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Importance of Non-HLA Gene Polymorphisms in Hematopoietic Stem Cell Transplantation

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1. Introduction

In the last 10 years, non-HLA genotypes have been investigated for their potential roles in the occurrence and severity of graft-versus-host disease (GvHD) as well as for their contribution to overall transplant-related mortality, infectious episodes, and overall survival.

These non-HLA-encoded genes include polymorphisms within the regulatory sequences of the cytokine genes, or genes associating with innate immunity: *KIR* (killer immunoglobulin-like receptor) genes, *MIC* (MHC class I chain-related) genes, and others.

The first studied non-HLA genes were polymorphisms in regulatory cytokine genes because of cytokine role in GvHD immunopathogenesis. Single nucleotide polymorphisms in several regions of cytokine genes were correlated with the transplant overcome in several studies (Kim et al., 2005; Laguila Visentainer et al., 2005; Lin et al., 2003; Mlynarczewska et al., 2004; Viel et al., 2007; reviewed in Dickinson, 2008).

2. Role of cytokines in graft-versus-host disease after allogeneic stem cell transplantation

The pathophysiology of acute GvHD can be considered a cytokine storm (Ferrara, 2000), initializing with the transplant conditioning regimen that damages and activates host tissues. Activated host cells secrete inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1. This initial cytokine release is further amplified in the second phase by presentation of host antigens to donor T cells and the subsequent proliferation and differentiation of these activated T cells. These cells secrete a variety of cytokines, such as IL-2, TNF-α, interferon (IFN)-γ, IL-4, IL-6, IL-10, and transforming growth factor-beta (TGF)-β1. Several reports have demonstrated the increase of these cytokines in the serum from patients with acute GvHD (Kayaba et al., 2000; Liem et al., 1998; Sakata et al., 2001; Visentainer et al., 2003).

Although chronic GvHD remains a frequent complication of hematopoietic stem cell transplantation (HSCT), the pathogenesis is still unclear. However, it is known that cytokines also play an important role in its development (Iwasaki, 2004; Letterio & Roberts, 1998; Liem et al., 1999; Margolis & Vogelsang, 2000; Zhang et al., 2006). Chronic GvHD is a multisystem alloimmune and autoimmune disorder characterized by immune

dysregulation, immunodeficiency, impaired organ function and decreased survival (Baird & Pavletic, 2006). It starts with the expansion of donor T cells in response to allo or auto-antigens that escape assessment thymus and the mechanisms of deletion. T cells induce damage in target organs by attacking cytolytic, inflammatory cytokines and fibrosis by activating B cells, with production of autoantibodies (Pérez-Simón et al., 2006).

Thus multiple cytokines are important in GvHD pathogenesis and regulation (Ferrara & Krenger, 1998; Jung et al., 2006; Kappel et al., 2009; Reddy et al., 2003; Tawara et al., 2008; Visentainer et al., 2005; Yi et al., 2008). Furthermore, the timing and duration of cytokine expression may be a critical factor determining the induction of the graft-versus-host (GvH) reaction, and cytokine dysregulation could potentially contribute to the severity of GvHD.

Recently, Choi et al. (2010) and Paczesny et al. (2010) reviewed the biology of acute GvHD, and concluded that the underlying mechanisms of GvHD have emerged as a complex network of immune interactions where the key players are the naive T cells, the host and donor APCs, CTLs and regulatory T cells, along with new players such as Plasmacytoid DCs (pDCs), B cells and Th17 cells.

2.1 Cytokine gene polymorphisms

The production of some cytokines is under genetic control. Polymorphisms in the regulatory regions of several cytokine genes may cause inter-individual differences in cytokine production (Wilson et al., 1997; Turner et al., 1997; Awad et al., 1998; Fishman et al., 1998; Pravica et al., 1999). As these polymorphisms segregate independently, each person is a mosaic of high-, intermediate-, and low-producing phenotypes. These cytokine polymorphisms are known to have functional relevance in post-transplant outcome, rejection and GvHD, following solid organ (Benza et al., 2009; Fernandes et al., 2002; Hahn et al., 2001; Karimi et al., 2011; Reviron et al., 2001) and hematopoietic stem cell transplantation (Ambruzova et al., 2009; Karimi et al., 2010; Laguila Visentainer et al., 2005; Leffell et al., 2001; Takahashi et al., 2000; Tambur et al., 2001), respectively.

2.2 Impact of cytokine gene polymorphisms on graft-vs-host disease

Many studies in recent years have focused on correlating donor and/or recipient genotype with GvHD risk. Table 1 summarizes the various polymorphisms in genes encoding both pro- and anti-inflammatory factors and their receptors that have been studied in GvHD.

3. Killer immunoglobulin-like receptors and hematopoietic stem cell transplantation

Natural killer (NK) cell effector function is regulated by a balance between activating receptors and inhibitory receptors for major histocompatibility complex (MHC) class I molecules (Joyce & Sun, 2011; Parham et al., 2006; Yokoyama et al., 2006). In the setting of allogeneic HSCT, donor NK cells may attack recipient cells that lack the appropriate HLA class I ligands for the donor KIR. Several studies have shown that certain combinations of killer immunoglobulin-like receptors and human leukocyte antigens (in both donors and recipients) can affect the chances of survival of transplant patients, particularly in relation to the graft-versus-leukemia effect, which may be associated to decreased relapse rates in certain groups (reviewed in Franceschi et al., 2011).

GvHD		
Acute	**Chronic**	
SNP/Genotype		**References**
	*IL1A-889*2*	Cullup et al. (2003)
IL6-174 G/C	*IL6-174 GG*	Lin et al. (2003)
	IL6-174 CC	Laguila Visentainer et al. (2005)
TNF-308 GG/GA		Takahashi et al. (2000)
	TNF-238 GA	Viel et al. (2007)
IL2-330 GT		Macmillan et al. (2003)
	IL10-1082,-819,-592 ATA/ATA	Kim et al. (2005)
IL10-592 A/A		Lin et al. (2003)
IL-10RB A/A	*IL-10RB A/A*	Sivula et al. (2009)
TGFB1+869,+915 TG/GG		Leffell et al. (2001)
TGFB1+869 T		Hattori et al. (2002)
TGF- beta1 codon 25 GG		Rashidi-Nezhad et al. (2010)
IFN-γ T+874A		Karimi et al. (2010)
IL-7RA		Shamim et al. (2011)

Table 1. Polymorphisms in genes encoding both pro- and anti-inflammatory factors and their receptors in GvHD

3.1 Killer immunoglobulin-like receptors

The group of *KIR* genes comprises a region of approximately 150 Kb in the leukocyte receptor complex (LRC) on chromosome 19q13.4 (Uhrberg et al., 1997). KIRs are members of a group of regulatory molecules on the surface of NK cells, in subgroups of Tγδ+ lymphocytes, effector Tαβ+ lymphocytes and memory lymphocytes (Rajagopalan & Long, 2005). The KIR family includes activating and inhibitory molecules. Inhibitory KIRs (2DL and 3DL) have a long cytoplasmic tail containing tyrosine-based inhibitory motifs (ITIMs) that trigger inhibitory events of cytotoxicity. In contrast, activating KIRs (2DS and 3DS) interact with the DAP12 molecule, which has tyrosine-based activation motifs (ITAMs) that cause a cascade that results in an increase in cytoplasmic granulation and the production of cytokines and chemokines, thereby initiating immune response (McVicar et al., 2001).

The balance between activation and inhibition of NK cells occurs through the binding of KIRs with HLA class I molecules present in all nucleated cells of an individual. Most KIRs bind to HLA-C molecules. It is worth remembering the importance of the dimorphism of amino acids, such as residue 80 of α-helix-1, in the definition of this HLA receptor. On this basis, HLA-C alleles may be defined as "Group 1" or "Group 2": C1 – HLA-Cw*01, *03, *07, *08, *12, *13, *14, and *16 and C2 – HLA-Cw*02, *04, *05, *06, *07, *15, *17, and *18, which are specific for KIR2DL2/2DL3/2DS2 and KIR2DL1/2DS1, respectively (Boyton & Altmann, 2007). Evidence suggests that HLA-Cw4 is a receptor for KIR2DS4 (Katz et al., 2001). The KIR2DL4, for example, specificity binds to the HLA-G molecule (Rajagopalan & Long, 1999), while the KIR3DL1 receptor binds to a subset of HLA molecules with the Bw4 epitope, present in approximately one third of all HLA-B molecules. The KIR3DS1 is highly homologous with 3DL1 and seems to share the Bw4 epitope as ligand, although this needs to be experimentally verified. The KIR3DL2 receptor is still being discussed, but studies suggest that HLA-A3 and HLA-A11 perform this role (O'Connor et al., 2006).

Based on the genetic content and pattern of segregation at the population level, *KIR* haplotypes are divided into two groups, A and B, varying in the type and number of genes present. The *KIR* group A haplotype is uniform in terms of gene content (*3DL3*, *2DL3*, *2DL1*, *2DP1*, *3DP1*, *2DL4*, *3DL1*, *2DS4*, and *3DL2*), of which all but 1 encode inhibitory receptors. In contrast, the *KIR* group B haplotype is more diverse in the *KIR* genes it contains, has more activating receptors, and is characterized by the *2DL2*, *2DS1*, *2DS2*, *2DS3*, and *2DS5* genes (Uhrberg et al., 1997).

3.2 Impact of killer immunoglobulin-like receptors and hematopoietic stem cell transplantation

Previous studies have examined the effect of donor and recipient *KIR* genotypes on the outcome of allogeneic HSCT (Bishara et al., 2004; Gagne et al., 2002; Sun et al., 2005). One study found a 100% risk of GvHD after unrelated donor BMT, when the donor contained *KIR* genes absent in the recipient, compared to a 60% risk of GvHD with other combinations (Gagne et al., 2002).

In 2004, one study carried out *KIR-HLA* genotyping of 220 related HLA identical donor-recipient pairs (112 for myeloid diseases and 108 lymphoid diseases) (Cook et al., 2004). For patients with myeloid diseases, survival was lower in those homozygous for Group 2 (C2) HLA-C compared to patients with Group 1 (C1). This effect was observed only when the donor had the *KIR2DS2* gene. As *KIR2DS2* is in strong linkage disequilibrium with *KIR2DL2* (receptor inhibited by C1), this would indirectly indicate lower survival in patients who do not have the receptor for *KIR2DL2*, an opposite result to the model in which this lack of inhibition could result in NK cell alloreactivity with a consequent elimination of residual leukemic cells (Witt et al., 2006). In 178 patients with AML, CML, ALL and primary myelodysplastic syndrome (MDS) who received HSCT with T cell depletion from HLA-identical related donors, some authors observed that the disease-free survival was significantly higher in patients with AML and MDS that did not have the HLA ligand for the inhibitory KIR of the donor (Hsu et al., 2005). Moreover, the relapse rate was lower in these individuals, which may be related to higher survival rates. The results differ from a study in which T cell depletion was not performed (Cook et al., 2004). In another study (Schellekens et al., 2008) involving 83 patients with different types of hematologic malignancies who received HSCT from related HLA-identical donors without T cell depletion, a high relapse rate was found when high numbers of activating KIRs were present in both the patient and donor. According to the authors, a consequence of this finding may be an increased alloreactivity of the host against graft, impairing the response of donor cells resulting in an insufficient graft-versus-leukemia effect and increased risk of leukemic relapse.

Nowadays, there is no unequivocal evidence that polymorphic genes for KIR involved in innate immunity sufficiently influence GvHD and transplant outcome to change clinical practice (Davies et al., 2002; Cooley et al., 2009; Giebel et al., 2003; Hsu et al., 2005; Ludajic et al., 2009; Miller et al., 2007; Moretta et al., 2009; Schellekens et al., 2008; Symons et al., 2010; Witt et al., 2006).

Using a large cohort of patients, Venstrom et al. (2010) demonstrated that individual donor activating KIR, recipient HLA class I ligands, and donor *KIR* gene copy number all impact KIR-driven NK effects. They also showed that not all *KIR* B haplotypes have equivalent clinical impact, and they proposed that future studies consider specific B haplotype subsets or individual *KIR* genes in their analyses.

However, there are conflicting results in many studies, which may be due to the heterogeneity in HSCT protocols employed, differences in inclusion criteria, the HSCT preparative regimen and graft content, the degree of donor HLA-incompatibility, and posttransplant immunosuppression. Beside of this, according to early studies, Symons et al. (2010) have described 4 models of NK cell alloreactivity to predict HSCT outcomes: 1) KIR ligand incompatibility; 2) receptor-ligand model; 3) missing ligand model; and 4) *KIR* gene-gene model. And, contradictory results obtained from these models have made it difficult to conclude which model is most predictive of transplant outcome.

4. *MICA* and *MICB* matching in bone marrow transplantation

Retrospective and prospective studies have shown that matching donors and recipients for non-HLA DNA sequences in the MHC (beta and delta block matching) can result in improved patient survival and less severe GvHD (Tay et al., 1995; Witt et al., 2000). One of these blocks, the beta block, spans about 300 kb and contains the immunologically relevant *HLA-B*, *HLA-C*, *MICA*, and *MICB* genes (Kitcharoen et al., 2006). The polymorphic MICA molecule likely may be a target for specific antibodies and T cells in solid organ grafts or in GvHD (Zhang & Stastny, 2006).

4.1 *MICA* and *MICB* genes

In 1994, two new polymorphic families of MHC class I related genes, termed MHC class I-related chain A (*MICA*) and B (*MICB*) were described (Bahram et al., 1994). These genes are highly polymorphic with at least 76 alleles for *MICA* and 31 alleles for *MICB* (IMGT/HLA database; http://www.ebi.ac.uk/imgt/hla/stats.html), and are located in the MHC classical class I region (Horton et al., 2004), 46.4 and 141.2 kb centromeric to *HLA-B*, respectively (Bahram et al., 1994; Bahram et al., 2000; Leelayuwat et al., 1994). They encode cell surface glycoproteins that do not associate with β_2-microglobulin. These molecules function as restriction elements for intestinal γδ T cells and they behave as cell stress molecules. MICA is expressed in endothelial cells, keratinocytes and monocytes, but not in CD4+, CD8+ or CD19+ lymphocytes (Zwirner et al., 1999).

The MICA gene products have been shown to play a role in some aspects of antigen presentation and T-cell recognition, and appear to be important in innate immunity as ligands to NKG2D receptor expressed on most γδ T cells, CD8 αβ T cells, and NK cells (Tieng et al., 2002).

4.2 *MICA* and *MICB* and relevance to stem cell transplantation outcome

Several studies have shown that the highly polymorphic MIC antigens are expressed in transplanted organs and may cause early graft rejection (Hankey et al., 2002; Mizutani et al., 2006; Narayan et al., 2011; Panigrahi et al., 2007; Sumitran-Holgersson, 2008; Terasaki et al., 2007). The polymorphisms of MICA and MICB may be involved in allogeneic BMT and GvHD (Gannage et al., 2008; Murai et al., 2003; Parmar et al. 2009; Przepiorka et al., 1995) because they are augmented by stress in epithelia (Groh et al., 1996) and are recognized by a subpopulation of intestinal γδ T cells (Zou et al. 2007). In addition to classical HLA class I and II matching, matches at *MICA* and *MICB* loci have been shown to increase patient survival (Kitcharoen et al., 2006).

Recent review has discussed the genetics and biology of the *MICA* gene and its products, and their importance in disease related to NK activity and allograft rejection or GvHD

(Choy & Phipps, 2010). According to Parmar et al. (2009), some HSCT cases with matched *HLA* but mismatched *MICA* showed an increased incidence of GvHD, and according to Boukouaci et al. (2009), MICA-129 valine and soluble MICA are risk factors for chronic GvHD, whereas the presence of anti-MICA antibodies that can neutralize soluble MICA confers protection.

A methionine to valine change at position 129 of the α2-heavy chain domain categorized the *MICA* alleles into strong (MICA-129 met) and weak (MICA-129 val) binders of NKG2D receptor (Steinle et al., 2001). Varying affinities of *MICA* alleles for NKG2D may affect thresholds of NK-cell triggering and T-cell modulation. According to Boukouaci et al. (2009), in the context of cGVHD, the weak engagement of NKG2D receptors by the weak binder MICA-129 val allele may impair NK/cytotoxic T lymphocyte cell activation/costimulation, possibly skewing the TH1 pathway toward TH2 with consequent B-cell activation and Ab production.

5. Conclusion

Analysis of non-HLA genetics may permit more accurate assessment of transplant-related complications, improve donor selection and individualized prophylaxis, and aid in the development of a prognostic risk index. Overall, this type of analysis could potentially define high- and low-risk patient groups, and to result in effective therapeutic strategies for GvHD.

6. References

Ambruzova, Z.; Mrazek, F.; Raida, L.; Jindra, P.; Vidan-Jeras, B.; Faber, E.; Pretnar, J.; Indrak, K. & Petrek, M. (2009). Association of IL6 and CCL2 gene polymorphisms with the outcome of allogeneic haematopoietic stem cell transplantation. *Bone Marrow Transplantation*, Vol.44, No.4, (August 2009), pp.227-235, ISSN 0268-3369

Awad, M.R.; El-Gamel, A.; Hasleton, P.; Turner, D.M.; Sinnott, P.J. & Hutchinson, I.V. (1998). Genotypic variation in the transforming growth factorb1 gene. *Transplantation*, Vol.66, No.8, (October 1998), pp.1014-1020, ISSN 0041-1337

Bahram, S. (2000). MIC genes: from genetics to biology. *Advances in Immunology*, Vol.76, (2000), pp.1-60, ISSN 0065-2776

Bahram, S.; Bresnahan, M.; Geraghty, D.E. & Spies, T. (1994). A second lineage of mammalian major histocompatibility complex class I genes. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.91, No.14, (Jul 1994), pp. 6259-6263, ISSN 0027-8424

Baird, K. & Pavletic, S.Z. Chronic graft versus host disease. (2006). *Current Opinion in Hematology*, Vol.13, No.6, (November 2006), pp. 426-435, ISSN 1065-6251

Benza, R.L.; Coffey, C.S.; Pekarek, D.M.; Barchue J.P.; Tallaj, J.A.; Passineau, M.J. & Grenett, H.E. (2009). Transforming growth factor-beta polymorphisms and cardiac allograft rejection. *The Journal of Heart and Lung Transplantation*, Vol.28, No.10, (October 2009), pp.1057-1062, ISSN 1053-2498

Bishara, A; De Santis, D.; Witt C.C.; Brautbar, C.; Christiansen, F.T.; Or, R.& Nagler, A., Slavin, S. (2004). The beneficial role of inhibitory KIR genes of HLA class I NK epitopes in haploidentically mismatched stem cell allografts may be masked by

residual donor-alloreactive T cells causing GVHD. *Tissue Antigens*, Vol.63, (March 2004), pp.204-211, ISSN 0001-2815

Boukouaci, W.; Busson, M.; Peffault de Latour, R.; Rocha, V.; Suberbielle, C.; Bengoufa, D.; Dulphy, N.; Haas, P.; Scieux, C.; Amroun, H.; Gluckman, E.; Krishnamoorthy, R.; Toubert, A.; Charron, D.; Socié, G. & Tamouza, R. (2009). MICA-129 genotype, soluble MICA, and anti-MICA antibodies as biomarkers of chronic graft-versus-host disease. *Blood*, Vol.114, No.25, (December 2009), pp.5216–5224, ISSN 0006-4971

Boyton, R.J. & Altmann, D.M. (2007). Natural killer cells, killer immunoglobulin like receptors and human leukocyte antigen class I in disease. *Clinical of Experimental Immunology*, Vol.149, No.1, (January 2007), pp.1-8, ISSN 0009-9104

Choi, S.W.; Levine, J.E. & Ferrara, J.L. (2010). Pathogenesis and Management of Graft-versus-Host Disease. *Immunology and Allergy Clinics of North America*, Vol.30, No.1, (February 2010), pp.75–101, ISSN 0889-8561

Choy, M.K. & Phipps, M.E. (2010). MICA polymorphism: biology and importance in immunity and disease. *Trends in Molecular Medicine*, Vol.16, No.3, (March 2010), pp.97-106, ISSN 1471-4914

Cook, M.A.; Milligan, D.W.; Fegan, C.D.; Darbyshire, P.J.; Mahendra, P.; Craddock, C.F.; Moss, P.A. & Briggs, D.C. (2004). The impact of donor KIR and patient HLA-C genotypes on outcome following HLA-identical sibling hematopoietic stem cell transplantation for myeloid leukemia. *Blood*, Vol.103, No.4, (February 2004), pp.1521-1526, ISSN 0006-4971

Cullup, H.; Dickinson, A.M.; Cavet, J.; Jackson, G.H. & Middleton, P.G. (2003). Polymorphisms of interleukin-1alpha constitute independent risk factors for chronic graft-versus-host disease after allogeneic bone marrow transplantation. *British Journal of Haematology*, Vol.122, No.5, (September 2003), pp.778-787, ISSN 0007-1048

Davies, S.M.; Ruggieri, L.; DeFor, T.; Wagner, J.E.; Weisdorf, D.J.; Miller, J.S.; Velardi, A. & Blazar, B.R. (2002). Evaluation of KIR ligand incompatibility in mismatched unrelated donor hematopoietic transplants. *Blood*, Vol.100, No.10, (November 2002), pp.3825-3827, ISSN 0006-4971

Fernandes, H.; Koneru, B.; Fernandes, N.; Hameed, M.; Cohen, MC.; Raveche, E. & Cohen, S. (2002). Investigation of promoter polymorphisms in the tumor necrosis factor-a and interleukin-10 genes in liver transplant patients. *Transplantation*, Vol.73, No.12, (June 2002), pp.1886-1891, ISSN 0041-1337

Ferrara, J.L. & Krenger, W. (1998). Graft-versus-host disease: the influence of type 1 and type 2 T cell cytokines. *Transfusion Medicine Reviews,* Vol.12, No.1, (January 1998), pp.1–17, ISSN 0887-7963

Ferrara, J.L. (2000). Pathogenesis of acute graft-versus-host disease: cytokines and cellular effectors. *Journal of Hematotherapy & Stem Cell Research*, Vol.9, No.3, (June 2000), pp. 299–306, ISSN 1061-6128

Fishman, D.; Faulds, G.; Jeffery, R.; Mohamedali, V.; Yudkin, J.S.; Humphries, S. & Woo, P. (1998). The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *The Journal of Clinical Investigation*, Vol.102, No.7, (October 1998), pp.1369-1376, ISSN 0021-9738

Franceschi, D.S.;de Souza, C.A.; Aranha, F.J.; Cardozo, D.M.; Sell, A.M. & Visentainer, J.E. (2011). Importance of killer immunoglobulin-like receptors in allogeneic hematopoietic stem cell transplantation. *Revista Brasileira de Hematologia e Hemoterapia*, Vol.33, No.2, (April 2011), ISSN 1516-8484

Gagne, K.; Brizard, G.; Gueglio. B.; Milpied, N. ; Herry, P.; Bonneville, F.; Chéneau, M.L.; Schleinitz, N.; Cesbron, A.; Folléa, G.; Harrousseau, J.L & Bignon, J.D. (2002). Relevance of KIR gene polymorphisms in bone marrow transplantation outcome. *Human Immunology*, Vol.63, (April 2002), pp.271-280, ISSN 0198-8859

Gannage, M.; Buzyn, A. ; Bogiatzi, S.I.; Lambert, M.; Soumelis, V; Dal Cortivo, L.; Cavazzana-Calvo, M.; Brousse, N. & Caillat-Zucman, S. (2008). Induction of NKG2D ligands by gamma radiation and tumor necrosis factor-alpha may participate in the tissue damage during acute graft-versus-host disease. *Transplantation*, Vol.85, No.6, (March 2008), pp.911-915, ISSN 0041-1337

Gasser, S. & Raulet, D.H. (2006). Activation and self-tolerance of natural killer cells. *Immunological Reviews*, Vol.214, No.1, (December 2006), pp.130-142, ISSN: 0105-2896

Giebel, S.; Locatelli, F.; Lamparelli, T.; Velardi, A.; Davies, S.; Frumento, G.; Maccario, R.; Bonetti, F.; Wojnar, J.; Martinetti, M.; Frassoni, F.; Giorgiani, G.; Bacigalupo, A. & Holowiecki, J. (2003). Survival advantage with KIR ligand incompatibility in hematopoietic stem cell transplantation from unrelated donors. *Blood*, Vol.102, No.3, (August 2003), pp.814-819, ISSN 0006-4971

Groh, V.; Bahram, S; Bauer, S.; Herman, A.; Beauchamp, M. & Spies T. (1996). Cell stress-regulated human major histocompatibility complex class I gene expressed in gastrointestinal epithelium. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.93, No.22 (October 1996), pp. 12445-12450, ISSN 0027-8424

Hahn, A.B.; Kasten-Jolly, J.C.; Constantino, D.M.; Graffunder, E. & Conti, D.J. (2001). TNF-alpha, IL-6, IFN-gamma, and IL-10 gene expression polymorphisms and the IL-4 receptor a-chain variant Q576R: effects on renal allograft outcome. *Transplantation*, Vol.72, No.4, (August 2001), pp.660-665, ISSN 0041-1337

Hankey, K.G.; Drachenberg, C.B.; Papadimitriou, J.C.; Klassen, D.K.; Philosophe, B.; Bartlett, S.T.; Groh, V.; Spies, T. & Mann, D.L. (2002). MIC expression in renal and pancreatic allografts. *Transplantation* Vol.73, No.2, (January 2002), pp. 304-306, ISSN 0041-1337

Hattori, H.; Matsuzaki, A.; Suminoe, A.; Ihara, K.; Nagatoshi, Y.; Sakata, N.; Kawa, K.; Okamura, J. & Hara, T. (2002). Polymorphisms of transforming growth factor-beta1 and transforming growth factor-beta1 type II receptor genes are associated with acute graft-versus-host disease in children with HLA matched sibling bone marrow transplantation. *Bone Marrow Transplanation*, Vol.30, No.10, (November 2002), pp.665-671, ISSN 0268-3369

Horton, R.; Wilming, L.; Rand, V.; Lovering R.C.; Bruford, E.A.; Khodiyar, V.K.; Lush, M.; Povey, S.; Talbot, C.C. Jr.; Wright, M.W.; Wain, H.M.; Trowsdale, J.; Ziegler, A. & Beck, S. (2004). Gene map of the extended human MHC. *Nature Reviews Genetics*, Vol.5, No.12, (December 2004), pp.889-899, ISSN 1471-0056

Hsu, K.C.; Keever-Taylor, C.A.; Wilton, A.; Pinto, C.; Heller, G.; Arkun, K.; O'Reilly, R.J.; Horowitz, M.M. & Dupont, B. (2005). Improved outcome in HLA-identical sibling hematopoietic stem-cell transplantation for acute myelogenous leukemia predicted

by KIR and HLA genotypes. *Blood*, Vol.105, No.12, (June 2005), pp.4878-4884, ISSN 0006-4971

Iwasaki, T. (2004). Recent advances in the treatment of graft-versus-host disease. *Clinical Medicine & Research*, Vol.2, No.4, (November 2004), pp.243-252, ISSN 1539-4182

Joyce, M.G. & Sun, P.D. (2011). The structural basis of ligand recognition by natural killer cell receptors. *Journal of Biomedicine and Biotechnology*, Vol.2011, (May 2011), pp.1-15, ISSN 1110-7243

Jung, U.; Foley, J.E.; Erdmann, A.A.; Toda, Y.; Borenstein, T.; Mariotti, J. & Fowler, D.H. (2006). Ex vivo rapamycin generates Th1/Tc1 or Th2/Tc2 effector T cells with enhanced in vivo function and differential sensitivity to post-transplant rapamycin therapy. *Biology of Blood and Marrow Transplantation*, Vol.12, No.9, (September 2006), pp.905–918, ISSN 1083-8791

Kappel, L.W.; Goldberg, G.L.; King, C.G.; Suh, D.Y.; Smith, O.M.; Ligh, C.; Holland, A.M.; Grubin, J.; Mark, N.M.; Liu, C.; Iwakura, Y.; Heller, G. & van den Brink, M.R. (2009). IL-17 contributes to CD4-mediated graft-versushost disease. *Blood,* Vol.113, No.4, (January 2009), pp.945–952, ISSN 0006-4971

Karimi, M.H.; Daneshmandi, S.; Pourfathollah, A.A.; Geramizadeh, B.; Ramzi, M.; Yaghobi, R. & Ebadi, P. (2010). The IFN-γ Allele Correlated to Moderate-to-Severe Acute Graft-Versus-Host Disease After Allogeneic Stem Cell Transplant. *Experimental and Clinical Transplantation,* Vol.8, No.2, (June 2010), pp.125-129, ISSN 1304-0855

Karimi, M.H.; Daneshmandi, S.; Pourfathollah, A.A.; Geramizadeh, B.; Yaghobi, R.; Rais-Jalali, G.A.; Roozbeh, J. & Bolandparvaz, S. (2011). A study of the impact of cytokine gene polymorphism in acute rejection of renal transplant recipients. *Molecular Biology Reports*, [Epub ahead of print], (May 2011), ISSN 0301-4851

Katz, G.; Markel, G.; Mizrahi, S.; Arnon, T.I. & Mandelboim, O. (2001). Recognition of HLA-Cw4 but not HLA-Cw6 by the NK cell receptor killer cell Ig-like receptor two-domain short tail number 4. *Journal of Immunology*, Vol.166, No.12, (June 2001), pp.7260-7267, ISSN 0022-1767

Kayaba, H.; Hirokawa, M.; Watanabe, A.; Saitoh, N.; Changhao, C.; Yamada, Y.; Honda, K., Kobayashi, Y.; Urayama, O. & Chihara, J. (2000). Serum markers of graft-versus-host disease after bone marrow transplantation. *The Journal of Allergy and Clinical Immunology*, Vol.106, No.2, (July 2000), pp. S40-S44, ISSN 00917-6749

Kim, D.H.; Lee, N.Y.; Sohn, S.K.; Baek, J.H.; Kim, J.G.; Suh, J.S.; Lee, K.B. & Shin, I.H. (2005). IL-10 promoter gene polymorphism associated with the occurrence of chronic GVHD and its clinical course during systemic immunosuppressive treatment for chronic GVHD after allogeneic peripheral blood stem cell transplantation. *Transplantation*, Vol.79, No.11, (June 2005), pp.1615-1622, ISSN 0041-1337

Kitcharoen, K.; Witt, C.S.; Romphruk, A.V.; Christiansen, F.T. & Leelayuwat, C. (2006). MICA, MICB, and MHC beta block matching in bone marrow transplantation: relevance to transplantation outcome. *Human Immunology*, Vol.67, No.3, (March 2006), pp.238–246, ISSN 0198-8859

Laguila Visentainer, J.E.; Lieber, S.R.; Lopes Persoli, L.B.; Dutra Marques, S.B.; Vigorito, A.C.; Penteado Aranha, F.J.; de Brito Eid, K.A.; Oliveira, G.B.; Martins Miranda, E.C.; Bragotto, L. & de Souza, C.A. (2005). Relationship between cytokine gene polymorphisms and graft-versus-host disease after allogeneic stem cell

transplantation in a Brazilian population. *Cytokine*, Vol.32, No.3-4, (November 2005), pp.171-177, ISSN: 1043-4666

Lanier, L.L. (2008). Up on the tightrope: natural killer cell activation and inhibition. *Nature Immunology*, Vol.9, No.5, (May 2008), pp.495-502, ISSN 1529-2908

Leelayuwat, C.; Townend, D.C.; Degli-Esposti, M.A.; Abraham, L.J. & Dawkins, R.L. (1994). A new polymorphic and multicopy RL: A new polymorphic and multicopy MHC gene family related to non mammalian class I. *Immunogenetics,* Vol.40, No.51, (1994), pp. 339-351, ISSN 0093-7711

Leffell, M.S.; Vogelsang, G.B.; Lucas, D.P.; Delaney, N.L. & Zachary, A.A. (2001). Association between TGF-beta expression and severe GVHD in allogeneic bone marrow transplantation. *Transplantation Proceedings*, Vol.33, No.1-2, (February-March 2001), pp.485-486, ISSN 0041-1345

Letterio, J.J. & Roberts, A.B. (1998). Regulation of immune responses by TGFbeta. *Annual Review of Immunology*, Vol.16, (April 1998), pp.137-161, ISSN 15453278

Liem, L.M.; Fibbe, W.E.; van Houwelingen, H.C. & Golmy, E. (1999). Serum transforming growth factor-b1 levels in bone marrow transplant recipients correlate with blood cell counts and chronic graft-versus-host disease. *Transplantation*, Vol.67, No.1, (January 1999), pp. 59-65, ISSN 0041-1337

Liem, L.M.; van Houwelingen, H.C. & Goulmy, E. (1998). Serum cytokine levels after HLA-identical bone marrow transplantation. *Transplantation*, Vol.66, No.7, (October 1998), pp.863-871, ISSN 0041-1337

Lin, M.T., Storer, B., Martin, P.J., Tseng, L.H., Gooley, T., Chen, P.J. & Hansen, J.A. (2003). Relation of an interleukin-10 promoter polymorphism to graft-versus-host disease and survival after hematopoietic-cell transplantation. *The New England Journal of Medicine*, Vol.349, No.23, (December 2003), pp.2201-2210, ISSN 0028-4793

Ludajic, K.; Balavarca, Y.; Bickeböller, H.; Rosenmayr, A.; Fae, I.; Fischer, G.F.; Kouba, M.; Pohlreich, D.; Kalhs, P. & Greinix, H.T. (2009). KIR genes and KIR ligands affect occurrence of acute GVHD after unrelated, 12/12 HLA matched, hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, Vol.44, No.2, (July 2009), pp.97–103, ISSN 0268-3369

Macmillan, M.L.; Radloff, G.A.; Kiffmeyer, W.R.; Defor, T.E.; Weisdorf, D.J. & Davies, S.M. (2003). High-producer interleukin-2 genotype increases risk for acute graft-versus-host disease after unrelated donor bone marrow transplantation. *Transplantation*, Vol.76, No.12, (December 2003), pp.1758-1762, ISSN 0041-1337

Margolis, J. & Vogelsang, G. (2000). Chronic graft-versus-host disease. *Journal of Hematotherapy & Stem Cell Research*, Vol.9, No.3, (June 2000), pp.339-346, ISSN 1061-6128

McVicar, D.W. & Burshtyn, D.N. (2001). Intracellular signaling the killer immunoglobulin-like receptors and Ly49. *Sciences´s STKE: signal transduction knowledge environment*, Vol.2001, No.75, (March 2001), pp. re1, ISSN 1945-0877

Mlynarczewska, A.; Wysoczanska, B.; Karabon, L.; Bogunia-Kubik, K. & Lange, A. (2004) Lack of IFN-gamma 2/2 homozygous genotype independently of recipient age and intensity of conditioning regimen influences the risk of aGVHD manifestation after HLA-matched sibling haematopoietic stem cell transplantation. *Bone Marrow Transplantation*, Vol.34, No.4, (August 2004), pp.339-344, ISSN 0268-3369

Miller, J.S.; Cooley, S.; Parham, P.; Farag, S.S.; Verneris, M.R.; McQueen, K.L.; Guethlein, L.A.; Trachtenberg, E.A.; Haagenson, M.; Horowitz, M.M.; Klein, J.P. & Weisdorf, D.J. (2007). Missing KIR-ligands are associated with less relapse and increased graft versus host disease (GVHD) following unrelated donor allogeneic HCT. *Blood*, Vol.109, No.11, (June 2007), pp.5058–5061, ISSN 0006-4971

Mizutani, K.; Terasaki, P.I.; Shih, R.N.; Pei, R. Ozawa, M. & Lee, J. (2006). Frequency of MIC Antibody in Rejected Renal Transplant Patients without HLA Antibody. *Human Immunology,* Vol.67, No.3, (March 2006) pp. 223–229, ISSN 0198-8859

Moretta, A.; Pende, D.; Locatelli, F. & Moretta, L. (2009). Activating and inhibitory killer immunoglobulin-like receptors (KIR) in haploidentical haemopoietic stem cell transplantation to cure high-risk leukaemias. *Clinical Experimental of Immunology,* Vol.157, No.3, (September 2009), pp.325–331, ISSN 0093-9104

Murai, M.; Yoneyama, H.; Ezaki, T.; Suematsu, M.; Terashima, Y.; Harada, A.; Hamada, H.; Asakura, H.; Ishikawa, H & Matsushima, K. (2003). Peyer's patch is the essential site in initiating murine acute and lethal graft-versus-host reaction. *Nature Immunology*, Vol.4, No.2, (February 2003), pp. 3154-3160, ISSN 1529-2908

Narayan, S.; Tsai, E.W.; Zhang, Q.; Wallace, W.D.; Reed, E.F. & Ettenger, R.B. (2011). Acute rejection associated with donor specific anti-MICA antibody in a highly sensitized pediatric renal transplant recipient. *Pediatric Transplantation*, Vol.15, No.1, (February 2011), pp.E1-7, ISSN 1397-3142

O'Connor, G.M.; Hart, O.M. & Gardiner, C.M. (2006). Putting the natural killer cell in its place. *Immunology,* Vol.117, No.1, (January 2006), pp.1-10, ISSN 0019-2805

Paczesny, S.; Hanauer, D.; Sun, Y. & Reddy, P. (2010). New perspectives on the biology of acute GVHD. *Bone Marrow Transplantation*, Vol.45, No.1, (January 2010), pp.1–11, ISSN 0268-3369

Panigrahi, A.; Gupta, N.; Siddiqui, J.A.; Margoob, A.; Bhowmik, D.; Guleria, S. & Mehra, N.K. (2007). Post Transplant Development of MICA and Anti-HLA Antibodies is Associated with Acute Rejection Episodes and Renal Allograft Loss. *Human Immunology,* Vol.68, No.5, (May 2007), pp.362–367, ISSN 0198-8859

Parham, P. (2006). Taking license with natural killer cell maturation and repertoire development. *Immunological Reviews*, Vol.214, No.1, (December 2006), pp.155-160, ISSN 1529-2908

Parmar, S.; Del Lima, M.; Zou, Y.; Patah, P.A.; Liu, P.; Cano, P.; Rondon, G.; Pesoa, S.; de Padua Silva, L.; Qazilbash, M.H.; Hosing, C.; Popat, U.; Kebriaei, P.; Shpall, E.J.; Giralt, S.; Champlin, R.E.; Stastny, P. & Fernandez-Vina, M. (2009). Donor-recipient mismatches in MHC class I chain-related gene A in unrelated donor transplantation lead to increased incidence of acute graft-versus-host disease. *Blood*, (October 2009), Vol.114, No.14, pp.2884–2887, ISSN 0006-4971

Pérez-Simón, J.A.; Sánchez-Abarca, I.; Díezcampelo, M.; Caballero, D. & San Miguel, J. (2006). Chronic Graft-Versus-Host Disease Pathogenesis and Clinical Management. *Drugs*, Vol.66, No.8, (2006), pp. 1041-1057, ISSN 0012-6667

Pravica, V.; Asderakis, A.; Perrey, C.; Hajeer, A.; Sinnott, P.J. & Hutchinson, I.V. (1999). In vitro production of IFN-gamma correlates with CA repeat polymorphism in the human IFN-gamma gene. *European Journal of Immunogenetics*, Vol.26, No.1, (February 1999), pp.1-3, ISSN 0960-7420

Przepiorka, D.; Weisdorf, D.; Martin, P.; Klingemann, H.G.; Beatty, P.; Hows, J & Thomas, E.D. (1995). 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplantation, Vol.15, No.6, (June 1995), pp. 825-828, ISSN 0268-3369

Rajagopalan, S. & Long, E.O. (1999). A human histocompatibility leukocyte antigen (HLA)-G-specific receptor expressed on all natural killer cells. *Journal of Experimental Medicine*, Vol.189, No.7, (1999), pp.1093-1100. ISSN 0022-1007

Rajagopalan, S. & Long, E.O. (2005). Understanding how combinations of HLA and KIR genes influence disease. *The Journal of Experimental Medicine,* Vol.201, No.7, (April 2005), pp.1025-1029, ISSN 0022-1007

Rashidi-Nezhad, A.; Azimi, C.; Alimoghaddam, K.; Ghavamzadeh, A.; Hossein-Nezhad, A.; Izadi, P.; Sobhani, M.; Noori-Daloii, A.R. & Noori-Daloii, M.R. (2010). TGF-Beta codon 25 polymorphism and the risk of graft-versus-host disease after allogenic hematopoietic stem cell transplantation. *Iranian Journal of Allergy, Asthma and Immunology*, Vol.9, No.1, (March 2010), pp.1-6, ISSN 1735-1502

Reddy, P. & Ferrara, J.L. (2003). Immunobiology of acute graft-versus-host disease. *Blood Reviews*, (December 2003), Vol.17, No.4, pp.187–194, ISSN 0268-960X

Reviron, D.; Dussol, B.; Andre, M.; Brunet, P.; Mercier, P. & Berland, Y. (2001). TNF-alpha and IL-6 gene polymorphism and rejection in kidney transplantation recipients. *Transplantation Proceedings*, Vol.33, No.1-2, (February-March 2001), pp.350-351, ISSN 0041-1345

Sakata, N; Yasui, M.; Okamura, T.; Inoue, M.; Yumura-Yagi, K. & Kawa, K. (2001). Kinetics of plasma cytokines after hematopoietic stem cell transplantation from unrelated donors: the ratio of plasma IL-10/sTNFR level as a potential prognostic marker in severe acute graft-versus-host disease. *Bone Marrow Transplantation*, Vol.27, No.11, (June 2001), pp. 1153-1161, ISSN 0268-3369

Schellekens, J.; Rozemuller, E.H.; Petersen, E.J.; van den Tweel, J.G.; Verdonck, L.F. & Tilanus, M.G. (2008). Activating KIRs exert a crucial role on relapse and overall survival after HLA-identical sibling transplantation. *Molecular Immunology*, Vol.45, No.8, (April 2008), pp.2255-2261, ISSN 0161-5890

Shamim, Z.; Ryder, L.P.; Christensen, I.J.; Toubert, A.; Norden, J.; Collin, M.; Jackson, G.; Dickinson, A.M. & Müller, K. (2011). Prognostic Significance of Interleukin-7 Receptor-α Gene Polymorphisms in Allogeneic Stem-Cell Transplantation: A Confirmatory Study. *Transplantation*, (April 2011), Vol.91, No.7, pp.731–736, ISSN 0041-1337

Sivula, J.; Turpeinen, H.; Volin, L. & Partanen, J. (2009). Association of IL-10 and IL-10Rβ gene polymorphisms with graft-versus-host disease after haematopoietic stem cell transplantation from an HLA-identical sibling donor. *BMC Immunology*, Vol.10, (May 2009), pp.24-30, ISSN 1471-2172

Steinle, A.; Li, P.; Morris, D.L.; Groh, V.; Lanier, L.L.; Strong, R.K. & Spies, T. (2001). Interactions of human NKG2D with its ligands MICA, MICB, and homologs of the mouse RAE-1 protein family. *Immunogenetics*, Vol.53, No.4, (May-June 2001), pp.279-287, ISSN: 0093-7711

Sumitran-Holgersson, S. (2008). Relevance of MICA and other non- HLA antibodies in clinical transplantation. *Current Opinion of Immunology,* Vol.20, No.5 (October 2008), pp.607–613, ISSN 0952-7915

Sun, J.Y.; Gaidulis, L.; Dagis, A.; Palmer, J.; Rodriguez, R.; Miller, M.M.; Forman, S.J. & Senitzer, D. (2005). Killer Ig-like receptor (KIR) compatibility plays a role in the prevalence of acute GVHD in unrelated hematopoietic cell transplants for AML. *Bone Marrow Transplantation*, Vol.36, No.6, (September 2005), pp.525-530, ISSN 0268-3369

Symons, H.J.; Leffell, M.S.; Rossiter, N.D.; Zahurak, M.; Jones, R.J. & Fuchs, E.J. (2010). Improved Survival with Inhibitory Killer Immunoglobulin Receptor (KIR) Gene Mismatches and KIR Haplotype B Donors after Nonmyeloablative, HLA-Haploidentical Bone Marrow Transplantation. *Biology of Blood and Marrow Transplantation*, Vol.16, No.4, (April 2010), pp.533-542, ISSN 1083-8791

Takahashi, H.; Furukawa, T.; Hashimoto, S.; Susuki, N.; Yamazaki, F.; Inano, K.; Takahashi, M.; Aizawa, Y. & Koike, T. (2000). Contribution of TNF-alpha and IL-10 gene polymorphisms to graftversus-host disease following allo-hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, Vol.26, No.12, (December 2000), pp.1317-1323, ISSN 0268-3369

Tambur, A.R.; Yaniv, I.; Stein, J.; Lapidot, M.; Shabtai, E.; Kfir, B. & Klein, T. (2001). Cytokine gene polymorphism in patients with graft-versus-host disease. *Transplantation Proceedings*, Vol.33, No.1-2, (February-March 2001), pp.502-503, ISSN 0041-1345

Tawara, I.; Maeda, Y.; Sun, Y.; Lowler, K.P.; Liu, C.; Toubai, T.; McKenzie, A.N & Reddy, P. (2008). Combined Th2 cytokine deficiency in donor T cells aggravates experimental acute graft-vs-host disease. *Experimental Hematology,* Vol.36, No.8, (August 2008), pp.988–996, ISSN 0301-472X

Tay, G.K.; Witt, C.S.; Christiansen, F.T.; Charron, D.; Baker, D.; Herrmann, R.; Smith, L.K.; Diepeveen, D.; Mallal, S. & McCluskey, J. (1995). Matching for MHC haplotypes results in improved survival following unrelated bone marrow transplantation. *Bone Marrow Transplantation*, Vol.15, No.3, (March 1995), pp.381–385, ISSN 0268-3369

Terasaki, P.I.; Ozawa, M. & Castro R. (2007). Four-year follow-up of a prospective trial of HLA an MICA antibodies on kidney graft survival. *American Journal of Transplantation,* Vol.7, No.2, (February 2007), pp. 408–415, ISSN 1600-6135

Tieng, V.; Le Bouguenec, C. ; du Merle, L.; Bertheau, P.; Desreumaux, P.; Janin, A.; Charron, D. & Toubert, A. (2002). Binding of Escherichia coli adhesin AfaE to CD55 triggers cell-surface expression of the MHC class I-related molecule MICA. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.99, No.5, (March 2002), pp.2977-2982, ISSN 0027-8424

Turner, D.M.; Williams, D.M.; Sankaran, D.; Lazarus, M.; Sinnott, P.J. & Hutchinson, I.V. (1997). An investigation of polymorphism in the interleukin-10 gene promoter. *European Journal of Immunogenetics*, Vol.24, No.1, (February 1997), pp.1-8, ISSN 0960-7420

Uhrberg, M.; Valiante, N.M.; Shum, B.P.; Shilling, H.G.; Lienert-Weidenbach, K.; Corliss, B.; Tyan, D.; Lanier, L.L. & Parham, P. (1997). Human diversity in killer cell inhibitory receptor genes. *Immunity*, Vol.7, No.6, (December 1997), pp.753-763, ISSN 1074-7613

Venstrom, J.M., Ted, A. Gooley, T.A.; Spellman, S.; Pring, J.; Malkki, M.; Dupont, B.; Petersdorf, E. & Hsu, K.C. (2010). Donor activating KIR3DS1 is associated with decreased acute GVHD in unrelated allogeneic hematopoietic stem cell transplantation. *Blood*, Vol.115, No.15, (April 2010), pp.3162-3165, ISSN 0006-4971

Viel, D.O.; Tsuneto, L.T.; Sossai, C.R.; Lieber, S.R.; Marques, S.B.; Vigorito, A.C.; Aranha, F.J.; De Brito Eid, K.A.; Oliveira, G.B.; Miranda, E.C.; De Souza, C.A. & Visentainer, J.E. (2007). IL2 and TNFA gene polymorphisms and the risk of graft-versus-host disease after allogeneic stem cell transplantation. *Scandinavian Journal of Immunology*, Vol.66, No.6, (December 2007), pp.703-710, ISSN 0300-9475

Visentainer, J.E.; Lieber, S.R.; Persoli, L.B.; Vigorito, A.C.; Aranha, F.J.; Eid, K.A.; Oliveira, G.B.; Miranda, E.C. & de Souza, C.A. (2003). Serum cytokine levels and acute graft-versus-host disease after HLA-identical hematopoietic stem cell transplantation. *Experimental Hematology*, Vol.31, No.11, (November 2003), pp. 1044-1050, ISSN 0301-472X

Wilson, A.G.; Symons, J.A.; Mcdowell, T.L.; Mcdevitt, H.O. & Duff, G.W. (1997). Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.94, No.7, (April 1997), pp.3195-319, ISSN 1091-6490

Witt, C.; Sayer, D.; Trimboli, F.; Saw, M.; Herrmann, R.; Cannell, P.; Baker, D. & Christiansen, F. (2000). Unrelated donors selected prospectively by block-matching have superior bone marrow transplant outcome. *Human Immunology,* Vol. 61, No.2, (February 2000), pp.85-91, ISSN 0198-8859

Witt, C.S. & Christiansen, F.T. (2006). The relevance of natural killer cell human leukocyte antigen epitopes and killer cell immunoglobulinlike receptors in bone marrow transplantation. *Vox Sanguinis*, Vol.90, No.1, (January 2006), pp.10-20, ISSN 0042-9007

Yi, T.; Zhao, D.; Lin, C.L.; Zhang, C.; Chen, Y.; Todorov, I.; LeBon, T.; Kandeel, F.; Forman, S. & Zeng, D. (2008). Absence of donor Th17 leads to augmented Th1 differentiation and exacerbated acute graft-versus-host disease. *Blood,* Vol.112, No.5, (September 2008), pp.2101–2110, ISSN 0006-4971

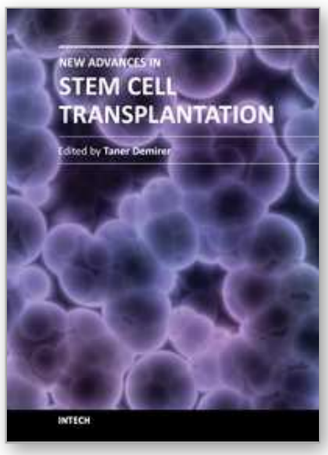
Yokoyama, W.M. & Kim, S. (2006). Licensing of natural killer cells by self major histocompatibility complex class I. *Immunological Reviews*, Vol.214, No.1, (December 2006), pp.143-154, ISSN 1529-2908

Zhang, C.; Todorov, I.; Zhang, Z.; Liu, Y.; Kandeel, F.; Forman, S.; Strober, S. & Zeng, D. (2006). Donor CD4+ T and B cells in transplants induce chronic graft-versus-host disease with autoimmune manifestations. *Blood*, Vol.107, No.7, (April 2006), pp.2993-3001, ISSN 0006-4971

Zhang, Y. & Stastny, P. (2006). MICA antigens stimulate T cell proliferation and cell-mediated cytotoxicity. *Human Immunology*, Vol.67, No.3, (March 2006), pp.215–222, ISSN 0198-8859

Zou, Y.; Stastny, P.; Susal, C.; Dohler, B. & Opelz G. (2007). Antibodies against MICA antigens and kidneytransplant rejection. *The New England Journal of Medicine*, Vol.357, No.13, (September 2007), pp. 1293-1300, ISSN 0028-4793

Zwirner, N.W.; Dole, K. & Stastny, P. (1999). Differential surface expression of MICA by endothelial cells, fibroblasts, keratinocytes, and monocytes. *Human Immunology*, Vol.60, No.4, (April 1999), pp.323–330, ISSN 0198-8859



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This book documents the increased number of stem cell-related research, clinical applications, and views for the future. The book covers a wide range of issues in cell-based therapy and regenerative medicine, and includes clinical and preclinical chapters from the respected authors involved with stem cell studies and research from around the world. It complements and extends the basics of stem cell physiology, hematopoietic stem cells, issues related to clinical problems, tissue typing, cryopreservation, dendritic cells, mesenchymal cells, neuroscience, endovascular cells and other tissues. In addition, tissue engineering that employs novel methods with stem cells is explored. Clearly, the continued use of biomedical engineering will depend heavily on stem cells, and this book is well positioned to provide comprehensive coverage of these developments.

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