NKG2D expression can be induced in a $CD4^+$ T-cell subset following stimulation of the T-cell-receptor complex (which results in T-cell activation). Co-stimulation of $NKG2D^+CD4^+$ T cells in the presence of MICA resulted in an increased number of $NKG2D^+CD4^+$ T cells, but proliferation of the $NKG2D^-CD4^+$ T cells was inhibited. The authors found that $NKG2D^+CD4^+$ T cells express soluble FAS ligand (FASL). This induces activation-induced cell-cycle arrest of $NKG2D^-CD4^+$ T cells, but $NKG2D^+CD4^+$ T cells remain resistant to the soluble FASL that they produce because they also downregulate expression of the FAS receptor. Moreover, supernatants isolated from $NKG2D^+CD4^+$ T cells induced apoptosis in FAS-sensitive tumour cell lines. Activated $NKG2D^+CD8^+$ T cells were also shown to express active FASL when cultured with Mic ligands, and the growth of $NKG2D^-CD8^+$ T cells was inhibited.

However, unlike $CD8^+$ T cells, prolonged exposure to Mic ligands does not seem to lead to NKG2D downregulation by $CD4^+$ T cells. Therefore, the authors conclude that in tumours that express Mic ligands, the activation of NKG2D-expressing T cells will result in proliferation and the secretion of FASL, which could lead to the elimination of FAS-sensitive tumour cells. However, after prolonged exposure to Mic ligands, $CD8^+$ T cells will downregulate the NKG2D receptor and become susceptible to the growth-suppressive effects of FASL, which is continually produced by the expanding population of $NKG2D^+CD4^+$ T cells.

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**ORIGINAL RESEARCH PAPER** Groh, V., Smythe, K., Dai, Z. & Spies, T. Fas ligand-mediated paracrine T cell regulation by the receptor NKG2D in tumor immunity. *Nature Immunol.* 28 May 2006 (doi:10.1038/ni1350)

TUMORIGENESIS

# New MYC target

Frye and Watt have identified a new RNA methyltransferase that is a direct target of MYC and contributes to tumorigenesis. MISU (MYC-induced SUN-domain-containing protein) is overexpressed in many human tumours, and its knockdown decreases proliferation and tumour growth in a xenograft model.

The authors used microarrays to screen RNA isolated from skin cells of mice that express an inducible form of MYC. One mRNA that was strongly induced by MYC encoded an unknown protein, which homology indicated might be an RNA methyltransferase. This activity was confirmed biochemically, and expression studies showed that it is expressed in epidermal cells and other cell types. In G1 phase it is found at low levels, predominantly in the nucleoli, where it interacts with transcripts that have been produced by RNA polymerase III. By contrast, during S phase it is more highly expressed and is more evenly distributed in other parts of the nucleus. Chromatin immunoprecipitation confirmed that *MISU* is a direct target of MYC.

RNA interference (RNAi) constructs against *MISU* were expressed in proliferating human keratinocytes. They caused a decrease in proliferation and inhibited MYC-induced differentiation. These effects, and the direct regulation by MYC, led the authors to look for MISU overexpression in tumours. MISU was highly expressed in murine benign epidermal papillomas and malignant squamous-cell carcinomas (SCCs). In humans, 7/7 breast carcinomas, 3/4 colon carcinomas and 2/5 oral SCCs had increased MISU expression, although no such increase was found in rectal cancer. In human SCC cells that were xenografted into mice, RNAi knockdown of *MISU* reduced tumour size.

Misu might be an important link in understanding MYC-induced tumorigenesis. It also represents a potential target for therapy, as it is only required at low levels in normal cells, and knocking down the levels in tumours to equivalent low levels is sufficient to reduce tumour growth.

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**ORIGINAL RESEARCH PAPER** Frye, M. & Watt, F. M. The RNA methyltransferase Misu (NSun2) mediates Myc-induced proliferation and is upregulated in tumors. *Curr. Biol.* **16**, 971–981 (2006)