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Endogenous Retroviruses and the Pregnancy Compensation Hypothesis: A Reply to David

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Mr M. David responded to our recent article in which we introduce the Pregnancy Compensation Hypothesis. Mr David writes to bring up the role of endogenous retroviruses (ERVs) in the evolution of placentation. While the mechanistic evolution of the machinery to build the placenta as an organ was out of the scope of our original article, we agree that the role of ERVs in evolution of the placenta and immune modulation is an interesting subject that may provide useful insights into the evolutionary mechanisms contributing to sex differences in gene expression, immune functions, and disease prevalence.

The function of ERVs as regulators of gene expression is well established. Recent studies have mapped ERV insertions associated with complex phenotypes, in particular, neurologic and immunologic diseases [1]. Notably, an ERV HERV-Fc1 in the X chromosome has been linked with multiple sclerosis [2], The accumulation of ERVs in the sex chromosomes may contribute to sex-specific gene expression and sex biases in complex phenotypes.

ERVs have accumulated in unique ways on the X and Y chromosomes. ERVs appear to have a substantial role in the evolution of the Y chromosome: the Y chromosome and autosome 19 have accumulated more ERVsthan other chromosomes [3]. Additionally, Sin *et al.* (2010) discovered that copies of the human ERV HERV-K14C are disproportionately abundant in the Y chromosome, and transcripts of this ERV are exclusively expressed in the testis [4]. Phylogenetic analysis of the long terminal repeats of the HERV-K14C on the Y chromosome suggests a role of this ERV in the diversification of the Y chromosome during primate evolution. However, the role of these ERVs in regulating male-specific gene expression, particularly in the immune system, has not been extensively investigated.

Studies on nonhuman species indicate that ERV integration may have a role in sex-chromosome evolution and sex-biased gene expression across mammalian species. Canine ERVs predominantly reside in the X chromosome and may impact gene expression [5]. Furthermore, retrotransposons, such as LINE elements, are particularly abundant in the X chromosome and may have a substantial role in X chromosome inactivation [6,7]. Still, the

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overall impacts of ERV integration on immune gene expression across taxa, populations, and tissues remain unclear.

Overall, ERVs are important for understanding the evolution of the placenta, are nonrandomly distributed throughout the genome, may have a role in the evolution of sex chromosomes, and thus may contribute to sex differences in immune functions.

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