KIDNEY CANCER

Resistance stems from tumour necrosis

Newly published research results show that cancer stem cells are found in increased numbers in perinecrotic areas of renal cell carcinoma (RCC) tumours, and that they could contribute to the development of resistance to antiangiogenic cancer therapies, which act through hypoxia-induced necrosis.

Cells expressing CD133 and CXCR4—which are common markers of stem cells—were observed in perinecrotic regions of primary tumour samples from seven patients with metastatic RCC (mRCC), both before treatment and after 3 months of sunitinib therapy.

CD133-expressing cells were significantly more numerous in perinecrotic areas than in perivascular regions of tumours before and after treatment ($P < 0.01$). 84.5% of cells in perinecrotic areas that expressed CD133 coexpressed CXCR4, and 95.0% of these coexpressing cells also expressed HIF1- α , a marker of hypoxia. The numbers of cells coexpressing CD133 and CXCR4

were significantly greater in the tumour samples after sunitinib therapy than before treatment ($P < 0.05$).

Six xenograft models, created by grafting primary tumours from patients with mRCC into nude mice, were assessed for the development of necrosis and their responsiveness to sunitinib treatment. Two of the models were observed to respond to sunitinib, and these responders experienced a significant increase in necrotic regions between day 0 and day 7 of therapy ($P < 0.05$). By contrast, 21 days elapsed before necrotic areas were seen in nonresponsive or untreated xenografts.

All xenograft models (both treated and untreated) had increased numbers of CD133-expressing cells in perinecrotic areas compared with perivascular regions. Significantly more cells expressing CD133 were also observed in the perinecrotic regions of treated xenografts, compared with untreated ($P < 0.05$).

Cells coexpressing CD133 and CXCR4 showed tumorigenic potential, inducing

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tumour growth when injected into nude mice, and this effect was significantly enhanced when cells were precultured under hypoxic conditions ($P < 0.05$). Hypoxia also reduced the effects of sunitinib in cells expressing both markers, indicating that these cells might be resistant to treatments that act by inducing tumour necrosis through hypoxia.

Louise Stone

Original article Varna, M. *et al.* Stem cells increase in numbers in peri-necrotic areas in human renal cancer. *Clin. Cancer Res.* doi:10.1158/1078-0432.CCR-14-0666