TUMOUR SUPPRESSION

Sharing the limelight

The cell surface membrane protein *CD44* is now an 'A-list' molecule owing to its expression on stem (and potential cancer stem) cells. However, new data from Samuel Godar, Robert Weinberg and colleagues suggest that CD44 might have to share its new-found fame with an old pro, *p53*.

Weinberg and colleagues had noticed that expression of CD44 in tumour tissue samples correlated with high expression levels of *p53*. Such levels of *p53* are indicative of mutant protein expression, so they investigated a putative link between these two molecules. They established that high levels of CD44 in *breast cancer* samples correlated with expression of mutant (transcriptionally compromised) *p53*, indicating that *p53* might negatively regulate CD44 expression. Using human mammary epithelial cells (BPECs) transfected with the catalytic subunit of telomerase (BPEC-T cells) to prolong their proliferation in culture, they showed that expression levels of CD44 were inversely related to *p53* levels. Moreover, expression of CD44 in breast tissue from *p53*-null mice showed high CD44 expression levels, and restoration of *p53* expression to this tissue resulted in decreased CD44 expression. Western blot and reverse transcriptase PCR experiments indicated that loss of *p53* expression affected *CD44* at the mRNA level, suggesting transcriptional control. Using a luciferase reporter vector containing the *CD44* promoter sequence the authors found that *p53* required a functional DNA binding domain to repress *CD44* expression, and gel-shift assays and chromatin immunoprecipitation experiments showed that *p53* is able to bind the *CD44* promoter both *in vitro* and *in vivo* by binding to a non-canonical *p53* consensus sequence.

Why does *p53* need to repress CD44 expression? CD44 can promote cell growth and resistance to apoptosis, and has been shown to stimulate epidermal growth factor (EGF) signalling. Expression of short hairpin RNAs (shRNAs) that targeted either *p53*, CD44 or both in BPEC-T cells showed that the basal expression levels of *p53* are enough to suppress CD44 expression and limit EGF-induced proliferation. In addition, ectopic expression of CD44 in these cells resulted in resistance to *p53*-mediated death in response to the chemotherapeutic drug *doxorubicin*. Therefore, *p53* needs to suppress CD44 expression in order to limit cell proliferation and enable apoptosis. However, *p53* regulates the expression of many genes that control cell-cycle progression and cell death, so how significant is this effect on CD44? Using BPLER cells, a transformed variant of BPECs that express SV40 large T antigen to inactivate *p53* function, the authors showed that knockdown of CD44 expression reduced BPLER cell

growth in mice, and increased the numbers of cells that needed to be injected to form tumours, consistent with CD44 being a marker of 'cancer stem' cells. CD44 expression can also enhance tumour progression, as suppression of *p53* using shRNAs in A459 lung adenocarcinoma cells that have normal levels of *p53* and CD44 resulted in increased tumour size compared with parent A459 cells and A459 cells expressing shRNAs that target both *p53* and CD44.

These results indicate that CD44 is more than a mere marker of stem cells — it is able to increase cell growth and reduce cell death and will induce chemotherapy resistance when overexpressed in cells with wild-type *p53*. They also clearly indicate that basal expression levels of *p53* have crucial functions within cells under physiological conditions, something that is often overlooked.

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ORIGINAL RESEARCH PAPER Godar, S. et al. Growth-inhibitory and tumour suppressive functions of *p53* depend on its repression of CD44 expression. *Cell* **134**, 62–73 (2008)

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