TRANSPLANTATION

Making space for HSCs

The requirement for generating space in the haematopoietic stem cell (HSC) niche to ensure efficient bone-marrow transplantation remains controversial, with some studies suggesting that donor HSCs can competitively replace endogenous HSCs, and other evidence suggesting that effective transplantation of HSCs requires pre-conditioning regimens to clear niche space and to prevent immunological rejection of the graft. Such pre-conditioning regimens can have serious side effects for recipients. Now, a study from Czechowicz and colleagues shows that HSC engraftment levels of up to 90% can be achieved following an antibody-based transient clearance of endogenous HSCs from HSC niches.

First, the authors looked at the ability of donor HSCs to competitively replace endogenous HSCs in a linear, dose-dependent manner in the absence of pre-conditioning. Transplantation of labelled HSCs into immunodeficient recipients resulted in mean engraftment levels of only 3%, even when 18,000 HSCs (representing ~70% of the total numbers of HSCs in an adult mouse) were transplanted, and a linear, dose-dependent increase in engraftment was only observed between doses of 10 and 250 donor HSCs.

Next, the authors studied the effects of ACK2, an antibody that targets KIT, the receptor for stem-cell factor (SCF). When they looked at the kinetics of antibody clearance *in vivo*, they could not detect ACK2 in the serum of mice 7 days after administration, at which point there was a ~99% decrease in endogenous HSC numbers compared with control mice. By day 23, HSC numbers had returned to wild-type levels. This provided a window of opportunity of around 2 weeks from day 7 onwards in which to repopulate recipients with donor HSCs.

So, how does ACK2 act in depleting HSCs? ACK2 did not deplete HSCs from the bone marrow by mobilizing them to the spleen, as transplantation of splenocytes from ACK2-conditioned animals resulted in donor HSC engraftment that was reduced by 95% compared with controls. When cultured with purified HSCs *in vitro*, ACK2 completely inhibited SCF-dependent proliferation, and it is this complete inhibition of KIT signalling that results in temporary HSC depletion.

To determine whether ACK2 treatment resulted in a large increase in the space in the HSC niche that is immediately repopulated with donor HSCs, or whether only a small fraction of donor HSCs engrafted that could then expand, the authors transplanted ACK2-conditioned immunodeficient mice with varying doses of HSCs. The result was a linear increase in engraftment with increasing doses of donor

HSCs, confirming that ACK2 does indeed produce a large increase in niche space and that donor HSCs can immediately fill this space. Furthermore, using numbers of HSCs that, if extrapolated, would be achievable in human transplant situations, engraftment levels of donor HSCs of up to 90% were obtained.

These results show that, if extrapolated to humans, depletion of HSCs using milder conditioning regimens might prove beneficial in enhancing the efficacy of bone-marrow transplantation.

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