inflammation, and ERVs with preserved open reading frames may even generate inflammatory retroviral proteins.

Concern over ERV oncogenesis was a major feature of early ERV research, and paleovirology offers a model that may explain the role of ERVs in the limited cancer protection seen in females. ERV phylogenies distinguish between recently endogenized ERVs with oncogenic potential, and the more ancient ones which appear to be 'domesticated.' The 1500 ERVs from early anthropoid endogenization that are now integrated into p53 binding sites [7], and the antitumor activity of derepressed ERV dsRNA [12], suggest a protective role in intracellular monitoring of disruptive expression patterns in cancer. ERVs endogenized since the Pliocene or later, like some ERV-K lineages, are more likely to retain functional open reading frames, and are associated with cancers in both sexes (including breast, lung, skin, and prostate cancer), and by a shared nuclear receptor superfamily may also drive thyroid cancer.

While conservation of sex-differentiated gene expression appears to substantially predate the endogenization of retroviruses into the eutherian lineage, the reproductive and regulatory roles into which ERVs have been exapted in the human lineage appear to have set up the perfect storm for female-biased autoimmune disease. The ongoing process of exaptation continues to drive unique adaptive compromises that yield benefits for both ERV and host genes, and the timeline for this exaptation sheds light on strategies we may use in fighting autoimmune diseases and cancer. The research implications are far reaching, and the biomedical implications for direct intervention, including epigenetic pharmacology, ERV vaccines, and ERV-protein antibody therapy, are already beginning to yield promising results.

[1]Texas A&M University, College of Medicine, Bryan, TX 77807, USA

*Correspondence:
mattdavid@tamu.edu

https://doi.org/10.1016/j.tig.2019.10.008

© 2019 Elsevier Ltd. All rights reserved.

References

1. Natri, H. *et al.* (2019) The pregnancy pickle: evolved immune compensation due to pregnancy underlies sex differences in human diseases. *Trends Genet.* 35, 478–488
2. Khashan, A.S. *et al.* (2011) Pregnancy and the risk of autoimmune disease. *PLoS One* 6, e19658
3. Mi, S. *et al.* (2000) Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. *Nature* 403, 785–789
4. Frank, J.A. and Feschotte, C. (2017) Co-option of endogenous viral sequences for host cell function. *Curr. Opin. Virol.* 25, 81–89
5. Monde, K. *et al.* (2017) Molecular mechanisms by which HERV-K Gag interferes with HIV-1 Gag assembly andparticle infectivity. *Retrovirology* 14, 27
6. Wang, J. *et al.* (2014) Primate-specific endogenous retrovirus-driven transcription defines naive-like stem cells. *Nature* 516, 405–409
7. Wang, T. *et al.* (2007) Species-specific endogenous retroviruses shape the transcriptional network of the human tumor suppressor protein p53. *Proc. Natl. Acad. Sci. U. S. A.* 104, 18613–18618
8. Chuong, E.B. *et al.* (2016) Regulatory evolution of innate immunity through co-option of endogenous retroviruses. *Science* 351, 1083–1087
9. Grandi, N. and Tramontano, E. (2018) HERV envelope proteins: physiological role and pathogenic potential in cancer and autoimmunity. *Front. Microbiol.* 9, 462
10. Garcia-Montojo, M. *et al.* (2013) The DNA copy number of human endogenous retrovirus-W (MSRV-type) is increased in multiple sclerosis patients and is influenced by gender and disease severity. *PLoS One* 8, e53623
11. Tokuyama, M. *et al.* (2018) ERVmap analysis reveals genome-wide transcription of human endogenous retroviruses. *Proc. Natl. Acad. Sci. U. S. A.* 115, 12565–12572
12. Chiappinelli, K.B. *et al.* (2015) Inhibiting DNA methylation causes an interferon response in cancer via dsRNA including endogenous retroviruses. *Cell* 162, 974–986

Letter

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

Heini Natri,[1,2] Angela R. Garcia,[1,2] Kenneth H. Buetow,[1,2] Benjamin C. Trumble,[2,3] and Melissa A. Wilson[1,2,*]

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 ERVs than 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 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.

[1]School of Life Sciences, Arizona State University, Tempe, AZ, USA

[2]Center for Evolution and Medicine, Arizona State University, Tempe, AZ, USA

[3]School of Human Evolution and Social Change, Arizona State University, Tempe, AZ, USA

*Correspondence:
mwilsons@asu.edu

https://doi.org/10.1016/j.tig.2019.10.006

© 2019 Elsevier Ltd. All rights reserved.

References

1. Wallace, A.D. *et al.* (2018) To ERV is human: a phenotype-wide scan linking polymorphic human endogenous retrovirus-K insertions to complex phenotypes. *Front. Genet.* 9, 298
2. Nexø, B.A. *et al.* (2011) The etiology of multiple sclerosis: genetic evidence for the involvement of the human endogenous retrovirus HERV-Fc1. *PLoS One* 6, e16652
3. Katzourakis, A. *et al.* (2007) Effects of recombination rate on human endogenous retrovirus fixation and persistence. *J. Virol.* 81, 10712–10717
4. Sin, H.-S. *et al.* (2010) Human endogenous retrovirus K14C drove genomic diversification of the Y chromosome during primate evolution. *J. Hum. Genet.* 55, 717–725
5. Mariano, R. and vonHoldt, B. (2016) The canine X chromosome is a sink for canine endogenous retrovirus transposition. *Gene Rep* 4, 169–176
6. Carrel, L. *et al.* (2006) Genomic environment predicts expression patterns on the human inactive X chromosome. *PLoS Genet* 2, e151
7. Wang, Z. *et al.* (2006) Evidence of influence of genomic DNA sequence on human X chromosome inactivation. *PLoS Comput. Biol.* 2, e113

Letter

Evolution of Immune Sexual Dimorphism in Response to Placental Invasiveness: A Response to Natri *et al.*

Shirley Greenbaum[1,*] and Gili Greenbaum[2]

In their recent article in *Trends in Genetics*, Natri *et al.* [1] addressed differences between sexes in rates of cancers and autoimmune diseases. They described the pregnancy compensation hypothesis (PCH), which suggests that these differences can be explained by evolved immune sexual dimorphism and life-history changes in modern societies. While we find their evolutionary approach interesting, we would like to highlight two important reservations to the PCH: (i) the suggested immune response to presumably low parity in modern societies is difficult to reconcile with our current understanding of immune mechanisms; and (ii) the hypothesis is inconsistent with a large body of epidemiological observations.

The PCH comprises two parts. The first suggests that increased exposure of the maternal immune system to fetal cells in humans led to the evolution of immune sexual dimorphism (Figure 1). To support pregnancies, females evolved immune tolerance to increased placental invasiveness, while this immune tolerance would be unnecessary in males. The second part of the PCH suggests that decreased pregnancy rates in modern societies led to immune systems expecting a stimulus (foreign fetal cells), which fails to arrive. This, according to the PCH, leads to dysregulation of the immune system, making it undampened and aggressive, resulting in differences in rates of cancer and autoimmune diseases.

The first part of the PCH is certainly plausible; to consider the plausibility of the second part, we could examine the immune-system attributes that it implies. The PCH links together three components: (i) privation of pregnancy stimulus; (ii) loss of self-tolerance; and (iii) autoimmune diseases. Examples of immune dysregulation triggered by privation of stimuli are rare, with the hygiene hypothesis, mentioned by Natri *et al.*, being the main example. Under this theory, privation of infectious stimuli during childhood results in a Th2-biased immune response, and increased atopy rates. Self-tolerance, the second component in the argument, is established during infancy in