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REVIEW

Genetic barriers in transplantation medicine

Hisham A Edinur, Siti M Manaf, Nor F Che Mat

Hisham A Edinur, Forensic Science Programme, School of Health Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

Siti M Manaf, Nor F Che Mat, Biomedicine Programme, School of Health Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

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Correspondence to: Hisham A Edinur, PhD, Forensic Science Programme, School of Health Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia. edinur@usm.my
Telephone: +60-9-7677641
Fax: +60-9-7677515

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Abstract

The successful of transplantation is determined by the shared human leukocyte antigens (HLAs) and ABO blood group antigens between donor and recipient. In recent years, killer cell receptor [*i.e.*, killer cell immunoglobulin-like receptor (KIR)] and major histocompatibility complex (MHC) class I chain-related gene molecule (*i.e.*, MICA) were also reported as important determinants of transplant compatibility. At present, several different genotyping techniques (*e.g.*, sequence specific primer and sequence based typing) can be used to characterize blood group, HLA, MICA and KIR and loci. These molecular techniques have several advantages because they do not depend on the availability of anti-sera, cellular expression and have greater specificity and accuracy compared with the antibody-antigen based typing. Nonetheless, these molecular techniques have limited capability to capture increasing number of markers which have been demonstrated to determine donor and recipient compatibility. It is now possible to genotype multiple markers and to the extent of a complete sequencing of the human genome using next generation sequencer (NGS). This high throughput genotyping platform has been tested for HLA, and it is expected that NGS will be used to simultaneously genotype a large number of clinically relevant transplantation genes in near future. This is not far from reality due to the bioinformatics support given by the immunogenetics community and the rigorous improvement in NGS methodology. In addition, new developments in immune tolerance based therapy, donor recruitment strategies and bioengineering are expected to provide significant advances in the field of transplantation medicine.

Key words: Transplantation; ABO blood group; Human leukocyte antigen; MICA; Killer cell immunoglobulin-like receptor; Graft rejection; Graft *vs* host disease

Core tip: Transplantation is a systematic medical procedure for patients with organ failure and haematological disorders. Immunologically compatible donor

and recipient are determined by several genetic markers which include matching for ABO blood group, human leukocyte antigen, MICA and killer cell immunoglobulin-like receptors. The elucidation of genes code for these markers of tissue identity reviewed here and significant advancement in the field of transplant immunology are expected to have a positive impact on transplantation medicine. These include both the waitlisted and transplanted patients.

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INTRODUCTION

Transplantation is a systematic medical procedure for patients with organ failure and haematological disorders[1,2]. Transplantation can be classified into four categories: Autograft, isograft, allograft and xenograft based on the origins and the recipients of the grafts (cells, tissues or organs). In autograft transplantation (also known as autologous transplantation), a graft is taken and transplanted from different parts of the same individual. The processes of transferring grafts between genetically identical and non-identical individuals of the same species are known as isograft and allograft transplantation, respectively. In contrast, xenograft refers to the transplantation of grafts between two different species such as from baboon to human. Implantation of human cancer cells in mice for tumour study is also assumed to be xenograft transplantation[3,4].

The current practice of allograft transplantation is to have as many match for ABO and human leukocyte antigen (HLA) loci as possible between the donor and recipient. However, this is not the case for isograft and autograft as the transplanted graft originated from the genetically identical resources. Incompatibility between donor and recipient will cause rejection since the graft will be considered as non-self by the recipient's immune surveillance and the rate of graft rejection will vary depending on time courses, types of tissue or organ grafted and the immune responses involved.

REJECTION AND GRAFT *VS* HOST DISEASE

In general, there are three types of graft rejections, *i.e.*, hyperacute, acute and chronic rejection[4]. These types of rejections are categorized based on the speed that the rejection occurs. For hyperacute rejection, this process may occur within minutes or hours, and is usually not longer than 24 h. Sometimes, hyperacute rejection may occur immediately during the surgery process. This type of rejection is due to preformed alloantibodies against the mismatched ABO and HLA antigens between patient and donor. The alloantibodies may exist due to previous transplantation or transfusion, pregnancy or infections[5]. This pre-existing antibody can activate the complement system and cause injury to the endothelial cells which will then lead to platelet adhesion and thrombosis. Therefore, the graft will never be vascularised and the organ must be removed immediately. The hyperacute rejection may be managed with systematic antibody screening and cross matching between donor and recipient[6].

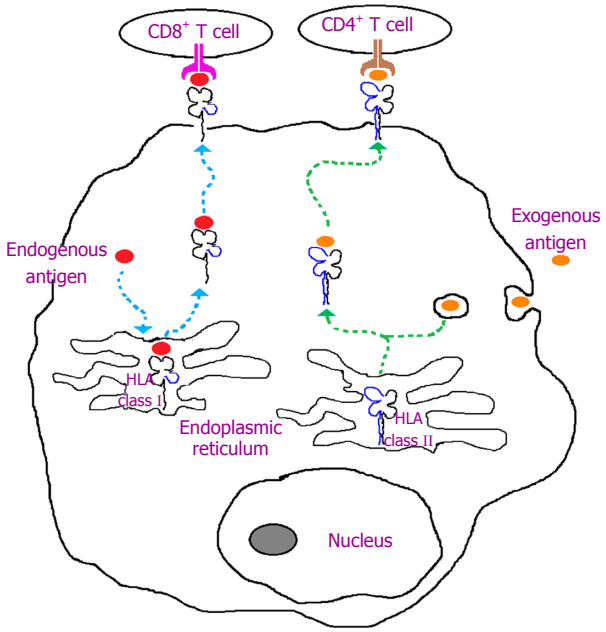

Figure 1 Schematic diagram of human leukocyte antigen class I and II antigenic peptide presentation to CD8$^+$ T and CD4$^+$ T cells, respectively. HLA: Human leukocyte antigen.

The most common type of graft rejection is acute rejection. The onset of rejection varies from weeks to months and is largely attributed to HLA incompatibility. This type of rejection involves both cellular- and humoral-mediated immunity. However, the cellular-mediated immune responses are more significant through either direct recognition of non-self HLA molecules on the surface of the graft or indirect antigenic peptide presentation by self HLA molecules to T cells[7-9] (Figure 1). The CD4$^+$ T cells will also secrete several types of cytokines such as interleukin-4 (IL-4) and IL-2. These cytokines will then lead to several mechanisms including inflammation, recruitment of other inflammatory cells and may also induce T and B cell proliferations[9]. The major histocompatibility complex (MHC) class I chain-related gene A (*MICA*) molecules are also important markers of tissue identity and have been implicated in transplant immunology[10,11]. The stress-induced MICA has previously known as PERB11.1 glycoproteins and are coded for by the gene located on the classical class I subregion of MHC[12] (Figure 2) and incompatibility between the donor and recipient for the MICA antigen

Table 1 List of killer cell immunoglobulin-like receptors and their human leukocyte antigen ligands

KIR	Alleles	Protein variants	HLA ligands
2DL1	43	24	C2
2DL2	28	11	C1, C2
2DL3	34	17	C1, C2
2DL4	46	22	G
2DL5	41	17	Unknown
2DS1	15	7	C2
2DS2	22	8	Unknown
2DS3	14	5	Unknown
2DS4	30	13	A*11, some C
2DS5	16	11	Unknown
3DL1	73	58	Bw4
3DS1	16	12	Unknown
3DL2	84	61	A*03,-11
3DL3	107	55	Unknown
3DP1	22	0	0
2DP1	23	0	0

The C1 are HLA-C allotypes with serine and asparagines at position 77 and 80 of α1 domain, respectively. The C2 are HLA-C allotypes with asparagines and lysine at position 77 and 80 of α1 domain, respectively. The Bw4 are HLA-B allotypes with isoleucine or threonine at position 80 of α1 domain. This table is adapted from Robinson *et al*[99] and Parham *et al*[104]. KIRs: Killer cell immunoglobulin-like receptors; HLA: Human leukocyte antigen.

will trigger cytotoxic activity of lymphocytes ($CD8^+$ and γδ T cells) and natural killer (NK) cells[11,13-15] (see the following sub-sections). The role of MICA in graft rejection and donor specific antibodies to MICA antigens have been reported by several others[11,16-18].

The third type of rejection is chronic rejection which takes place months to years following transplantation procedure. It induces chronic damage *via* the production of cytokines and alloantibodies which activate the classical pathway of complement system[19,20]. However, the actual mechanism of this rejection is not very well understood. It is usually characterized by fibrosis and arteriosclerosis, due to extensive proliferation of smooth muscle cells. Repairing process of damaged tissues and macrophages activation in chronic rejection can lead to fibrosis formation[21-23].

The transplanted allograft can also trigger immune reactions [*i.e.*, graft *vs* host disease (GVHD)] against mismatched antigens possessed by the recipients. The GVHD is predominantly occurs in bone marrow transplantation which involves alloreactivity of donor's lymphocytes against the incompatible tissues of the immune-suppressed host [8]. However, improved outcomes were observed in haplo-identical (*i.e.*, a single HLA haplotype-mismatched) stem cell transplantation[24-26]. In this context, donor's NK cells will recognize leukaemia cells as non-self and initiate alloreactivity (*i.e.*, graft *vs* leukaemia effect) against the cancerous cells after haplo-identical stem cell transplantation[27-29]. The inhibitory and alloreactivity of NK cells are determined by HLA molecules which acting as ligands (Table 1) for their immunoglobulin-like receptors [*i.e.*, killer cell immunoglobulin-like receptors (KIRs)][29,30] (see the following sub-sections). Thus, this receptor-ligand incompatible might lead to either NK alloreactivity against transplanted graft or GVHD. Our understanding of this immune surveillance has provided the basis for the adoptive infusion of NK cells as part of immunological based modality in transplantation and ultimately reduce the potential toxicity effects of other immunosuppression agents[29,31,32] (see later).

MANAGEMENT OF GRAFT REJECTION

The immunosuppressive therapy is used to increase the survival rate of the graft, especially during acute rejection. However, this therapy cannot be used for chronic rejection since it is difficult to manage. This therapy does not only involve drugs but also antibodies[33,34]. Examples of the drugs that have been used in immunosuppressive therapy are like mycophenolate mofetil, cyclosporine, tacrolimus and sirolimus[35-38]. Each of these drugs has their own mechanism of action which will result in immune cells suppression. For example, mycophenolate mofetil is administered to block proliferation of lymphocytes by inhibiting the key enzyme that is important for purine synthesis and DNA replication[36] while cyclosporine is given to inhibit transcription factor for T-cell activation[39,40]. For antibodies, a number of monoclonal and polyclonal antibodies have been given to the patients in preventing graft rejection. Most of these antibodies are specific for T cells or T cell sub-populations and they are very effective for blocking T cells activation and binding[41,42].

However, most of the immunosuppressive agents can cause various side effects to the recipient on their long term use. Besides that, the immunosuppression effects of the agents are not specific only on the graft, but also attack the overall body systems including the lymphocyte maturation. Hence, this will put the recipient at a high risk of getting other infections, cancer, cardiovascular diseases and metabolic bone diseases[33,43-45]. Additionally, the recipient will have a chance of getting transplant rejection once they stop taking these immunosuppression agents. As an alternative, researchers are working on finding a new therapy that maintains the health of the graft without compromising the immune system. This new method involves inducing immune tolerance and mainly focus on T cell depletion in thymus (*i.e.*, central tolerance) and suppression of mature T cells in lymph nodes (*i.e.*, peripheral tolerance)[20,46].

The key element in tolerance induction is specificity, which means the recipient immune system is not completely paralyzed. For example, the traditional antithymocyte globulin (TGA) was used as immunosuppressive agent drugs to prevent an acute rejection in organ transplantation[47-49]. As an alternative, this treatment is replaced with another antibody known as anti-IL-2Rα receptor antibodies. This type of antibody is widely used to replace TGA as it does not cause chronic expression of cytokines and improves the development of immune

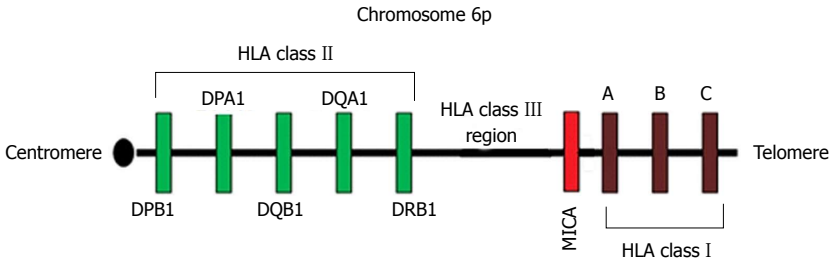

Figure 2 Approximate locations of human leukocyte antigen class I and II and major histocompatibility complex class I chain-related gene A loci on the short arm of chromosome 6. HLA: Human leukocyte antigen; MICA: Major histocompatibility complex class I chain-related gene A .

tolerance[50-53]. Besides anti-IL-2Rα, the combination of costimulatory molecule blockage with inhibitory of signal activation also appear to be effective in inducing tolerance in a few animal studies. Interaction between T cell receptor and costimulatory signals such as CD28 is required for T cell activation. Thus, blockage of the CD28 and its ligands (*i.e.*, B7 family molecules) resulted in transplantation tolerance[46,54,55] and induction of anergic state in T cells activation[56]. In addition, another molecule that binds to ligand for T cell activation (*e.g.*, CD152 or also known CTLA-4) also has a potential in inducing tolerance. For example, treatment with CTLA-4 immunoglobulin (Ig) during bone marrow transplantation in murine models was able to induce long-term survival rate of allograft[57]. Similarly, Ig treatment of other ligand for T cell receptor (*e.g.*, PD-1) and costimulatory molecule (*e.g.*, CD40) have also been shown to limit T cell proliferation and activation[58-60]. Acute rejection in non-human primates is also preventable by anti-CD40L treatment with or without CTLA-Ig[61,62].

Besides using inhibitory molecules, Treg ($CD4^+CD25^+$) and NK cells can also be used to suppress $CD4^+$ and $CD8^+$ T cell proliferation[63-67] and reduced rejection and GVHD[68-74]. Other than post-transplant, infusion of Treg cells before a transplant procedure is found to promote immune reconstitution and improve immunity to opportunistic infection, hence, preventing GVHD[75]. By increasing NK cells by total lymphoid irradiation, the immune tolerance is induced after organ and HSC transplantation[76]. A study suggests that the interaction of NK cells and Treg cells can promote immune tolerance. IL-4, which is secreted by NK cells, induces the expression of negative costimulatory molecules on the Treg cells[77]. The purification of NK cells in allogeneic transplantation may be achieved by depleting $CD3^+$ cells followed by $CD56^+$ cell enrichment[78]. Donors are also reported safe in completed clinical trials of NK cells infusion[79-81]. Stimulated NK cells with IFN-γ, IL-2 and anti-CD3 show MHC-independent cytotoxicity effect and NK cells infusion is proven safe to use after autologous HSCT[82]. The strategies of using immune cell infusion therapy have significantly increased the level of immune tolerance against allogeneic graft. New discoveries on Treg and NK cells administration posit that they appear to be effective in inducing transplant tolerance and rapid immune reconstitution. This may help to induce a better protection of infection or cancer relapse and consequently reducing GVHD incidence.

GENETIC MARKERS

Immunologically compatible donor and recipient are determined by several genetic markers which include matching for ABO blood groups, HLA, MICA and KIRs (see preceding sections). These antigens are encoded by highly polymorphic and independent loci in our genome and are distributed differently between individuals and populations. Incompatibility between the donor and recipient for these antigens will lead to either allograft lost or GVHD. In the following sub-sections, we discuss the molecular bases for the genes encoded for the determinants of transplant compatibility.

ABO

The ABO is important blood group in transfusion and transplantation and consists of three antigens; A, B and O. These red cell antigens are determined by the ABO allelic variants (*A*, *B* and *O* alleles) on the long arm of chromosome 9. The co-dominant *A* and *B* alleles differ by four nucleotide substitutions (C526G, G703A, C796A and G803C) while the Δ261G deletion differentiates between the recessive *O* and *A* alleles[83-85]. The α1,3-N-acetylgalactosaminyltransferase encoded by *A* allele and α1,3-D-galactosyltransferase encoded by *B* alleles then convert H antigens, the products of *H* gene located on human chromosome 19 to either A or B antigens, respectively[86]. In contrast, there is no enzymatic activity on H antigen for those bearing the *O* allele due to the Δ261G deletion on the background of *O* allele. Thus, the A, B, O and AB phenotypes are determined by the three ABO allelic variants; *A*, *B* and *O* alleles.

HLA

The HLA class I molecules consist of a non-polymorphic β_2-microglobulin and a highly polymorphic α-chain glycoprotein encoded by the genes within MHC on the chromosome 6[87-89]. There are three types of HLA class I molecules (A, C and B) with their specificities depend on the polymorphic α-chain encoded by *HLA-A,*

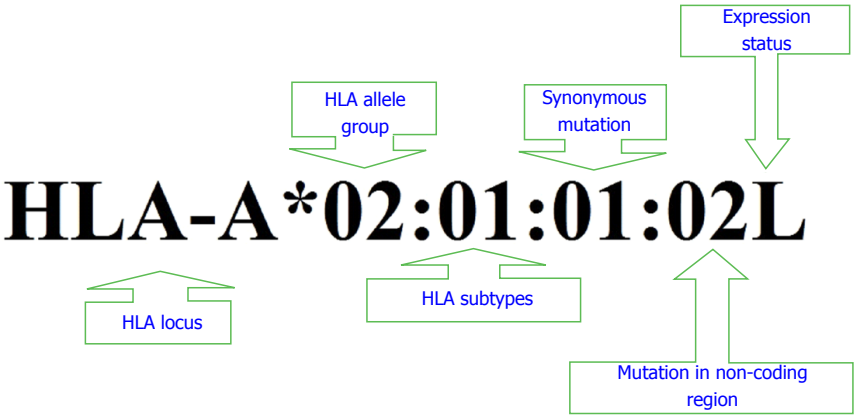

Figure 3 Systematic human leukocyte antigen nomenclature developed by the World Health Organization Nomenclature Committee for Factors of the human leukocyte antigen system. HLA: Human leukocyte antigen.

-B and *-C* genes in the classical class Ⅰ sub-region of MHC[90]. In contrast, both α- and β-chains of class Ⅱ HLA molecules (DP, DQ and DR) are encoded by genes in the classical class Ⅱ sub-region of MHC[12] (Figure 2). The *HLA* class Ⅰ and Ⅱ gene clusters within MHC are separated by the class Ⅲ sub-region which codes for complement components and not part of endogenous and exogenous peptide presentation to $CD8^+$ and $CD4^+$ cells, respectively[91-93] (Figure 1).

The World Health Organization has developed an alphanumeric nomenclature to name *HLA* antigens, genes and alleles (Figure 3). This systematic alphanumeric nomenclature begins with letters representing specific *HLA* gene and followed by an asterisk and two sets of digits specific for *HLA* allele group and glycoprotein. Two additional sets of digits are then used to specify synonymous nucleotide changes and mutation outside the non-coding region, respectively. Suffixes (*e.g.*, L: low cell surface expression, N: Null, C: Allele is expressed in cytoplasm but not on the cell surface and A: Aberrant expression) may be added to the end of this string of numbering system to indicate expression status of particular *HLA* alleles[12,94].

MICA

The MICA molecules are stress induced antigens encoded by a gene within MHC region (Figure 2) and are expressed by a wide range of cells including monocytes, keratinocytes and fibroblasts[14,87,95-97]. Unlike HLA class I molecule, MICA is not linked to β_2-microglobulin and NK cells and $CD8^+$ T (αβ and γδ) cells reactivity are stimulated through interaction of MICA and its ligand, the NKG2D receptor[13-15,98]. Variants of *MICA* gene are largely due to single nucleotide polymorphism and repeated units of alanine (*i.e.*, 4 to 10 Ala residues) in exons 2, 3 and 4 and exon 5, respectively[99-102] (see González-Galarza *et al*[100] for the list of populations characterized for MICA). The diversity within *MICA* gene reflect its role in immunity and as a marker of tissue identity[96,97].

KIR

The NK cells recognize healthy and unhealthy cells through either their lectin-like or immunoglobulin-like receptors encoded by NK and leukocyte receptor complexes located on human chromosome 12 and 19, respectively[103,104]. The leukocyte receptor complex also code for KIRs, one of the highly polymorphic transmembrane glycoprotein receptors expressed by NK cells[105,106]. Currently there are *16 KIR* genes and more than 570 genotypes (combinations of haplotype A and B *KIR* genes - Table 2) and 600 alleles were documented in public databases[99,100].

Each KIR is classified according to the number of their extracellular immunoglobulin (two and three domains and assigned as 2D and 3D, respectively) and the length of cytoplasmic (short and long and assigned as S and L, respectively) domains, respectively[107]. The KIRs with short and long cytoplasmic domains are activating and inhibitory receptors and transduce their signals through DAP-12 and tyrosine-based motifs, respectively. The only exception is for KIR2DL4 which transmits both, inhibitory and stimulatory signals[99]. The highly diverse and complex of KIRs were also reported for their ligands, the HLA class Ⅰ molecules (Table 1) and both have significant influences in transplantation and pathogenesis of various diseases[108].

COMPATIBILITY TESTING BETWEEN DONOR AND RECIPIENT

Typing of ABO and HLA, antibody screening and cross matching are three important procedures in determining the compatibility between donors and recipients. These procedures have been largely conducted using serological approaches (*e.g.*, complement dependent cytotoxicity test, ELISA, Luminex and flow cytometric assays; see Howell *et al*[8] for details). Alloantibodies against the transplanted organs/cells are usually developed in highly transfused patients or due to previous transplantation and pregnancy. These are the three main

Table 2 Here are the examples of both, gene content and allelic variations of the genes code for killer cell immunoglobulin-like receptors

KIR gene	KIR haplotype					
	A	A	A	B	B	B
[1]*KIR3DL1*	*015	*086	*005	*007	*086	X
[1]*KIR2DL1*	*003	*003	*003	*010	*004	X
[1]*KIR2DL3*	*001	*001	*001	X	X	X
[1]*KIR2DS4*	*001	*001	*010	*003	*001	X
[2]*KIR2DL2*	X	X	X	*003	*001	*001
[2]*KIR2DL5*	X	X	X	*B002	*B002	A*001
[2]*KIR3DS1*	X	X	X	X	X	*013
[2]*KIR2DS1*	X	X	X	X	X	*002
[2]*KIR2DS2*	X	X	X	*001	*001	X
[2]*KIR2DS3*	X	X	X	*001	*003	X
[2]*KIR2DS5*	X	X	X	X	X	*001
[3]*KIR2DL4*	*001	*028	*011	*006	*028	*005
[3]*KIR3DL2*	*002	*002	*010	*002	*002	*007
[3]*KIR3DL3*	*013	*002	*009	*014	*013	*003
[1]*KIR2DP1*	*009	*001	*001	*004	*007	*007
[3]*KIR3DP1*	*001	*001	*003	*001	*003	*003

[1,2,3]The haplotype A and B and framework *KIR* genes, respectively. The X indicates the absent of *KIR* genes/alleles.

events where individuals might be exposed to non-self antigens including the clinically important transplant antigens such as ABO antigens, HLA and MICA. Thus, antibody screening and cross matching are crucial to avoid allograft lost. Nowadays, molecular typing techniques such as those using sequence specific oligonucleotide primer, and Sanger sequencing have largely been used for genotyping of *ABO*, *HLA* and *MICA* and *KIR* genes. These molecular techniques have several advantages as they are not dependent on the availability of anti-sera, cellular expression and have greater specificity and accuracy as compared with the antibody-antigen based typing (recently reviewed by Howell *et al*[8], Dunn[109] and Edinur *et al*[110]).

FUTURE DEVELOPMENTS AND CONCLUDING REMARKS

Advances in the field of molecular biology and genetics have contributed immense benefits to the medical field including in transplantation medicine. A number of molecular techniques have been developed following the elucidation of molecular bases of the genes encoding for transplant determinants. Currently, several different genotyping platforms can be used to screen blood group, HLA, MICA, and KIR loci (see Howell *et al*[8], Dunn[109], Edinur *et al*[110] and Finning *et al*[111]). It is now possible to genotype multiple markers and to the extent of complete sequencing of human genome using the next generation sequencer (NGS). This high throughput genotyping platform has been tested for HLA (*e.g.*, see Bentley *et al*[112], Holcomb *et al*[113], Wang *et al*[114] and Skibola *et al*[115]) and it is expected that NGS will be used to simultaneously genotype large number of clinically relevant transplantation genes in near future. This is not far from reality due to bioinformatics support given by the immunogenetics community and the rigorous improvement in NGS methodology (see Robinson *et al*[94] and Grada *et al*[116]). In addition, new developments in immune tolerance based therapy, donor recruitment strategies and bioengineering (tissue engineering and regenerative medicine) will provide significant advances in the field of transplantation medicine. This paper provides only brief discussions of these new developments, while others[20,46,110,117,118] have conducted systematic reviews of them.

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