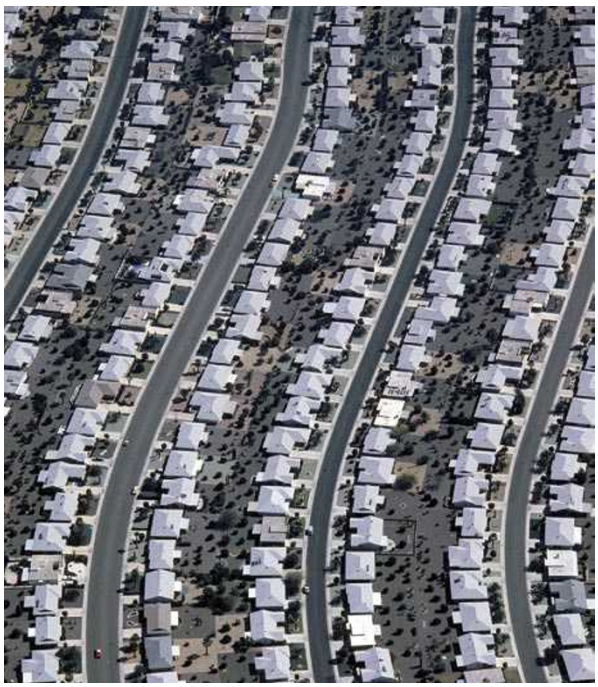
THERAPY

Developmental parallels



Numerous epithelial cancers are reported to be reliant on ligand-dependent Hedgehog (Hh) signalling, providing a rationale for the development of Hh inhibitors. However, physiological Hh signalling is mediated in many tissues through paracrine effects on mesenchymal cells. Yauch, Gould and colleagues provide evidence that tumour epithelial cancer cells have a parallel mechanism.

On treating a panel of cancer cell lines with cyclopamine or a potent small molecule antagonist (HhAntag), both of which target the serpentine receptor smoothened (SMO), the authors show that cell growth inhibition requires much higher concentrations of inhibitor than that needed to block the Hh signal. In addition, there was no correlation between sensitivity to the inhibitors and tissue-specificity or markers of Hh pathway activation. Expression analysis of human tumour samples indicated that the Hh ligands sonic hedgehog (SHH) and Indian hedgehog (IHH) are significantly upregulated in a subset of cancers, but given their initial results de Sauvage and colleagues decided to check whether these ligands were functional. They co-cultured representative tumour cell lines with fibroblasts and found that the levels of SHH and IHH expression correlated with Hh pathway activation in the fibroblasts, indicating that the secreted ligands are active and support paracrine signalling. Analysis of xenografts of pancreatic cancer cell lines expressing Hh ligands in *Ptch1*–lacZ;*Rag2*$^{-/-}$ mice also revealed that the pathway can be activated *in vivo* in stromal cells adjacent to tumour epithelia. Moreover, levels of SHH and IHH expression in surgical biopsy samples implanted into nude mice significantly correlated with the activation of Hh signalling in infiltrating stromal cells.

So, are tumours actually reliant on this paracrine Hh pathway? Human pancreatic and colonic adenocarcinomas can express IHH and/or SHH, and xenografts of these tumours in mice treated with HhAntag showed significant growth delay (29% and 49% reduction, respectively). This response was recapitulated using the Hh-ligand-blocking antibody 5E1, indicating that the response to HhAntag was specific to the inhibition of Hh signalling. In addition, they showed that the growth of tumour cells expressing luciferase was significantly reduced when co-injected with *Smo*-deficient mouse embryonic fibroblasts. Together, these findings indicate that HhAntag specifically inhibits Hh pathway activation in infiltrating stromal cells, which contribute to tumour progression. The mechanism(s) by which the stroma influences tumour growth following Hh stimulation remain to be elucidated. The authors note that inhibition of Hh signalling in the stroma affected components of the insulin-like growth factor and Wnt signalling pathways in the tumour cells.

These data provide novel insight into the mechanisms by which Hh signalling is deregulated in cancer, which has implications for targeting the pathway in the clinic and the development of some of the currently available Hh pathway inhibitors.

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ORIGINAL RESEARCH PAPER Yauch, R. L. *et al.* A paracrine requirement for hedgehog signalling in cancer. *Nature* 27 Aug 2008 (doi:10.1038/nature07275)