IMMUNOTHERAPY

It takes two to tango

Much of the recent work on the development of active, specific immunotherapy of cancer has focused on the induction of CD8^{+} cytotoxic T-lymphocyte (CTL) responses, and several studies have shown that it is possible to stimulate tumour-specific CTLs using dendritic cells (DCs) that are loaded with tumour antigens. But CD4^{+} T-helper type 1 (T$_H$1) cells are also important components of effective immune responses. In this study, Schuler–Thurner and colleagues provide the first evidence that DCs that are loaded with tumour-specific peptides can rapidly induce T$_H$1 responses in cancer patients that are readily detectable ex vivo.

The DCs that were used for vaccination in this study were derived from blood monocytes that were matured ex vivo using a defined cocktail (consisting of interleukin (IL)-1β, IL-6, tumour-necrosis factor and prostaglandin E$_2$) and cryopreserved before use. Aliquots of cells were thawed on the day of vaccination and loaded with various MHC class-I- and class-II-restricted peptides. Patients with incurable melanoma were treated with five biweekly vaccinations of DCs, followed by assessment one month after the final vaccination.

The results showed that the vaccination protocol induced a rapid T$_H$1 response in patients, both to a control immunizing antigen and also to defined MHC class-II-restricted tumour antigens. Immune responses were assessed on the basis of interferon-γ production using ELISPOT assays and antigen-specific proliferative responses.

So, the results from this Phase I trial provide convincing evidence that cryopreserved DCs can induce T$_H$1 responses against tumour antigens without significant toxicity, and it also encourages further development of DC-based vaccination technology.

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ONCOGENES

Fusion power

Although many leukaemias have been associated with chromosomal translocations, the means by which a resulting fusion protein can transform a cell is not well understood. For instance, the AML1–ETO fusion protein, which is associated with acute myeloid leukaemia (AML), immortalizes haematopoietic progenitor cells by an unknown mechanism. In the July issue of *Nature Medicine*, Bryan Linggi *et al.* report that AML1–ETO can repress transcription of the ARF tumour suppressor.

The t(8;21) translocation, which is associated with 12–15% of all AML cases, fuses the DNA-binding domain of AML1 and the eight-twenty-one (ETO) corepressor. This fusion protein binds to the same DNA sequence as normal AML1, but functions as a transcriptional repressor instead of an activator. *AML1–ETO* expression extends the lifespan of primary myeloid progenitor cells in culture, so Linggi *et al.* investigated whether it affects components of the p53 checkpoint pathway.

The authors started by looking for AML1 binding sites in various gene promoters. Although the *TP53* gene (which encodes p53) itself does not have an AML1-binding site, the *CDKN2A* (which encodes ARF; also known as p14 in humans and p19 in mice) promoter contains eight AML1-binding sites. ARF antagonizes MDM2 to stabilize p53, and loss of ARF has been shown to impair p53-mediated growth arrest and apoptosis.

The authors found that expressing *AML1* in cultured cells activates the transcription of the ARF transcript, and also induces senescence in fibroblasts. Expression of *AML1–ETO*, on the other hand, blocked AML1-mediated induction of the ARF-transcript promoter and repressed endogenous ARF-transcript expression, leading to immortalization. INK4a (also known as p16) has the same genetic locus as the ARF transcript, but is transcribed from a distinct promoter that lacks AML1-binding sites. Linggi *et al.* did not observe a significant difference in INK4A levels in cells expressing *AML1–ETO*, indicating that repression by this fusion protein is specific for ARF.

But is expression of the ARF transcript reduced in human leukaemia cells? Bone-marrow and blood samples from two cohorts of patients with t(8;21)-associated AML were independently tested for the expression of the ARF transcript by real-time polymerase chain reaction. These cells were found to express significantly less ARF-transcript mRNA than other types of leukaemia cells. The repression of ARF-transcript expression might therefore explain why *TP53* is not mutated in these tumours. The authors suggest that ARF might also be repressed by other cancer-associated translocations that affect AML function.

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