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Immunogenetics of Human Placentation

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Abstract

Natural killer (NK) cells are a population of lymphocytes that function in both immune defense and reproduction. Diversifying NK cell phenotype and function are interactions between NK cell receptors and major histocompatibility complex (MHC) class I ligands. As a consequence of strong and variable selection these ligand-receptor systems are polymorphic, rapidly evolving, and considerably species-specific. Counterparts to the human system of HLA class I ligands and killer cell immunoglobulin-like receptors (KIR) are present only in apes and Old World monkeys. HLA-C, the dominant ligand for human KIR and the only polymorphic HLA class I expressed by trophoblast, is further restricted to humans and great apes. Even then, the human system appears qualitatively different from that of chimpanzees, in that it has evolved a genetic balance between particular groups of receptors and ligands that favor reproductive success and other groups of receptors and ligands that have been correlated with disordered placentation. Human populations that have survived successive episodes of epidemic disease and population bottlenecks maintain a breadth of diversity for KIR and HLA class I, implying that loss of such diversity disfavors long-term survival of a human population.

Keywords

HLA; natural killer cells; balancing selection; evolution; immunity; reproduction

Immunogenetics was a term coined originally to describe the use of antibodies as tools for distinguishing the alternative alleles of genes that influence the structure of proteins and carbohydrates on blood cell surfaces [1]. As it developed, immunogenetics adapted and expanded to include all manner of studies that examine the natural, inherited variation of immune-system genes. Consequently, immunogenetics focuses on the less conventional genes without a dominant wild-type having ‘optimal’ function, but are represented instead by a variety of ‘sub-optimal’ forms having complementary functions maintained by balancing selection. For such genes, the members of a population exhibit different allele combinations; making it necessary to consider gene function, not only in the context of the individual, but also of the species and its constituent populations.

Perhaps the most obvious example of balancing selection is the maintenance of both chromosomes X and Y in human populations, reflecting the synergistic functions of men and women in reproduction. While many women appreciate that presence of a Y chromosome is not necessary for the development and survival of a healthy human

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Conflict of Interest
The authors have no conflict of interest to declare.

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individual, the presence in a population of XY males, as well as XX females, is essential for creating the next generation and for long-term species survival. Given this centrality of balancing selection in human reproduction, it is hardly surprising that certain molecular and cellular processes of reproduction are also subject to balancing selection and the compromises such selection implies. In particular, formation and function of the placenta involves a nine-month co-operation between the cells of two individuals who share one haploid genome, but differ at the other.

Pregnancy, Transplantation and Immunological Alloreactivity

The unusual physiological situation in pregnancy, where a genetically disparate fetus is implanted within a mother's womb, was famously compared to that of a foreign organ graft. Ever since Peter Medawar's influential ruminations on the subject some sixty years ago [2], immunologists have questioned and disputed why the pregnant mother's immune system does not reject the genetically histoincompatible baby she carries. Less contentious are the positive data showing that pregnant women do indeed eject the babies they carry, but only after an appropriate nine-month period of gestation. It is only then, with the physical trauma of childbirth, that the mother's immune system is stimulated to make antibodies against those protein products of the child's paternally-inherited genes that differ in sequence from their maternal counterparts. Antibodies raised against such intra-species (allogeneic) differences are called alloantibodies, their target antigens, alloantigens.

The abundance and strength of alloantibodies can increase with each successive baby a mother conceives by the same father, but this progression has no apparent deleterious effects on reproductive success. Sera donated by multiparous women were a crucial element to the discovery and characterization of the human major histocompatibility complex (MHC), a ~5 megabase region on the short arm of human chromosome 6 that contains the most highly polymorphic genes in the human genome. These genes are also the principal cause of acute graft rejection following organ transplantion and of acute graft-versus-host disease (GVHD) following bone-marrow transplantation. The human MHC was named the human leukocyte antigen (HLA) complex because the highly polymorphic alloantigens it encodes are expressed by the white cells of the blood (leukocytes), but not the red cells (erythrocytes), whose A/B/O, rhesus and other alloantigens had been a previous focus of investigation for several HLA pioneers [3].

Acute graft rejection and acute GVHD are diseases mediated by T-lymphocytes (commonly called T cells) that are stimulated by HLA differences between the transplant donor and the transplant recipient. Acute rejection of an organ transplant is caused by recipient T cells, whereas graft-versus-host disease is caused by donor-derived T cells in the bone-marrow graft that attack and damage the recipient's tissues, particularly the skin and the intestinal epithelium. Despite the non-physiological circumstances of their occurrence, the T-cell response in these transplantation syndromes reflects the natural physiological function of highly polymorphic HLA molecules. Namely the presentation of peptide antigens to αβ T-cell receptors, engagements necessary for generating protective T-cell mediated immune responses against infection and cancer, as well as a spectrum of undesirable autoimmune and hypersensitivity diseases.

Extra-villous Trophoblast expresses MHC class I but not MHC class II

Polymorphic HLA molecules are of two types that present peptide antigens to functionally distinctive classes of T cell: HLA class I (HLA-A, -B and -C) present antigens to CD8 T cells, whereas HLA class II (HLA-DP, -DQ and -DR) present antigens to CD4 T cells. Of these two structural variations on a common ancestral theme, the class II molecules have the more specialized function as evidenced by their restricted expression to professional

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antigen-presenting cells (dendritic cells, macrophages, monocytes and B cells) and by their dedicated function as ligands for the αβ TCR of CD4 T cells. In contrast, class I molecules are expressed on a wide range of the body's cells where they serve as ligands for receptors of the lymphocytes known as natural killer (NK) cells, as well as for the αβ TCR of CD8 T cells. These contrasting characteristics, along with several other lines of circumstantial evidence, are all consistent with an evolutionary model in which class I is closer to the ancestral form of the MHC molecule and MHC class II is more recently derived.

Until recently, all species investigated for the presence of MHC molecules were found either to have or lack both MHC class I and II. Breaking this tie were the results obtained from sequencing the genome of Atlantic cod. This bony fish genome was found to be enriched for *MHC class I* genes but lacking in genes for MHC class II and also for auxiliary proteins that are dedicated to the MHC class II pathway of antigen presentation [4]. Such species-wide immunodeficiency is consistent with MHC class II being the more specialized and dispensable form of MHC molecule, with MHC class I being the more plastic, but less dispensable, form. In human pregnancy, the only fetal cells that both contact the maternal circulation and have the capacity to stimulate maternal lymphocyte responses against HLA antigenic differences inherited from the father are the extravillous trophoblasts (EVT) of the placenta. Like Atlantic cod, EVT express a variety of forms of HLA class I but do not express HLA class II at all [5, 6]. Consequently, this review will concentrate on MHC class I.

The co-ordinated emergence of HLA-C and NK cells in immunological research

The *HLA* region contains six functional class I genes (*HLA-A*,-*B*,-*C*, -*E*, -*F*, and -*G*,) all of which are present on all *HLA* haplotypes (that is, they are fixed genes) (Figure 1). *HLA-E*, -*F*, and –*G* are conserved in the human species and resisted discovery until the late 1980s, when systematic genomic analysis was first used to characterize the class I genes and pseudogenes of the *HLA* complex [7, 8]. Being highly polymorphic, the *HLA-A*, -*B*, and –*C* genes were susceptible to detection by the alloantisera obtained from multiparous women. More variable and immunogenic than HLA-C, the HLA-A and HLA-B antigens were first uncovered. Throughout the 1960s an ever-increasing number of HLA-A and –B antigens were serologically detected, defined and named [9], a progression facilitated by the initiation of the International Histocompatibility Workshops, a series of HLA-based immunogenetics meetings that continues to the present day [10] (Figure 1). The 16th International Histocompatibility Workshop and Conference will be held at Liverpool, England in 2012 [11].

Not until the 1970s did evidence for HLA-C antigens as a third highly polymorphic locus begin to emerge. The discoverer of HLA-C was Erik Thorsby, then a young Norwegian clinician scientist working for his PhD, who studied and collaborated with Flemming Kissmeyer-Nielsen in Aarhus, Denmark [12] before returning to make his name in Oslo [13]. (Although now officially retired from being Professor of Immunology at the University and Chairman of the Institute of Immunology at the Rikshospitalet, Thorsby remains internationally very active in HLA immunogenetics.) Despite the strength of Thorsby's data and his advocacy for the locus, *HLA-C* remained a cinderella throughout the 1970s and 1980s, overshadowed by its sister loci: *HLA-A* and –*B*. That was an era when the presentation of peptides to killer CD8 T cells was considered the exclusive function of polymorphic HLA class I. Pushing HLA-C slowly towards the limelight were observations in the 1990s that HLA-C influenced the alloreactive response of the natural killer (NK) cell [14, 15], a type of lymphocyte that, in common with HLA-C, had been in the shadow of two meretricious siblings, the gene-rearranging B cells and T cells. Compounding interest in

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HLA-C, among leukemia patients receiving a bone-marrow transplant from an HLA haploidentical family member (a contrived clinical situation resembling that of physiological pregnancy) certain HLA-C mismatches stimulated alloreactive NK cell responses that correlated with protection from leukemic relapse [16, 17].

NK cells, long visualized by morphologists as the large granular lymphocytes of healthy blood [18], are distinguished by functional activities, notably antibody-dependent cellular cytotoxicity (ADCC), that were first observed by immunologists in the 1960s [19] and increasingly became chosen as a topic for investigation in the 1970s [20–22]. NK cells were often encountered as the annoying source of a high, 'non-specific', background killing in cytotoxic assays of T-cell function. Unlike T cells, NK cells did not require several days of stimulation in culture in order to become competent at killing target cells. They were named natural killer cells because when isolated from blood or tissue they had a natural ability to kill certain tumor target cell lines. A further, and critical, defining characteristic of NK cells was their propensity to kill cells having abnormally low levels of HLA class I on their surfaces: the extent of killing being inversely correlated with the amount of cell-surface MHC class I [23–25]. Because NK cells responded to the loss of self MHC class I (a frequent consequence of viral infection and malignant transformation) Karre and colleagues envisaged NK cells as recognizing 'missing self' [26]. The molecular basis for this correlation was found to lie with inhibitory NK cell receptors that recognize MHC class I and prevent NK cell attack (Figure 2). Three types of human inhibitory NK cell receptor recognize different features of HLA class I. A highly conserved interaction is that between HLA-E and CD94:NKG2A [27]. Also conserved is LILRB1, which binds a determinant (epitope) carried by a wide-range of HLA class I forms. However, LILRB1 has strongest avidity for HLA-G [28], which among healthy human cells is expressed only by extra-villous trophoblast [29]. Binding to polymorphic determinants of HLA-A, B and C are the killer cell immunoglobulin-like receptors (KIR) that contribute to the immunogenetics of human placentation [30].

Evolution of HLA class I recognition by Killer cell immunoglobulin-like receptors

Human killer cell immunoglobulin-like receptors (KIR) are encoded by a variable and polymorphic family of up to 15 genes in the leukocyte-receptor complex on human chromosome 19 [31]. Population studies demonstrate that variation in *KIR* gene-content, combined with extensive polymorphism for some of the genes (Table I), for example *KIR3DL1/S1* [32, 33], make human *KIR* variability comparable to that of *HLA*. Beside the genes encoding inhibitory KIR anticipated from missing-self recognition, the locus was found to harbor an unanticipated cohort of genes encoding activating KIR. According to their content of inhibitory and activating *KIR* genes, distinctive group *A* and group *B KIR* haplotype groups were defined [34] and refined [35] (Figure 3). From species comparisons, the *KIR* gene family is now clearly seen to be highly diverse, rapidly evolving [36, 37], extensively species-specific, and to have originated from one *KIR* gene in an ancestral simian primate [38]. The vast majority of mammalian species, including prosimians and rodents, do not have NK cell receptors corresponding to the human KIR. Whereas placental reproduction evolved >160 million years ago [39], the system of KIR that is now central to the immunogenetic modulation of placentation in humans and other simian primates, although the latter needs incisive investigation, is from an evolutionary perspective recently elaborated during the last ~85 million years [40].

Targets for KIR recognition are limited to just four HLA class I epitopes (A3/11, Bw4, C1 and C2) that centre on the helix of the α_1 domain and involve residues 78–83. These four epitopes appear to be mutually exclusive variations on a structural theme, in that no HLA

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class I molecule can carry more than one of them [41]. Thus individual HLA-A, B, C allotypes carry either one of these epitopes or none of them (Figure 4). Carrying the A3/11 epitope is a small minority of HLA-A allotypes, whilst the Bw4 epitope is carried by a larger minority of HLA-A and HLA-B allotypes, such that ~50% of *HLA* haplotypes furnish a Bw4 ligand, another example of balancing selection [32]. Consequently the majority of HLA-A and HLA-B allotypes do not function as ligands for KIR, meaning they can give dedicated service to the demands of T-cell immunity. In contrast every HLA-C allotype has either the C1 or C2 epitope and functions as a KIR ligand. This is but one of several lines of evidence indicating that HLA-C evolved specifically to provide KIR ligands. Consistent with this proposition, all human individuals have at least C1 or C2, whereas a substantial fraction of individuals lack both A3/11 and Bw4.

HLA-B*73 and HLA-B*46 are two unusual HLA-B allotypes that carry the C1 epitope and are ligands for C1-specific KIR [41, 42]. Consistent with the epitope exclusion principle, neither HLA-B*73 nor HLA-B*46 carries the Bw4 epitope, a feature of around one third of HLA-B allotypes. *HLA-B*73* has an exceptionally divergent sequence, a very strong linkage-disequilibrium with *HLA-C*15:05*, and is most common in western Asia. These properties are consistent with *HLA-B*73* having entered the modern human population as a consequence of meeting and mating with archaic humans who were already living in western Asia during the migration out of Africa some 65 thousand years ago [43]. Neanderthal and Denisovan *HLA* genotypes suggest this phenomenon of adaptive introgression of archaic *HLA class I* alleles has had a major influence on the *HLA* system of today's European, Asian and Melanesian populations [43]. *HLA-B*46* is restricted to south-east Asia where frequencies of up to 25% suggest it has been strongly selected. Unlike *HLA-B*73:01* the sequence of *HLA-B*46* is not divergent and could have arisen de novo by recombination and mutation in the 'modern' human population of south-east Asia [44]. However, it is also possible that the emergence of *HLA-B*46* was a consequence of adaptive introgression. For both HLA-B*73 and HLA-B*46 their shared functional property, which may have conferred their selective advantage over other HLA-B allotypes, is the capacity of their C1 epitopes to influence NK cell biology.

In comparisons of human HLA class I to MHC class I of other primate species, we will use the terms MHC-A, MHC-B, and MHC-C to describe the orthologs of HLA-A, HLA-B, and HLA-C, respectively. Such comparison shows that MHC-C emerged more recently than MHC-A or -B, being present only in great apes and humans. By contrast, counterparts of HLA-A and HLA-B are also present in Old World monkeys [38, 45], and in considerable abundance [46, 47]. MHC-C likely evolved from an MHC-B like ancestor, which diverged under natural selection to become a superior ligand for KIR [44, 48]. The focus for this divergence was the α_1 helix [49], a major site of contact between KIR and HLA-C [50]. Corresponding with this specialization of MHC-C is the change from using lineage II KIR with three Ig-like domains (D0, D1, and D2) to recognize epitopes of MHC-A and MHC-B to the use of lineage III KIR with two Ig-like domains (D1 and D2) to recognize epitopes of MHC-C. Although the human lineage III KIR do not have a D0 domain, their genes preserve an exon 3 which once encoded this domain, but became inactivated and in various different ways [51]. In contrast to the human situation, some of the chimpanzee lineage III KIR that recognize C1 or C2 retain a D0 domain. Our experiments to remove these D0 domains by mutagenesis had no detectable effect on the avidity and specificity for MHC-C [52].

The MHC-B like ancestor of MHC-C is predicted to have carried the C1 epitope [44], consistent with all orangutan MHC-C allotypes carrying C1 [53]. Evolution of C2 from C1, by replacement of asparagine 80 with lysine, occurred in the common ancestor of human, chimpanzee and gorilla, after separation from the orangutan line. Comparison of the human and chimpanzee KIR/MHC systems revealed substantial differences. In humans the C1 and

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C2 epitopes are almost completely restricted to HLA-C, but in chimpanzee the C1 epitope is also carried by around one quarter of Patr-B allotypes (the chimpanzee ortholog to HLA-B). Although both species have a similar number of *KIR* genes, with a majority being lineage III KIR that recognize C1 or C2, the chimpanzee receptors are functionally more potent than their human counterparts [44, 54] (Figure 5). Notably, several of the human lineage III activating KIR (KIR2DS2, 2DS3 and 2DS5) have been under selection to reduce or lose their capacity to recognize HLA class I, as is also the case for lineage II KIR3DS1. These attenuated KIR are characteristic of the human group *B KIR* haplotypes and define their main differences from the group *A* haplotypes. Overall the chimpanzee *KIR* haplotypes are closer to human *A* haplotypes, whereas the *B* haplotypes are uniquely human (Figure 5). In addition to these qualitative differences, the alleles of other *KIR* that are associated with *B* haplotypes tend to be weaker than those associated with *A* haplotypes. For example, KIR2DL1*004, associated with *B* haplotypes, is a weaker receptor than KIR2DL1*003 associated with *A* haplotypes [55, 56]. This comparison indicates that the progressive evolution in hominoids of a system of potent MHC-C receptors, reaches its peak in the chimpanzee and has reversed in human evolution, where balance and compromise between potent *A* haplotypes and attenuated *B* haplotypes is now evident.

Uterine NK cells and placentation

During embryo implantation and placentation, fetal extra-villous trophoblast (EVT) invades the uterine decidua and the inner myometrium with consequent remodeling of the spiral arteries into wider vessels that can better supply the placenta with blood. Among pregnancies there is natural variation in the depth and extent of invasion, which at the extremes of the normal distribution is correlated with a variety of pregnancy complications or disorders. Implicated in control of these processes are the distinctive uterine NK cells (uNK) that populate the decidua and which have phenotype and functional properties that distinguish them from peripheral blood NK cells. EVT, the only HLA class I expressing fetal cells that make direct contact with the maternal circulation and can interact directly with uNK, have a unique combination of HLA class I proteins on the cell surface: HLA-C, HLA-E and HLA-G. All three are ligands for NK cell receptors, but it is the interactions between HLA-C and lineage III KIR that have the greatest immunogenetic potential to vary the co-operation between EVT and uNK and ultimately the course of pregnancy. Consistent with this analysis, uNK cell populations have a bias, not seen for peripheral blood NK cells, towards expression of the lineage III KIR that recognize HLA-C [57, 58].

In a series of epidemiological studies [59–63], Moffett and colleagues have shown that susceptibility to several disorders of implantation (pre-eclampsia, recurrent abortion, and fetal growth restriction) is associated with the same genetic combination of a mother who is homozygous for group *A KIR* haplotypes and a baby who carries the C2 epitope, particularly if the C2 is paternally inherited and absent from the mother. The negative impact of this combination is reflected in the relative frequencies of the *KIR A* haplotype and the C2 epitope in human populations worldwide (Figure 6). They are inversely correlated, pointing to the strong selective pressure exerted by the consequences of implantation disorders: recurrent abortion represents a failure to reproduce, pre-eclampsia can kill both mother and child, and fetal growth deficit produces less competitive offspring. Although the inverse correlation appears to be universal the frequencies of group *A KIR* haplotype and C2 epitopes varies between populations. At the extremes are the Japanese, who have high *KIR A* and low C2 frequencies, and aboriginal Australians who have high *KIR B* and high C2 frequencies.

The principal NK cell receptors that recognize the C2 epitope are inhibitory KIR2DL1 and activating KIR2DS1. *KIR2DL1* is a fixed gene of *KIR A* haplotypes, while *KIR2DS1* is

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only present on *KIR B* haplotypes. Thus implantation disorders are associated with C2 on EVT interacting with KIR2DL1 on uNK cells to cause delivery of a strong inhibitory signal to the NK cells. This suggests a model in which inhibition of the NK cells causes insufficient invasion of the decidua by the EVT and insufficient remodelling of the spiral arteries. As implantation disorders are associated with *KIR A* homozygosity, a maternal *KIR B* haplotype can provide dominant protection against implantation disorder. Whereas all *KIR A* haplotypes have a fixed gene content, the *B* haplotypes exhibit gene content variability (Figure 3). Some *B* haplotypes have inhibitory *KIR2DL1* in combination with activating *KIR2DS1*. The presence of *KIR2DS1* reduces the likelihood of C2-mediated pregnancy disorder, indicating that interaction of KIR2DS1 with C2 on EVT transduces activating signals to NK cells that serve to counterbalance the inhibitory signals generated by C2 interactions with KIR2DL1 [59, 61]. Another type of *KIR B* haplotype, which has *KIR2DS1* in the absence of *KIR2DL1*, might be expected to favor reproductive success. That this *B* haplotype has an unusually high frequency of 47% in Yucpa Amerindians (Figure 7A), a population that has survived successive disease epidemics and population bottlenecks while retaining *HLA* (Figure 7B) and *KIR* (Figure 7C) diversity, is consistent with this thesis [64]. It will be important to dissect out the influence of this *2DL1-negative B* haplotype in future epidemiological studies of pregnancy disorders. Such analysis will, however, require improvements in the typing and assignment of *KIR* haplotypes combined with larger study cohorts than has been achieved to date.

In addition to the presence or absence of the *KIR2DL1* and *KIR2DS1* genes on *KIR* haplotypes, a further dimension to the variation is provided by allelic polymorphism, particularly for *KIR2DL1*. In many populations the common allotype, KIR2DL1*003, is both strong and highly specific. In contrast, KIR2DL1*004, that is associated with *B* haplotypes, has one substitution in the transmembrane that weakens the signal transduction [55] and others in the extracellular D2 domain that reduces the strength of its binding to C2 (unpublished data). Thus the presence of this weaker form of KIR2DL1 on some *B* haplotypes may also contribute to the protection they offer against implantation disorders. We are currently comparing the strength and specificity of the ~20 different KIR2DL1 variants that have been defined to date. Polymorphism in the diverse set of HLA-C allotypes that carry the C2 epitope is also likely to be a factor that further diversifies the interaction of KIR2DL1 and KIR2DS1 with C2. The quantitative binding assay that we have used to assess the strength and specificity of KIR for HLA class I shows there is reproducible variation in the binding of the same KIR2DL1 allotype to different C2 bearing HLA-C [42]. We hypothesize, that such differences arise from the different spectra of peptides that are bound to each HLA-C allotype and the extent to which they are permissive for KIR2DL1 binding.

Concluding remarks

Although Medawar's analysis of immunological aspects to the feto-maternal relationship remains widely cited by reproductive immunologists [65, 66], his assessment of MHC polymorphism and challenge to the emerging field of immunogenetics has proved less of a touchstone. At the time of Medawar's discussion of '*Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates*' [2], nothing was known of the human HLA system. In contrast, for inbred laboratory mice considerable knowledge of an extensive system of MHC class I alloantigens had been acquired through using sera obtained from inter-strain immunizations and serological assays of red-cell agglutination (mouse MHC class I being detectable on red cells), as well as genetic analysis of experimental transplantation [1, 3]. The complexity of these immunogenetic data, combined with their lack of any plausible physiological foundation, induced a bafflement in all but the most broad-minded of non experts that cannot be exaggerated, and continued for

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another twenty years, well into the 1970s. This is aptly captured by the following two quotes from Medawar [2]:

> "It is an interesting fact that the only known consequences of this antigenic diversity are wholly harmful. By 'antigenic diversity' I must be understood to mean antigenic diversity as such. If chemistry were a less backward science, all the differences that we are now obliged to recognize as antigenic differences would be chemically defined, and the agglutination tube would be dispossessed of its functions by the ordinary test-tube."

> "Although there are no factual grounds for supposing that antigenic diversity is anything but an unfortunate consequence of constitutional differences between the individuals of a species, yet one is under some obligation to rack one's brains for evidences of any good it might conceivably do. Only thus can antigenic polymorphism be made genetically respectable"

Although papers and lectures on MHC polymorphism are still reliably capable of baffling their readers and listeners, the 58 years of research since Medawar's challenge has without doubt given the antigenic diversity of highly polymorphic MHC class I molecules, chemical, genetic, and functional respectability. One proof of this pudding being that 'antigenic diversity of MHC' is a phrase no longer used. Essential to this achievement has been the comparison, genotypically, of very many humans with very few mice, members of two species who differ significantly, not only in the nature of their MHC class I molecules, but also in the methods and philosophy investigators have used to study them [67, 68]. Further proof is the individuality that HLA and KIR impose on human immune systems and the reliability with which these polymorphisms are most strongly associated with an extraordinarily wide range of human disease. Following in the twentieth century footsteps of HLA a series of international KIR workshops was initiated in this twenty-first century [69].

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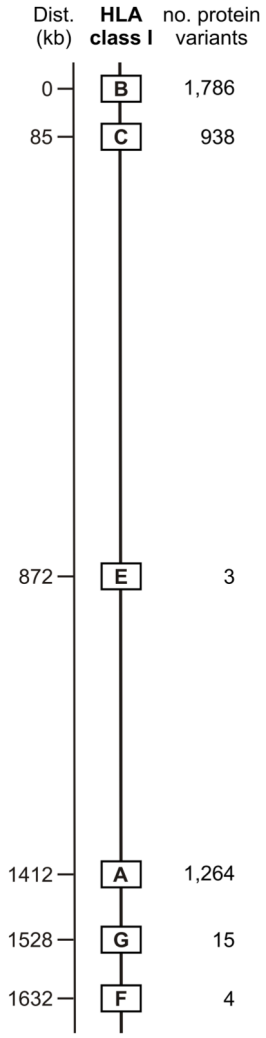

Figure 1.

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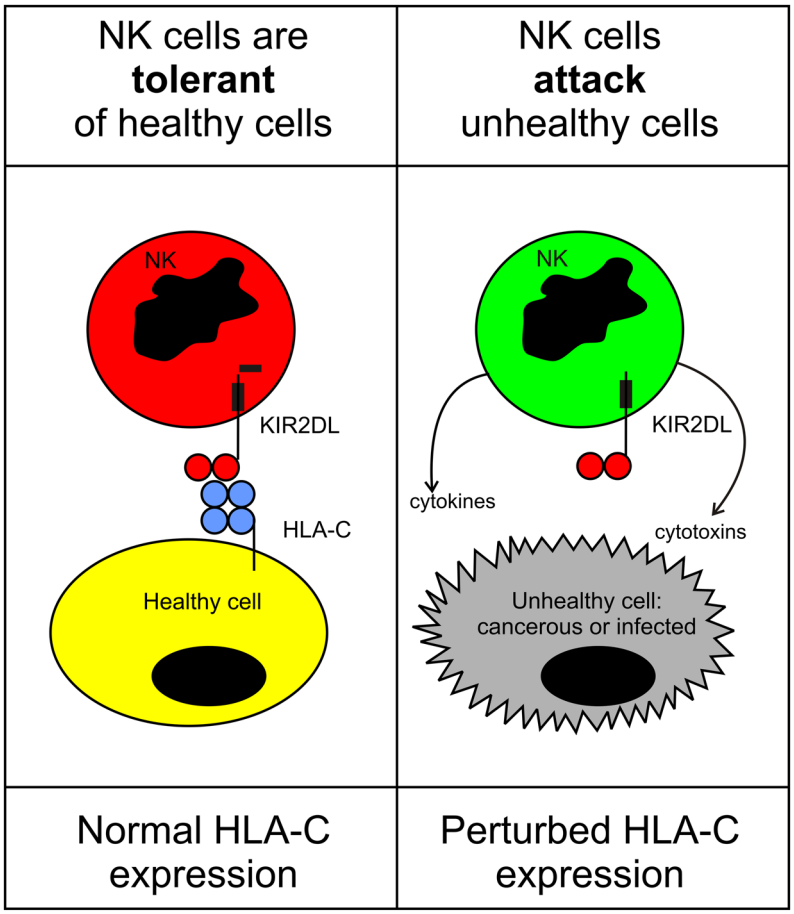

Figure 2.

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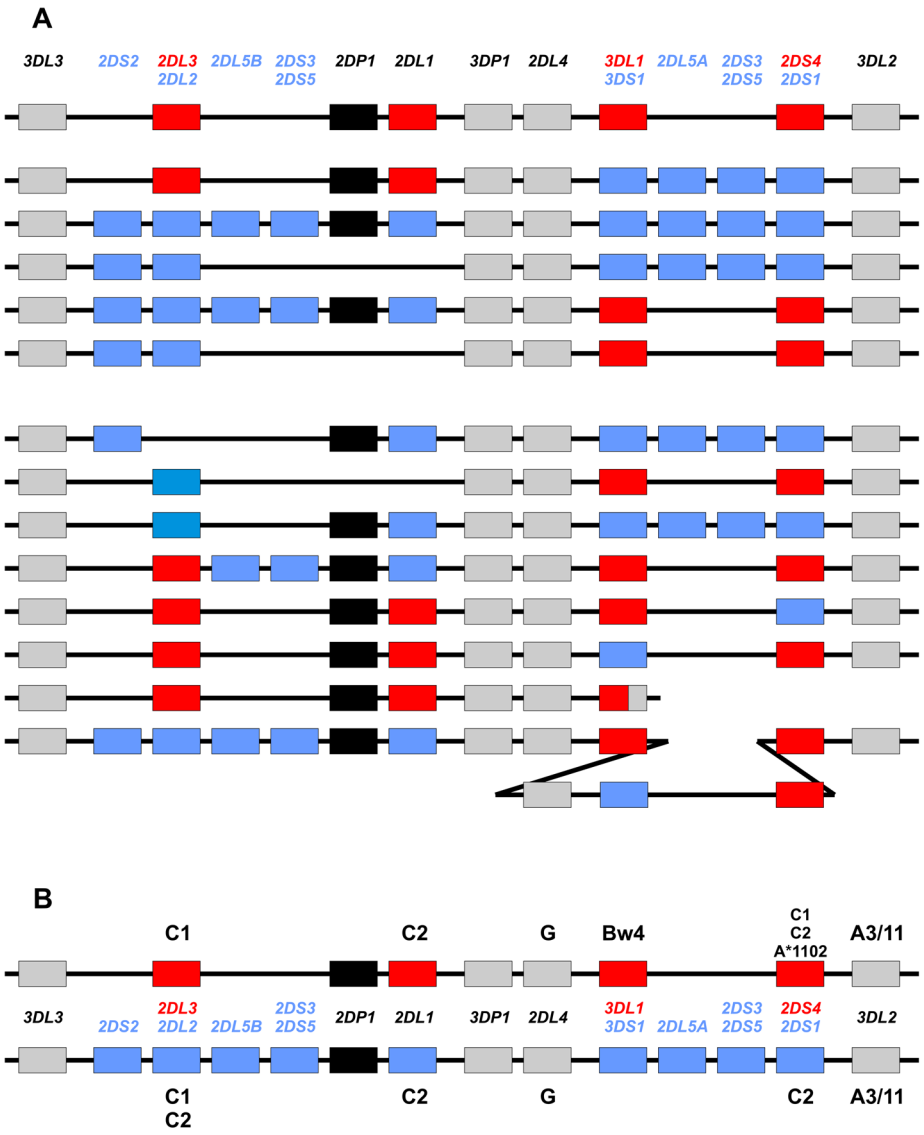

Figure 3.

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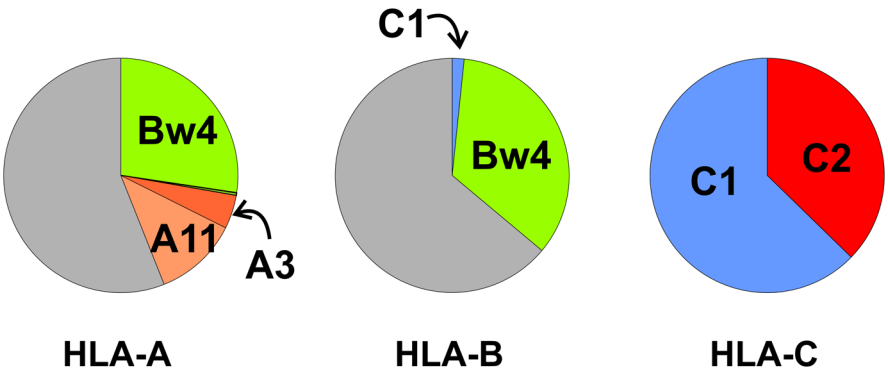

Figure 4.

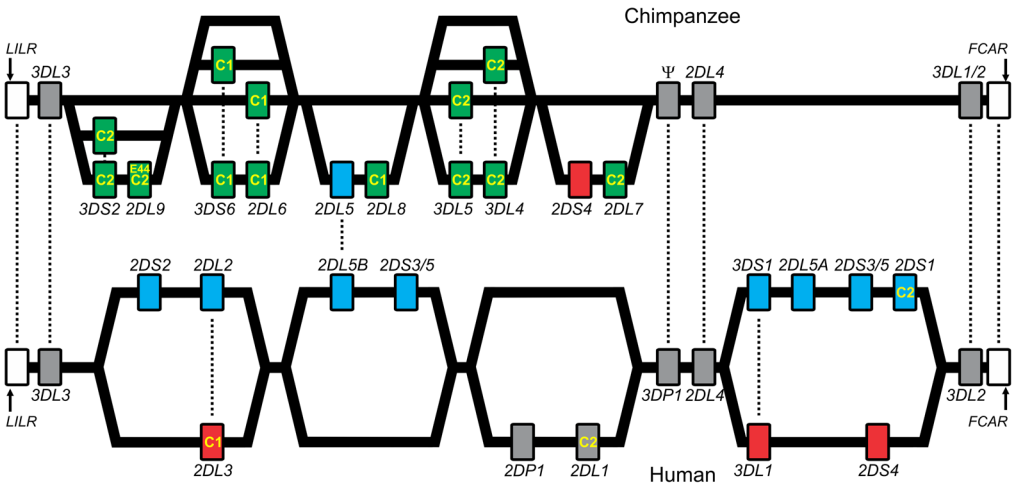

Figure 5.

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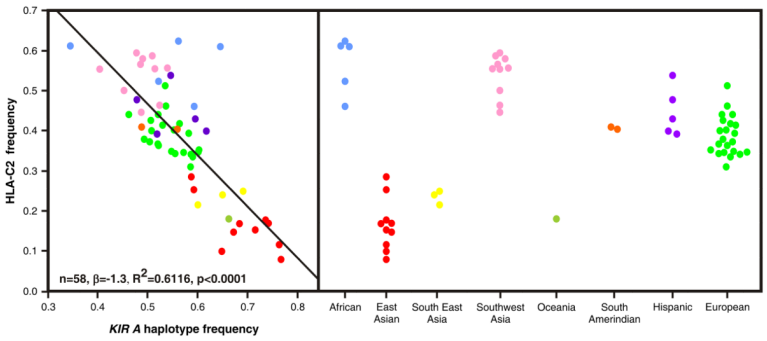

Figure 6.

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A

B

HLA Allele Frequencies

Locus	Allele	KIR ligand	Freq. (%)
HLA-A	*68:01		46.7
	*02:04		27.8
	*02:12		0.8
	*02:13		0.8
	*24:02	Bw4	17.2
	*31:01		6.5
HLA-B	*39:03		41.8
	*39:05		34.4
	*52:01	Bw4	9.8
	*35:12		7.4
	*35:43		1.6
	*40:02		4.1
	*40:04		0.8
HLA-C	*07:02	C1	79.2
	*15:03	C2	9.8
	*04:01	C2	7.4
	*03:02	C1	4.1
	*03:04	C1	0.8
	*01:02	C1	1.6

C

KIR Allele Frequencies

Centromeric			Telomeric		
Locus	Allele	Freq. (%)	Locus	Allele	Freq. (%)
3DL3	*00301	49.1	*2DL4*	*005	51.6
	*01002	26.2		*001	43.4
	*00901	16.4		*011	4.9
	*00802	7.4	*3DL1/S1*	*013	51.6
	*00402	0.8		*029	22.1
2DS2	*001	49.9		*01502	21.3
2DL2	*003	49.9		*005	4.9
2DL3	*009	37.4	*2DL5A*	*001	51.6
	*008N	7.4	*2DS5*	*002	51.6
	*001	8.2	*2DS1*	*002	51.6
2DP1	*00201	50	*2DS4*	*00101	43.4
2DL1	*003	50		*010	4.9
3DP1	*00302	50	*3DL2*	*007	51.6
	*007	49.9		*002	43.4
2DL5B		0		*010	4.9
2DS3		0			

Figure 7.

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Table I

KIR genes, number of encoded proteins, and HLA ligands. Number of encoded proteins from http://www.ebi.ac.uk/ipd/kir/stats.html accessed Oct. 2011.

KIR	No. protein variants	HLA class I ligands
2DL1	24	C2
2DL2	11	C1, C2
2DL3	17	C1
2DL4	22	G?
2DL5A	5	-
2DL5B	11	-
2DS1	7	C2
2DS2	8	-
2DS3	5	-
2DS4	13	A11, some C
2DS5	11	-
3DL1	58	Bw4
3DS1	12	-
3DL2	61	A3/11
3DL3	55	-
3DP1	0	O
2DP1	0	O