specific long-term antitumour immunity.

Could homeostatic proliferation be useful for the treatment of established tumours? Lymphopaenic mice were challenged with melanoma cells, and when the tumours reached a specific size, the mice were transfused with lymph-node cells. Tumour growth was markedly inhibited in treated mice compared with controls.

These data indicate that, in the clinic, it might be beneficial to begin tumour immunotherapy soon after the completion of chemotherapy to induce effective homeostatic T-cell proliferation.

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ANGIOGENESIS

Endostatin and Wnt signalling

Although *Xenopus* is more often used as a model for embryogenesis than for cancer research, it has recently provided insight into the mechanisms of endostatin signalling, as Hanai and colleagues report in the 5 August issue of *The Journal of Cell Biology*. Endostatin is an anti-angiogenic factor, and recombinant endostatin, which inhibits tumour growth in animal models, is now in clinical trials.

Hanai *et al.* found that injection of high concentrations of endostatin RNA into *Xenopus* blastomeres caused developmental abnormalities in cement-gland and eye formation. Injection of inactivated mutated endostatin, however, had no effect on development. The defects seen are characteristic of those observed when key components of the Wnt signalling pathway are manipulated — this pathway is important for regulation of cell proliferation, differentiation, motility and morphogenesis. From these observations, the authors hypothesized that endostatin might have a role in Wnt signalling.

When Wnt binds to Frizzled, cytoplasmic Dishevelled (Dsh) proteins are activated. These proteins then antagonize glycogen synthase kinase (GSK)3, leading to stabilization of β -catenin — an essential mediator of Wnt signalling. β -catenin translocates to the nucleus and binds to members of the T-cell-specific factor (TCF) transcription-factor family, stimulating transcription of target genes that encode such proteins as c-Myc and cyclin D.

So, does endostatin modulate the Wnt pathway? Experiments by Hanai *et al.* showed that endostatin inhibits β -catenin activity — injection of β -catenin into *Xenopus* led to the development of double-headed embryos, and co-injection of endostatin inhibited this abnormal phenotype. Inhibition of the Wnt pathway was confirmed in human umbilical-vein endothelial cells (HUVECs) that were transfected with β -catenin and endostatin.

Although Hanai and co-workers now knew that endostatin directly inhibited the Wnt/ β -catenin pathway, they wanted to find out how and where in the pathway endostatin acts. They therefore tested the ability of endostatin to block signal transduction at different levels, in both *Xenopus* embryos and endothelial cells. Co-injection of endostatin with a TCF construct that lacked the β -catenin binding site — and so constitutively activates transcription independently of β -catenin — failed to inhibit axis duplication, but axis duplication induced by

Dsh overexpression was inhibited by endostatin expression. Furthermore, endostatin, but not mutant endostatin, decreased the levels of a form of β -catenin that is insensitive to upstream antagonists of Wnt signalling. The data therefore indicate that endostatin modulates the Wnt pathway by regulating β -catenin stability via a novel GSK3-independent mechanism.

In addition, the authors showed that endostatin inhibition of endothelial-cell migration and entry into the S phase of the cell cycle — properties of endostatin that have been reported by these authors and other groups to be linked with its anti-angiogenesis activity — is due to endostatin modulation of the Wnt pathway. The constitutively activated form of TCF could rescue the inhibitory effects of endostatin on angiogenesis in HUVECs.

This paper provides insight into a possible function of the Wnt/ β -catenin pathway in angiogenesis and shows that endostatin has a role in inhibiting this pathway. Understanding the mechanism of action of endostatin should facilitate the development of selective and effective endostatin therapies for the treatment of cancer.

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