signalling is the key driver of tumour development in bile duct cancer, with Notch-3 receptor differentially overexpressed in comparison to other notch receptors. Therapeutic targeting of this receptor could provide anti-tumorigenic effects in patients, and act as a chemotherapeutic agent with minimal side-effects.

The Challenge
Bile duct cancer (BDC) is an aggressive primary liver cancer with increasing global incidence and very poor prognosis. Current treatments provide modest effects, and surgery remains the only curative treatment. The difficulties in detecting this cancer means by the time it is diagnosed, the tumour is too advanced for surgery. There is a need for a novel therapeutic target with extensive anti-tumorigenic effects and minimal off-targets affects to treat bile duct cancer patients.

Technology
Notch signalling is crucial during development and in many forms of cancer. Researchers at the University of Edinburgh have demonstrated that Notch-3 is differentially upregulated in BDC compared to the other notch receptors and plays a key role in driving tumorigenesis. Notch-3 signalling sustains tumour cell survival through PI3k/Akt activation, a non-canonical mechanism that is independent of the classical mechanism. Therefore, specifically inhibiting Notch-3 signalling could be a means of treating BDC and avoiding the gastro-intestinal side effects that are usually seen with pan-notch inhibitors.

Exemplification Data
Surgically resected BDC tumours from human samples show differential overexpression of Notch-3 receptor compared to matched non-cancerous livers. In vivo proof of concept studies in animal models of BDC demonstrated that Notch-3 promotes tumorigenesis throughout the development of BDC. The knockdown of Notch-3 leads to reduction in tumour mass and volume and proto-oncogenes were found to be down-regulated when Notch-3 was inhibited. Further validation of the role of Notch-3 in BDC was done using primary human cell lines and ex vivo xenograft model.

Applications
- Oncology diagnosis
- Oncology target for drug discovery

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