Nature Reviews Cancer | AOP, published online 18 January 2008; doi:10.1038/nrc2314

TUMORIGENESIS

First or last?

Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL, also known as TNFSF1) is a member of the TNF superfamily that can induce apoptosis in susceptible cancer cell lines. Drugs that augment the TRAIL–TRAIL receptor (TRAIL-R) signalling pathway are currently in clinical trials, and results from two papers indicate that the tumour stages for which they could be useful might be determined by tumour type.

TRAIL binds to two receptors in humans that induce apoptosis, but only one in mice, so mouse models that are deficient in TRAIL-R have been generated. Anne Grosse-Wilde and colleagues investigated the effect of TRAIL-R loss on the development of skin cancer using the classical DMBA–TPA carcinogenesis protocol. They found that heterozygous or nullizygous *Trailr* mice develop skin lesions at the same rate as wild-type mice. Indeed, progression from benign to malignant carcinoma did not differ between the mouse models, so the authors conclude, in agreement with previous studies, that TRAIL–TRAIL-R-induced apoptosis is not tumour-suppressive in the early stages of carcinogenesis. However, *Trailr*-null mice developed lymphoid metastases at a significantly higher frequency (32%) than either heterozygous or wild-type mice (8% and 9%, respectively). Further experiments indicated that loss of adherence to the basement membrane (which is required for metastasis) results in sensitivity to TRAIL (and CD95 ligand)-induced apoptosis, possibly through the inactivation of a mitogen-activated protein kinase 3 survival pathway. Loss of this sensitization in *Trailr*-null cells increases the incidence of metastases, and indicates that cancer cells in the early stages of metastasis might be more susceptible to TRAIL-mediated cell death.

Niklas Finnberg and colleagues used several different mouse models to investigate the function of TRAIL-R in tumorigenesis. They found that mice that are heterozygous for *Trailr* are more susceptible to lymphoma development mediated by the *Eμ–Myc* transgene than wild-type mice. Loss of both *Trailr* alleles did not increase the rate of lymphomagenesis over that seen for the heterozygous mice. Both heterozygous and null *Trailr Eμ–Myc* mice had more aggressive disease, associated with an increased inflammatory infiltrate. These authors also found that *Trailr*-null mice were more susceptible to lung cancer development as a result of a sublethal dose of radiation. *Trailr*-null mice developed bronchopneumonia involving a substantial immune response that correlated with the development of hyperplastic regions within the lung. Finally, in a liver carcinogenesis model, these authors showed that loss of *Trailr* was associated with larger tumours in the liver, but that there was no difference in the incidence and development of early, pre-neoplastic lesions. Thus, in these models, loss of TRAIL-R contributes to the tumorigenic process and this can be associated with an inflammatory response; however, the precise function of TRAIL-R seems to be tissue-specific.

Whether such findings will prove informative in the treatment of human tumours remains to be seen, but they indicate that TRAIL-based drugs might be useful for the treatment of early-stage lymphomas and later-stage carcinomas with metastasizing cells.

Nicola McCarthy

ORIGINAL RESEARCH PAPERS Grosse-Wilde, A. *et al.* TRAIL-R deficiency in mice enhances lymph node metastasis without affecting primary tumour development. *J. Clin. Invest.* 13 Dec 2007 (doi: 10.1172/JCI33061) | Finnberg, N., Klein-Szanto, A. J. P. & El-Deiry, W.S. TRAIL-R deficiency in mice promotes susceptability to chronic inflammation and tumorigenesis. *J. Clin. Invest.* 13 Dec 2007 (doi: 10.1172/JCI29900)