TUMOUR IMMUNOTHERAPY

Shifting the balance

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Among the most promising strategies in cancer immunotherapy is adoptive cell transfer (ACT), which consists of the infusion of autologous, *ex vivo* activated, tumour-reactive T cells. ACT has proven successful in melanoma treatment when combined with a non-myeloablative regimen that reduces the host lymphocyte number and enables the tumour-specific adopted $CD8^+$ T cells to expand. Claudia Wrzesinski, Nicholas Restifo and colleagues have now shown that increasing the intensity of lymphodepletion to a level that requires haematopoietic stem cell (HSC) transplantation results in a significantly increased anti-tumour response following ACT.

The authors used the pmel-1 TCR-transgenic mouse model, in which $CD8^+$ T cells recognize the gp100 melanoma antigen, to assess whether tumour treatment by ACT could be improved following myeloablative total body irradiation (TBI) and HSC transplantion. They found a striking improvement in the anti-tumour response (compared with mice that received non-myeloablative TBI), which corresponded to the expansion of the pmel-1 $CD8^+$ T-cell compartment. However, the increase in tumour-reactive cells was dependent on the HSC transplantation, rather than on the increased intensity of lymphodepletion.

So, do transplanted HSCs achieve the same effect in non-myeloablative conditions? Surprisingly, HSCs increased the proliferation of the adopted cells to the same levels obtained after a myeloablative regimen, but this did not result in increased anti-tumour activity, suggesting that myeloablation was crucial for an effective anti-tumour response. They found that HSCs also promoted the expansion of other host cells that survived TBI, such as regulatory T cells, which have previously been shown to reduce the effectiveness of ACT.

To determine whether the surviving host cells could inhibit ACT-mediated tumour destruction, the authors evaluated the anti-tumour response in myeloablated mice that lacked $CD8^+$ and $CD4^+$ T cells, and found an improved response compared with wild-type mice. These data indicated that even the small number of endogenous $CD8^+$ and $CD4^+$ T cells (which include regulatory T cells) that survived the myeloablative regimen could inhibit ACT anti-tumour efficacy. The authors showed that it was the ratio between the number of anti-tumour T cells and host inhibitory cells that consistently determined the treatment outcome, and in myeloablated mice this ratio shifted in favour of the tumour-reactive cells compared with non-myeloablated mice. Finally, HSC transplantation also increased ACT efficacy in non-myeloablated hosts following the reduction of inhibitory cells by genetic lymphodepletion.

These findings provide new important insights for the design of more effective immunotherapeutic anti-tumour strategies.

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ORIGINAL RESEARCH PAPER Wrzesinski, C. *et al.* Hematopoietic stem cells promote the expansion and function of adoptively transferred antitumour $CD8^+$ T cells. *J. Clin. Invest.* **117**, 492–501 (2007)