VACCINES

Extra boost

Patients with acute promyelocytic leukaemia (APL) are typically treated with all-*trans* retinoic acid (ATRA), but this drug provides only short-term remission, so additional strategies are needed. In the November issue of *Nature Medicine*, Rose Ann Padua and colleagues describe a vaccine that prolongs survival when administered in combination with ATRA in a mouse model of this cancer.

APL is associated with a chromosome translocation that causes production of the PML–RARα fusion protein, which disrupts differentiation of the myeloid-cell lineage. A transgenic mouse model of this disease has been developed and can be used to test new treatment strategies. Because PML–RARα is not normally expressed by cells, it represents a good target for immunotherapy.

Padua *et al.* vaccinated mice with DNA that encoded PML–RARα fused to the *FrC* gene, which encodes the highly immunogenic tetanus toxin fragment C. These mice mounted a strong immune response against PML–RARα, as shown by production of antibodies and a T-cell response against the oncoprotein, as well as increased interferon-γ production. The addition of the *FrC* gene to the vector markedly enhanced the immune response against PML–RARα. Furthermore, 56% of leukaemic mice that received the *PML–RARA–FrC* vaccine had significantly extended survival, compared with mice injected with vector alone.

But how does this vaccine compare with ATRA treatment? Vaccine-treated mice lived almost as long as ATRA-treated mice. When the two therapeutics were combined, however, mice could live over 40% longer than with either treatment alone. The authors suggest that, by boosting the immune response against tumour antigens, DNA vaccination can provide added value in the control of residual disease after ATRA therapy in humans.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Padua, R. A. *et al.* PML–RARA-targeted DNA vaccine induced protective immunity in a mouse model of leukemia. *Nature Med.* **9**, 1413–1417 (2003)

NOVEL THERAPEUTICS

Active state

Inhibiting a protein that regulates many signalling pathways in cancer cells is an attractive approach for cancer therapy. HSP90 is a molecular chaperone that regulates the function and stability of many important signalling proteins and has been implicated in the survival of tumour cells. The problem is that HSP90 is also present in normal cells, and there was concern that when the HSP90 inhibitor 17-AAG entered Phase I clinical trials, unacceptably toxic effects would be seen. However, 17-AAG seems to be well tolerated, and now Adeela Kamal *et al.* provide some explanations as to why — the drug only binds to HSP90 when in an activated state as part of a multichaperone complex.

Kamal and colleagues first showed that 17-AAG does have a higher affinity for HSP90 in tumour cells — in this case, BT474 breast carcinoma cells (IC50 6 nM) — than in normal cells (IC50 600 nM). 17-AAG specifically inhibits the ATP-binding site of HSP90, and the binding affinity of ATP was tenfold higher in the tumour cell lines. 17-AAG also had higher affinity for HSP90 in ERBB2-overexpressing cancer cell lines.

To understand how HSP90 differs between normal and tumour cells, the authors looked at the levels of two essential components of multichaperone HSP90 complexes — P23 and HOP — in the cell lines. They used immunoprecipitation assays to show that more HSP90 was present in complexes with P23 and HOP in tumour cells compared with normal cells. Tumour HSP90 also had markedly higher ATPase activity than HSP90 from normal cells.

So, why is it that 17-AAG has a higher affinity for HSP90 in tumour cells — is it because of the co-chaperones? *In vitro* reconstitution of purified HSP90 with HSP70, HSP40, P23 and HOP increased the affinity of 17-AAG from 600 nM for HSP90 alone to 12 nM for the complex. The *in vitro* observations were also borne out *in vivo* — in breast cancer and colon cancer tissue from patients.

The authors suggest that dependence of cancer cells on activated HSP90 could make the multichaperone complex a unique cancer target with great potential for exploitation in cancer therapy.

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References and links

ORIGINAL RESEARCH PAPER Kamal, A. *et al.* A high-affinity conformation of Hsp90 confers tumour selectivity on Hsp90 inhibitors. *Nature* **425**, 407–410 (2003)

WEB SITE

Francis Burrows' lab: http://www.conformacorp.com