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Expression of HLA-G and its receptors in relation to transplant acceptance

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Following its initial description in 1990 [1], the non-classical class I HLA molecule HLA-G has been well-characterised on extravillous cytotrophoblast as a molecule intimately involved in protection of the foetus from attack by the maternal immune system [2]. In addition to its expression on trophoblast, HLA-G is also found at lower levels in thymus, cornea, nail matrix, haematopoietic progenitors and pancreas [3], where its function is less clear. Unlike classical class I HLA molecules, HLA-G can be expressed as a variety of cell-bound and soluble isoforms [4], including several soluble forms (sHLA-G).

As well as this diversity of protein isoforms, there is additional variation at the genetic level, with several alloantigens being described. Furthermore, 3' untranslated region polymorphisms lead to diversity in levels of HLA-G expression [5]. Particular UTR polymorphisms have been associated with high, intermediate or low levels of HLA-G expression [6,7]. This has been confirmed in a study of plasma levels of sHLA-G in healthy individuals of different HLA-G 3'UTR haplotypes [8], whereas other authors have not found there to be complete correlation between observed sHLA-G levels and predicted levels of expression according to UTR genotype [9,10].

Any functions of HLA-G are dependent upon expression of its cellular ligands. The three well-described ligands are LILRB1/ILT2 and LILRB2/ILT4, inhibitory receptors expressed mainly on monocytic cells [11]. The third ligand for HLA-G, KIR2DL4, is expressed by most natural killer (NK) cells and has features of both activating and inhibitory receptors [12].

As well as having a role in protection of the foetus from maternal immune responses, HLA-G has been reported to be expressed in some tumours, potentially leading to inhibition of anti-tumour responses [13]. It may also have a role in protection of allografts against rejection and there is a correlation between HLA-G levels and organ graft acceptance [14]. A number of viruses have been reported to induce expression of HLA-G as a mechanism of immune evasion [15]. In our earlier work, we reported that human cytomegalovirus (HCMV) was able to induce expression of HLA-G on some leukocyte subsets in healthy subjects [16]. B cells, CD56+ T cells and monocytes were the main cell types affected, with NK cells and both CD4+ and CD8+ T cells less so [16]. Cell surface KIR2DL4 expression on CD56+ T cells was unaffected by CMV but was increased in the presence of IL-2 [16].

HLA-G expression has previously been reported on small subsets of human leukocytes including monocyte/macrophages [3], particularly of the M2 lineage [17], regulatory T cells [18-20] and CD8+ cytotoxic T cells [21]. In the context of clinical transplantation, increased expression of HLA-G was noted by CD4+ and CD8+ alloreactive T cells in mixed lymphocyte reactions *in vitro* [22]. In our current report into HLA-G expression by peripheral leucocytes from renal transplant patients, we found that proportions of CD4+ T cells expressing HLA-G were significantly increased in the first few months post transplantation whereas other leucocyte subsets did not show significant changes [23]. This also applied to both CD45RA+, CD45RO+ and CD69+ subsets, indicating that both naïve and activated cells were involved [23].

Most related reports in kidney transplant patients have supported the concept that enhanced cellular and/or soluble expression of HLA-G is beneficial to transplant acceptance [14,24-33]. In one of these studies [32], donor HLA-G types were involved, indicating that either donor-derived dendritic cells or structural cells of the kidney or their sHLA-G production were involved. However, one study showed a correlation between HLA-G alleles associated with lower expression and graft acceptance [34] and another showed that HLA-G on CD4+ T cells was a predictor of rejection [35]. Enhanced HLA-G expression on structural cells of the kidney as well as T lymphocytes or dendritic cells [36] would increase inhibition of leukocytes expressing HLA-G ligands and hence potentially inhibit graft rejection. Dendritic cells have been reported to secrete HLA-G following treatment with the immunosuppressive molecule CTLA4-Ig [37].

Our recent report also showed that short-term culture of human leukocytes from healthy subjects *in vitro* in the presence of therapeutic concentrations of immunosuppressive drugs routinely used to prevent kidney rejection led to significantly increased proportions of HLA-G+ CD56+ T cells and B cells, but not other T cell subsets [23]. There are only limited studies of the effects of immunosuppressants on HLA-G expression. In one report, rapamycin was found to downregulate the HLA-G receptor ILT-2 on dendritic cells but nevertheless induced T cell tolerance [38]. A further report showed that rapamycin enhanced dendritic cell ILT-4 expression, potentially facilitating allograft acceptance [39]. In heart transplant patients, everolimus was associated with sHLA-G expression [40].

Together, these studies suggest that one mechanism of action of current immunosuppressive therapies may be to enhance expression of donor or recipient HLA-G or its receptors. Future studies could usefully address to what extent alloreactive T cells may be induced to express HLA-G or its receptors as this would potentially allow their inhibition and hence prevention of allograft rejection.

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