

Settling For Second Best – Not So Bad, After All

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Hematopoietic cell transplantation outcomes are strongly influenced by the extent of genetic matching between donors and recipients; a closer match enhances the chances of engraftment, and decreases the risk of graft-versus-host disease (GVHD). Histocompatibility is determined by human leucocyte antigen (HLA) genes, which define tissue type and are known for their extensive DNA sequence diversity. Each alternative arrangement encodes different forms, or allelic variants, of the HLA genes, which can affect the production of antibodies. The resulting genetically determined differences in antibodies are called allotypes, which enable "high resolution" donor matching for HLA alleles. The risks of adverse effects after transplantation can thus be reduced using DNA-based laboratory testing of blood serum from patients and donors. HLA-C allotype mismatching is a particularly important risk factor for the development of GVHD, but there are indications that some HLA-C mismatches are better tolerated than others.

In 2013, a large collaborative HIV study demonstrated that the surface expression of HLA-C can be quantified through measurement of mean fluorescence intensity (MFI), and that the intensity level was specific for each allotype (Apps et al., 2013). The technique enabled another unique international collaborative study, in which samples from 1,975 patients were retrospectively analyzed and correlated with treatment outcome. All patients had received a hematopoietic cell transplant from unrelated donors with whom they had one single HLA-C mismatch. The results of the extensive study were recently published in *Blood*, with Fred Hutch's Dr. Effie Petersdorf as first author. In addition to Dr. Petersdorf, Drs. Ted Gooley and Mari Malkki from the Clinical Research Division also contributed.

"In the current study, we hypothesized that some HLA mismatches are better tolerated than others, and that the level of cell surface expression of the patient's mismatched HLA allotype contributes to its immunogenicity," Dr. Petersdorf said.

Indeed, their findings indicated that the risks of post-transplant complications were influenced by the expression level of the non-shared HLA-C. Lower risk of GVHD was demonstrated for mismatches with lower expression levels, whereas highly expressed mismatches were significantly associated with adverse effects such as acute GVHD, non-relapse mortality and mortality. "We demonstrate that when the patient's mismatched HLA-C allotype is expressed at higher levels, risks of GVHD and

transplant-related mortality are higher than when the allotype is expressed at lower levels. These data indicate a role for HLA expression levels in the immunogenicity of HLA mismatching in transplantation," Dr. Petersdorf said.

A possible explanation for the observed correlation is that less expressed allotypes are more likely to escape detection by the recipient, thereby avoiding an adverse immune reaction. For patients who lack an HLA-matched donor these results could provide a crucial approach for increasing the use of selected non-matched donors, instead of flat-out disqualifying all mismatches. "The HLA-C allotypes encoded by patients may be assessed prior to transplantation as to whether there are 0, 1 or 2 high-expression alleles. When HLA-C matched donors are not available, avoidance of mismatching for the high-expression HLA-C allotype in the patient may help to lower risks of GVHD after transplantation," Dr. Petersdorf explained.

Up next for the team of researchers is further exploration of the mechanisms involved in regulating HLA-C expression, as they are not yet entirely known. The more information they can gather, the better our understanding of transplant-related immune responses in humans will be.

[Petersdorf EW, Gooley T, Malkki M, Bacigalupo AP, Cesbron A, Du Toit E, Ehninger G, Egeland T, Fischer GF, Gervais T, Haagenson MD, Horowitz MM, Hsu K, Jindra P, Madrigal A, Oudshoorn M, Ringden O, Schroeder ML, Spellman SR, Tiercy J-M, Velardi A, Witt CS, O'Huigin C, Apps R, Carrington M.](#) 2014. HLA-C expression levels define permissible mismatches in hematopoietic cell transplantation. *Blood*. [Epub ahead of print]

See also: [Apps R, Qi Y, Carlson JM, Chen H, Gao X, Thomas R, Yuki Y, Del Prete GQ, Goulder P, Brumme ZL, Brumme CJ, John M, Mallal S, Nelson G, Bosch R, Heckerman D, Stein JL, Soderberg KA, Moody MA, Denny TN, Zeng X, Fang J, Moffett A, Lifson JD, Goedert JJ, Buchbinder S, Kirk GD, Fellay J, McLaren P, Deeks SG, Pereyra F, Walker B, Michael NL, Weintrob A, Wolinsky S, Liao W, Carrington M.](#) 2013. Influence of HLA-C expression level on HIV control. *Science*. 340(6128):87-91.



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