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Killer cell Immunoglobulin-like Receptors (KIRs) and hematopoietic stem cell transplantation outcomes. A review of the literature

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ABSTRACT

Natural killer (NK) cells are a type of cytotoxic lymphocytes that have an important role in innate immunity. These cells are equipped with a number of surface receptors, inhibitory, activating, or both, that control their activity. A major group of these regulatory receptors is called the Killer-cell Immunoglobulin-like Receptors (KIRs) which have been studied in numerous diseases. One of the most important aspects of KIR genotyping is its association with bone marrow transplantation outcomes; however, studies have not been conclusive in this regard. This is the first review article in the literature that reports on the association of KIR genotype with outcome of hematopoietic peripheral blood bone marrow stem cell transplantation using a four dimensional level of analysis based on the variable cellular interaction modalities of the KIR receptors: the ligand-ligand model, the missing-ligand model, the receptor-ligand model, and the haplotype model.

Contents

1. Introduction

Natural killer (NK) cells are a type of cytotoxic lymphocytes that have an important role in innate immunity; they act against both virally infected and tumor cells. NK cells are constitutionally cytotoxic due to the presence of cytoplasmic granules (containing *granzymes* and *perforin*) that lead to cell lysis or apoptosis. Usually, immune cells such as T cells recognize peptides presented by the Major Histocompatibility Class (MHC) molecules on the surface of infected or abnormal cells. NK cells, however, are unique in that they do not require this peptide presentation as part of their immune surveillance. They can recognize a cell as "self" and spare it by the presence of self-markers, namely MHC I molecules, which are present on all nucleated cells in our body; and thus whenever a cell is missing self-MHC I molecules ('missing-self hypothesis'), it is considered as an altered self and destroyed by

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NK cells (Hsu et al., 2002). This is of crucial importance since it implies that an abnormal cell missing self-MHC I, be it an infected cell, a neoplastic cell, or an auto-reactive cell, that cannot be detected by T cells, can otherwise be recognized and destroyed by NK cells. The latter also have the ability to interact with components of the adaptive immune system (T cells and dendritic cells) implying their involvement in variable diseases such as infectious, autoimmune diseases, and cancers.

There are a number of surface receptors, inhibitory, activating, or both, that control NK cell activity. A major group of these regulatory receptors is called the Killer-cell Immunoglobulin-like Receptors (KIRs). KIRs are present additionally on a subtype of T cells, the cytotoxic T cells (Khakoo and Carrington, 2006). Most KIRs are inhibitory (iKIRs), meaning that their recognition of certain MHC I molecules inhibits the cytotoxic response of NK cells. Fewer identified KIRs are activating (aKIRs), but their ligand specificities have not yet been well elucidated (Khakoo and Carrington, 2006). Activation occurs when the NK cell receives a signal from the aKIRs that recognize affected or tumor cells that lack the normal HLA structures on its surface membrane (Impola et al., 2014).

Though KIR has been studied in a wide variety of clinical entities, be it for a negative or positive association, this review article will be focusing on the role of KIRs and their ligands in allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for hematologic malignancies.

One may speculate that NK cell alloreactivity contributes to what is called the *Graft*-versus-*tumor effect* (GVT), since a mismatched ligand or a missing ligand for a particular iKIR, taken independently, would mean the absence of inhibitory signal for NK cell cytotoxicity. By that, the NK cell would destroy the tumor cell with the mismatched or missing ligand for its iKIR. Consequently, this would lead to lower relapse rate and increased survival after the transplant. However, one should bear in mind that the selection of a related or unrelated HSCT donor needs matching of MHC molecules, also called HLA (for Human Leukocyte Antigens), to minimize *Graft*-versus-*Host Disease* (GVHD). Furthermore, the picture is complicated by the substantial variation in gene content and expression, allelic polymorphism, and haplotypic diversity of KIR genes. The ultimate goal is to try and elucidate which KIR profiles maximize antitumor while minimizing anti-host effects.

This unique review article sheds light on the various genotypes and haplotypes profiles of KIR in what concerns hematopoietic stem cell transplantation (HSCT) outcomes from a perspective that covers the different theories of KIR receptors interactions.

1.1. KIR haplotypes

KIR molecules are encoded by the Leukocyte Receptor Complex (LRC) present on human chromosome 19 which is segregated independently from the HLA genes. LRC is polygenic and individual genes exhibit polymorphism where 17 KIR genes are officially recognized (Dorak, 2007).

Two broad families can be identified according to the number of extracellular domains (designated KIR2D and KIR3D for 2 and 3 extracellular domains respectively), and the length of cytoplasmic tails (*S* for short and *L* for long). Generally, KIRs with long cytoplasmic tails are inhibitory (KIR2DL and 3DL groups) while those with short cytoplasmic tails are activating (2DS and 3DS groups) (Hsu et al., 2002). KIR2DL4 is an exception in that despite having a long cytoplasmic tail, it has both inhibiting as well as activating functions and is also present on all haplotypes (Beksaç and Dalva, 2012).

Based on the gene content, there has been segregation of KIR haplotypes into two basic groups: haplotype A and B.

Haplotype A, which is the most common one, is usually inhibitory as it contains 6 inhibitory genes: KIR2DL1, KIR2DL3 (most characteristic), KIR3DL1, KIR3DL2, KIR3DL3 and KIR2DL4 and one activating gene: KIR2DS4. These genes are more frequently found in haplotype A than B but are not exclusive to it and also have a substantial allelic diversity (Dorak, 2007).

Haplotype B, on the other hand, has a very diverse gene content in addition to minor allelic diversity. It is mostly activating and has a variable number of activating KIRs (ranging from 2 to 7), and a similar number of inhibitory KIRs than haplotype A. Certain genes, however, occur exclusively on haplotype B such as: KIR2DS1, KIR2DS2-2DL2 (most characteristic), KIR2DS3, KIR2DS5, KIR2DL2, KIR2DL5 and KIR3DS1 (Dorak, 2007).

Regarding the ligands, KIRs generally interact with MHC class I molecules with the exception of KIR2DS4 that interacts with HLA-Cw4 as well as non-MHC ligands. The specificities for iKIRs have been clearly defined for certain receptors. For example, KIR2DL1 binds HLA-C2 group, KIR2DL2/3 binds HLA-C1 group, KIR3DL1 binds HLA-B-Bw4, KIR3DL2 binds HLA-A, and KIR2DL4 binds HLA-G. As for the aKIRs, the specificities have been harder to define. For instance, KIR2DS1, 2DS2, and 3DS have the same ligands as KIR2DL1, 2DL2/3 and 3DL1, respectively, but bind weakly to them. Other KIRs have no known ligands yet (Khakoo and Carrington, 2006). Moreover, NK alloreactivity has been grouped into four models: The *KIR-ligand incompatibility* or *ligand-ligand model*, the *receptor-ligand model*, the *haplotype model* (*receptor-receptor* or *KIR gene-gene model*), and the *missing ligand* model (Beksaç and Dalva, 2012). However, the *receptor-ligand model* was not addressed in this manuscript due to the minute amount of data in the literature; further research should be done in order to account for it in such a review article. Table 1 summarizes the different authors' studies under model type and outcome.

The balance of inhibitory and activating KIRs determines the susceptibility or the protection against certain diseases such as viral infections, auto-immune diseases, and neoplastic transformations.

KIRs have been shown to play a role in HIV infection where individuals having the KIR3DS1 gene and homozygous for the HLA-B-Bw4 gene had a slower decline in CD4+ T-cell count, a marker of disease progression in HIV infected patients (Khakoo and Carrington, 2006). A similar protective role of KIR3DS1 and HLA-B-Bw4 was found in HCV infection and there was an additional increased frequency of KIR2DL3 in combination with HLA-C1 in patients who cleared of HCV infection compared to those who remained chronically infected (Khakoo and Carrington, 2006). KIR was also associated with the autoimmune disease rheumatoid arthritis as there was an expansion of CD4+ CD28− T cells expressing the aKIR, KIR2DS2, in the absence of the corresponding iKIR in the peripheral blood of patients with rheumatoid arthritis. Additionally, in diabetes mellitus, an association, albeit weak, was found between KIR2DS2 and HLA-C1 group (Khakoo and Carrington, 2006).

The activity of NK cells against malignant cells has been known for a long time; however, it was only in the late 90s that the impact of KIR ligands on allogeneic HSCT was studied (Beksaç and Dalva, 2012). After an allogeneic HSCT, an NK cell receptor repertoire became established according to the KIR genes of the donor cells. NK cells can then contribute to GVT effect, as first demonstrated in T cell depleted haploidentical HSCT where this was shown to depend on *KIR ligand mismatch*. The contribution of *KIR ligand mismatch* to NK cell alloreactivity in unrelated HSCT was confirmed in some subsequent studies, but not in others (Clausen et al., 2010). In the setting of HLA-identical HSCT, however, NK cell alloreactivity must be explained by a mechanism other than *KIR ligand mismatch*, most likely by the *missing ligand* model (Beksaç and Dalva, 2012). In the latter model, NK cells may become uninhibited in the early post-transplant period, thus lysing target recipient cells for which corresponding ligands are absent (Bao et al., 2010a, 2010b). A hypothesis was built afterwards suggesting that allogeneic HSCT selected for lack of recipient HLA ligands for donor iKIRs would allow the development of alloreactive donor NK cells that could kill host tumor (GVT), because of the triggering effect of aKIR. Without an impedance by the iKIRs, binding of the aKIRs to their ligands would result in NK cell stimulation. The presence of more aKIR genes in donors further confirmed this as it was associated with a lower TRM and a better survival. However, this NK reactivity may also have a negative effect on outcome by