Bone Marrow Transplantation (2010) 45, 968–969

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EDITORIAL

Reconstitution of repertoire of natural killer cell receptors after transplantation: just a question of time?

Bone Marrow Transplantation (2010) **45,** 968–969; doi:10.1038/bmt.2010.116

Natural killer (NK) cells, key members of the natural immune system which each single individual possesses, are known to have a crucial role in innate defence against viruses, as well as against tumour cells.[1,2] In a self-environment, NK lymphocytes sense and kill target cells lacking MHC class I molecules and release various cytokines upon activation.[3] The discovery of HLA class I-specific inhibitory receptors (namely, killer Ig-like receptors, KIRs), as well as of various activating receptors and their ligands,[1–5] provided the basis for understanding the molecular mechanism of NK cell activation and function, thus permitting exploitation of the GVL effect mediated by these cells of innate immunity in the successful therapy of patients with high-risk leukaemias given allogeneic haematopoietic SCT (HSCT).[6–9] The most important human inhibitory KIRs are (i) KIR2DL1, which recognizes HLA-C alleles characterized by Lys at position 80 (HLA-C^{Lys80} also named C2 group); (ii) KIR2DL2/3 recognizing HLA-C alleles characterized by Asn at position 80 (HLA-C^{Asn80} C1 group); and (iii) KIR3DL1, which recognizes HLA-B alleles sharing the Bw4 supertypic specificity (HLA-B^{Bw4} Bw4 group).[10] In an allogeneic setting, this type of inhibitory KIR repertoire can lead to alloreactivity in HLA-disparate HSCT through the mechanism of 'missing self'-recognition.[11] In detail, donor-origin NK cells can kill recipient-derived leukaemia cells when they express inhibitory KIRs, which do not recognize any of the HLA-class I alleles (that is, KIR ligands) present on recipient cells, this leading to a KIR/KIR-ligand mismatch in graft-vs-host direction. Alloreactive NK cells have been found to positively affect the outcome of HSCT from an HLA-haploidentical relative in adults with AMLs, as well as in children with ALL.[7–10] The peculiar GVL effect mediated by NK cells is completely separated by the occurrence of GVHD, this indicating that NK cells are able to kill leukaemia targets (as well as cells of haematopoietic origin as suggested by data obtained in the animal model,[7]) while sparing normal tissues. The molecular basis of the resistance of recipient normal tissues, other than haematopoietic cells, to the NK cell-mediated attack is the lack of ligands for the activating NK receptors.[12] Indeed, there is large experimental evidence that killing of allogeneic cells also depends on the surface density of activating receptors on NK cells and on the expression of their ligands, these latter being expressed on target cells of different histotypes only upon cell stress infection or tumour transformation.[13]

In view of the key role of alloreactive NK cells in eradicating leukaemias, at least in haplo-HSCT, it is important to ask when such NK cells are originated, when they become fully immune competent and how long they persist in the recipient. Early studies suggested that in haplo-HSCT, the transplanted stem cells gave rise to an NK cell wave that contained alloreactive NK cells.[14] More recently, in a study involving 21 children transplanted from an NK-alloreactive parent, it was documented that NK cells of donor origin able to kill leukaemia blasts emerge since some weeks after the allograft, persist for years and significantly contribute to the eradication of the malignant clone.[10] In some patients, the proportion of alloreactive NK cells was even higher in the recipient than in the donor, suggesting that these cells were selected/expanded preferentially *in vivo*.[10]

The study by Giebel *et al.*[15] published in this issue of the Journal provides another useful piece of information for better understanding of how NK cells reconstitute the repertoire of their receptors. Indeed, the authors demonstrate that, in patients given an unmanipulated allograft from either an HLA-identical relative or from an highly histocompatible unrelated volunteer, the expression of inhibitory KIRs was generally lower as compared with the donors and the dynamics of inhibitory KIR recovery varied among particular receptors, as acquisition of KIRs by NK cells is sequential and starts with KIR3DL1, followed by KIR2DL2-3 and KIR2DL1, the NKG2A being overexpressed within 6 months after transplantation. The analysis of factors influencing KIR expression revealed that the frequency of $KIR2DL1^+$ NK cells correlated with increased number of $CD34^+$ cells in the graft and that the NK cell phenotypic maturation is negatively affected by the use of steroids after transplantation. In view of these results, Giebel *et al.*[15] speculate that differences in dynamics of inhibitory KIR reconstitution may be essential for prediction of the beneficial NK cell alloreactivity.[15]

For the time being, there is neither clinical nor experimental evidence that patients in whom the alloreactivity depend on C2 group disparity have a lower chance of benefiting from the GVL effect mediated by alloreactive NK cells than patients transplanted with donors displaying other alloreactivities. However, the study by Giebel *et al.*[15] stimulates further investigations in the setting of highly T-cell-depleted HSCT from a donor with KIR/KIR-ligand mismatch in graft-vs-host direction. It could be, indeed, possible that removal of T cells from the graft favours the kinetics of reconstitution of KIR repertoire different from that observed in patients given an unmanipulated allograft. The correlation between the

expression of KIR2DL1 and the CD34$^+$ cell dose infused found in the study by Giebel *et al*.[15] provides further biological support to the recent study showing that children with ALL given a T-cell-depleted haplo-HSCT have a better outcome when they received number of CD34+ cells greater than 12×10^6 progenitors/kg.[16]

There is still much more to be learned about NK cells and there is no doubt that, in view of the role played by these cells in HSCT recipients, all studies contributing to elucidating the most sophisticated mechanisms of their function are more than welcome.

Conflict of interest

The authors declare no conflict of interest.

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