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Recurrent Spontaneous Abortion (RSA) and Maternal *KIR* Genes: A Comprehensive Meta-Analysis

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ABSTRACT

Natural killer cells (NKs) are the most important cells in the fetomaternal immune tolerance induced through interaction of maternal killer-cell immunoglobulin-like receptors (KIR) and fetal human leucocyte antigens (HLA). Hence, we intend to perform a meta-analysis on the role of maternal *KIR* genes diversity in recurrent spontaneous abortion (RSA). The present paper is a meta-analysis of previous genetic association studies and our previous original study. The results showed that *KIR3DL1* was a significantly protecting factor for RSA (p=0.044; OR=0.833 [0.698-0.995]; fixed effect model). *KIR2DS2* (p=0.034; OR=1.195 [1.013-1.408]; fixed effect model) and *KIR2DS3* (p=0.013; OR=1.246 [1.047-1.483]; fixed effect model) were significantly risk factors for RSA. For *KIR2DS1* there was a high heterogeneity and publication bias. Briefly, the inhibitory gene *KIR3DL1* was a protecting factor, and the activating genes *KIR2DS2* and *KIR2DS3* were risk factors for RSA. However, the effect sizes were not suitable. We suggest further studies on different causes of pregnancy loss, to find the role of *KIR2DS1*.

Keywords: recurrent spontaneous abortion, killer-cell im-munoglobulin-like receptor, human leukocyte antigen, me-ta-analysis

INTRODUCTION

Rationale

Recurrent spontaneous abortion (RSA) and pregnancy loss have different pathogeneses, consisting of genetic and chromosomal abnormalities (Hume & Chasen, 2015), environmental toxicities and oxidative stress (Gupta *et al*., 2007), infectious agents (Ambühl *et al*., 2016), hormonal causes, etc. Among them, immunological causes and their involving molecules are still controversial and unknown topics. The immune system is a fascinating system, one that does not normally reject the semi-allograft fetus. The immune system has two roles in implantation and pregnancy; preventing the formation of abnormal embryos, and protecting the fetomaternal interaction by releasing angiogenic factors, cytokines and adhesive molecules. The fascinating point is how a system can have two mutually exclusive features; protection and rejection. Indeed, the immune system is the bodyguard of the body through self- and non-self recognition. However, pregnancy is a semi-allograft transplantation. So the question is what the im-mune system does in this situation; rejection or protection (Akbari *et al*., 2018; Würfel, 2016)?!

Immune tolerance is the best answer for the above question (Akbari *et al*., 2018; Würfel, 2016). Natural killer cells (NKs), which name is self-explanatory, are one of the most important lymphocytes in immune tol-erance. They identify self-cells through their killer-cell immunoglobulin-like receptors (KIRs) expressed on their surface. The KIRs interact with their ligands, the human leukocyte antigens (HLAs) - the identification cards of self-cells. These interactions usually result in immune tolerance under normal conditions. Both *KIR* and *HLA* genes in human genome have loci (not locus), inherited as haplotypes. In addition, each gene in their loci is polymorphic. Thus, interaction of different KIR molecules with different HLA molecules results in dif-ferent outcomes consisting of inhibitory and activating responses. *KIR* gene cluster is located on chromosome 19. This cluster has two types of genes, including 8 inhibitory and 6 activating genes, and 2 pseudogenes. Some of these genes exist in all individuals, like the *KIR2DL4*. From the viewpoint of medical anthropology, different people from different ethnicities have different KIR-HLA interactions (Alecsandru *et al*., 2014; Ashou-ri *et al*., 2016; Middleton *et al*., 2008; Norman *et al*., 2016; Solgi *et al*., 2011).

HLA has two classes, I and II, and the class I can be further divided into classical and non-classical HLA. KIR2DL4 is an inhibitory KIR binding to the trophoblast HLA-G, which is a non-classical HLA. The combination KIR2DL4+HLA-G triggers the immune tolerance. Both *KIR2DL4* and *HLA-G* are polymorphic genes. Therefore, anthropological variations can contribute to implanta-tion success and pregnancy maintenance. For example, HLA-G*01:03:01 is a risk factor for implantation failure; because its connection with KIR2DL4 is not sufficient to trigger inhibitory signals (Nardi et al., 2012).

NKs may have the CD16 marker, which is the weapon of antibody-depended cell-mediated cytotoxicity (ADCC). Usually $CD56_{dim}$ NKs are $CD16_{+}$. So $CD16_{+}CD56_{dim}$ NKs are known as cytotoxic NKs, whereas $CD16^{-}CD56_{bright}$ NKs are known as immune-regulatory NKs (Ghafouri-an *et al*., 2015). About 90% of uterine NKs (UNKs) are immune-regulatory. In conclusion, UNKs are not usu-ally cytotoxic for the embryo (Ghafourian et al., 2015; Sacks, 2015).

Objectives

As we mentioned above, KIR and HLA have different genes and interactions. KIR has 8 inhibitory (*2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 3DL1, 3DL2* and *3DL3*) and 6 activating