LETTER

Uterine selection for immunocompetent offspring

Classic MHC molecules present short peptides at the cell surface and play a key role in the recognition of self or nonself antigens. One of the exceptional properties of the MHC is its polymorphism, expressed at the population level in a vast number of alleles and at the sequence level in excessive allele divergence (1). Each MHC molecule binds a specific range of antigens, and heterozygote advantage (i.e., increased surveillance against invading pathogens due to an optimal level of MHC diversity) is proposed as one of the main mechanisms for the maintenance of this polymorphism. In this light, the recently reported MHC-dependent maternal–fetal immune interactions in mice by Madeja et al. (2) provide the potential basis for an intriguing mechanism for the selection of genetically diverse offspring. Their work showed that dilation of uterine vessels and thus blood supply for the fetus is dependent on the combination of paternal and maternal MHC class I genotypes. Using a sophisticated crossing of mouse lines with known MHC alleles, they showed that particularly the MHC class I H2-K genotype explained a substantial part of the effect. However, the beneficial outcome was not balanced and only occurred for fetuses with the paternal H2-K^b genotype in a maternal H2-K^d mother's uterus.

If this effect is the result of a naturally evolved mechanism, offspring with an H2-K^b genotype must have an advantage and thus provide increased fitness to the H2-K^d mother. The increased blood supply indeed translated directly into fetal growth and has therefore a significant effect on fitness (2). An intuitive explanation for the observation would be heterozygote advantage (3), but then also the H2-K^b uterus should provide increased blood supply to H2-K–dissimilar offspring. Because this was not observed, there must be something particular about the H2-K^b fetus in the H2-K^d maternal uterus. Here I propose that the interaction between Ly49C receptors on maternal uterine natural killer (uNK) cells and self-peptide–presenting MHC H2-K molecules on fetal trophoblasts provides a molecular mechanism to estimate the quantitative dissimilarity between maternal and paternal H2-K genotypes. Resources are then allocated accordingly, to provide most nutrition to the offspring with the most promising immune repertoire.

Using computational peptide binding prediction (4, 5), I show that the H2-K^d molecule indeed seems to bind and consequently present less different self-peptides than the H2-K^b molecule (Fig. 1). Hence, the H2-K^d–presented fetal peptides may trigger a weaker activation of uNK cells in a maternal H2-K^b background than in the reverse case. In addition to avoiding homozygous offspring, such a mechanism would also lead to offspring MHC genotypes of optimal sequence divergence and potentially to enhanced pathogen recognition (5). This effect would explain the puzzling unbalanced result of Madeja et al. (2) and represents a unique molecular mechanism for the maintenance of an optimal MHC polymorphism.

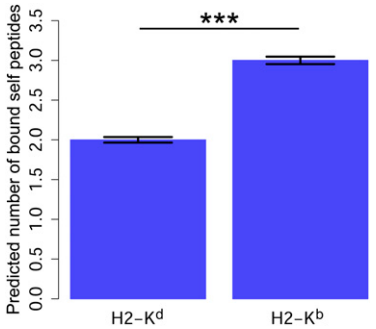

Fig. 1. Self-antigens presented by MHC class I H2-K^d and H2-K^b molecules. Median number of bound peptides per self-protein as predicted by the peptide-binding prediction server NetMHCpan (4). Predictions for both MHC class I molecules are made on all known protein-coding genes of the mouse genome (Ensembl release 61, Biomart database, Mus musculus NCBIM37 assembly, 20,166 proteins). Overlapping peptides between MHC alleles are removed, and both groups are cleaned of outliers, resulting in 18,118 proteins. Wilcoxon signed rank test, $W = 70{,}025{,}101$; $P < 0.001$. Error bars represent 95% confidence intervals.

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