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TUMOUR IMMUNOLOGY

CD4$^+$ T cells sponsor oncogene addicts

Naturally occurring tumours have multiple and complex genetic abnormalities, but their growth and survival can often be inhibited by the inactivation of a single oncogene. This phenomenon — known as 'oncogene addiction' — can explain the effects of some of our most successful cancer therapeutics, such as the tyrosine kinase inhibitor imatinib mesylate (Gleevec; Novartis). Oncogene inactivation was thought to have cell-autonomous effects on tumour cell apoptosis, proliferation, differentiation and senescence, but new research published in *Cancer Cell* shows that an intact immune system is necessary for 'addicted' tumour cells to respond to oncogene withdrawal.

The authors used a transgenic mouse model of *Myc*-induced haematopoietic tumorigenesis, in which *Myc* can be inactivated by administering doxycycline, to investigate the role of the immune system in oncogene addiction. Following transplantation of tumour cells from these mice into various immunocompromised mouse strains and subsequent inactivation of *Myc*, the kinetics of tumour regression were found to be significantly delayed compared with wild-type hosts. The immunodeficient hosts also showed a significant increase in minimal residual disease and in tumour recurrence. Deficiency of CD4$^+$ T cells, but not CD8$^+$ T cells, in the transplantation hosts was sufficient to impede tumour regression after *Myc* inactivation.

There were no differences between wild-type and immunodeficient hosts in terms of the increased tumour cell apoptosis or decreased proliferation that occur after *Myc* inactivation, showing that these effects do not depend on the immune system. However, whereas tumour cells that were transplanted into wild-type hosts had increased expression of senescence-associated markers after *Myc* inactivation, this did not occur in immunodeficient *Cd4*$^{-/-}$ mice. Similarly, in *Cd4*$^{-/-}$ mice, *Myc* inactivation failed to inhibit angiogenesis, and the higher mean vascular density in *Cd4*$^{-/-}$ mice compared with wild-type mice after *Myc* inactivation was associated with decreased production of the anti-angiogenic protein thrombospondin 1 (TSP1; encoded by *Thbs1*). So, the absence of CD4$^+$ T cells impairs the induction of cellular senescence and the inhibition of angiogenesis following oncogene inactivation.

The role of CD4$^+$ T cells in the effects of oncogene inactivation was confirmed by showing that the reconstitution of immunodeficient hosts with CD4$^+$ T cells, but not CD8$^+$ T cells, completely eliminated minimal residual disease and prolonged tumour-free survival after *Myc* inactivation. Also, CD4$^+$ T cells rapidly localized to the tumour site after *Myc* inactivation and were associated with the increased production of 'antitumour' cytokines such as TSP1 and the decreased production of 'pro-tumour' cytokines such as vascular endothelial growth factor. Reconstitution of immunodeficient mice with *Thbs1*$^{-/-}$*Thbs2*$^{-/-}$ splenocytes failed to prevent tumour relapse after *Myc* inactivation, showing the importance of thrombospondins for tumour regression.

These data indicate that oncogene addiction is not entirely cell autonomous and that changes in the cytokine milieu elicited by CD4$^+$ T cells are required for cellular senescence and the shutdown of angiogenesis, which might be involved in constraining minimal residual disease. This highlights the importance of testing targeted oncogene therapies in immunocompetent models and the potential for combining such therapies with immunotherapeutic agents that boost the CD4$^+$ T cell response.

Kirsty Minton

ORIGINAL RESEARCH PAPER Rakhra, K. *et al.* CD4$^+$ T cells contribute to the remodeling of the microenvironment required for sustained tumor regression upon oncogene inactivation. *Cancer Cell* **18**, 485–498 (2010)