TUMOUR IMMUNOLOGY

Tumour surveillance by NKG2D

Natural killer (NK) cells, as well as various T-cell subsets, express the stimulatory receptor natural-killer group 2, member D (NKG2D), which recognizes several ligands that are frequently upregulated by tumour cells. The expression of NKG2D ligands by tumour cell lines has been shown to render the cells susceptible to NK-cell killing. Now, Raulet and colleagues show that NKG2D has an important role in tumour surveillance in spontaneous cancer models *in vivo*.

The authors generated NKG2D-deficient mice by targeting the NKG2D-encoding *Klrk1* gene. These mice developed normally, with typical phenotypic development of lymphocytes and NK cells, and the loss of NKG2D did not affect the activation of NK cells through other stimulatory receptors. These mice were then crossed with TRAMP (transgenic adenocarcinoma of the mouse prostate) mice, in which spontaneous prostate tumours develop. The development of highly malignant, early arising tumours in male *Klrk1*$^{-/-}$ TRAMP mice was three times more frequent than in *Klrk1*$^{+/+}$ TRAMP mice, indicating that NKG2D-mediated tumour surveillance is required to limit the early development of spontaneous prostate adenocarcinomas.

Further analysis showed that large, early arising tumours from *Klrk1*$^{-/-}$ TRAMP mice expressed higher levels of NKG2D ligands than those from *Klrk1*$^{+/+}$ TRAMP mice. These data indicate that NKG2D-dependent immunoediting — the generation of tumour variants with reduced immunoreactivity, which might therefore escape from the immune response — results in the loss of NKG2D ligands on the early arising aggressive tumours that are not eliminated in wild-type TRAMP mice.

The authors then assessed the role of NKG2D in a model of lymphoid tumorigenesis using transgenic mice in which the oncogene *Myc* is constitutively expressed in B cells. The Myc-driven B-cell lymphomas arose significantly earlier in the *Klrk1*$^{-/-}$ transgenic mice than in *Klrk1*$^{+/+}$ transgenic mice, again identifying a role for NKG2D-dependent tumour surveillance in limiting early tumour development. In this model, however, no difference in NKG2D-ligand expression was observed, indicating that evasion of NKG2D-dependent surveillance was independent of the loss of NKG2D ligands by the escaping tumours. In contrast to the other two models, no difference in the incidence of fibrosarcoma was observed between *Klrk1*$^{-/-}$ and *Klrk1*$^{+/+}$ mice in a model of carcinogen-induced sarcomas.

So, this study provides genetic evidence of a role for NKG2D in early tumour surveillance of prostate and lymphoid malignancies *in vivo*, which indicates that cancer immunotherapy could include therapeutic manipulation of NKG2D-dependent tumour surveillance. However, this therapy will need to be tailored to specific cancer subtypes, as the susceptibility of tumours to NKG2D-dependent tumour surveillance is not universal, as illustrated by the model of carcinogen-induced sarcomas.

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ORIGINAL RESEARCH PAPER Guerra, N. *et al.* NKG2D-deficient mice are defective in tumor surveillance in models of spontaneous malignancy. *Immunity* **28**, 571–580 (2008)