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.

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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

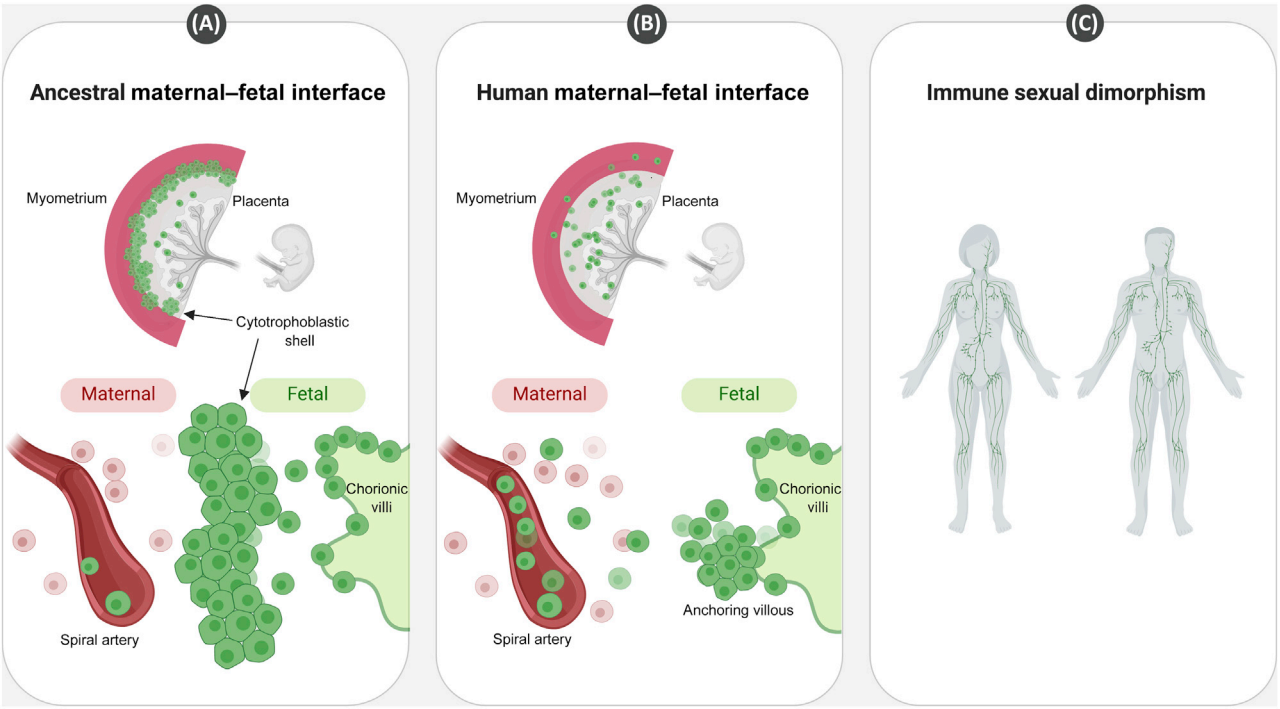

Figure 1. Schematic Representation of the Evolution of Immune Sexual Dimorphism due to Increased Placental Invasiveness.
(A) In the presumed ancestral state, inferred from non-hominid primates, the placenta invades minimally into maternal tissue. Mother and fetus are separated by the cytotrophoblastic shell, with only few fetal cells penetrating into the decidua and spiral arteries. The maternal immune system is only mildly exposed to fetal cells. (B) In humans (and other hominids), the cytotrophoblastic shell disintegrates in the early stages of pregnancy, and fetal cells invade extensively into the spiral arteries and as deep as the inner myometrium. The maternal immune system is significantly exposed to fetal cells. (C) In a hypothesized evolutionary process, immune mechanisms adaptively evolved in females to allow immune tolerance at the maternal–fetal interface, but remained unchanged in males. This evolved immune sexual dimorphism may manifest in other immune-related processes, such as in differences in susceptibility to cancer or autoimmune diseases. As in other cases of sexual dimorphisms, immune sexual dimorphism may involve genome-wide differences in gene expression between sexes, in sex chromosomes as well as in autosomes. Figure created with BioRender.

the thymus, through negative selection of self-reactive T cells, and by generation of regulatory T cells (Tregs). Lastly, various mechanisms have been suggested for autoimmunity, such as molecular mimicry and suboptimally functioning Tregs, none of which involves lack of stimuli. Taken together, the PCH would require that privation of repeated pregnancy stimuli in adulthood would overwrite previously established thymic self-tolerance and other fail-safe mechanisms, and that this would result in distinct autoimmune diseases, rather than atopy. Such a mechanism has not yet been described. Therefore, for the second part of the PCH to work, evidence would need to be provided for an unusual and unique composition of currently unknown immune components.

Another way to examine the plausibility of the PCH is to generate predictions and contrast them with observations. The second part of the PCH draws a causal link between unmet reproductive potentials of individual females in modern societies and epidemiological observations. Specifically, the authors suggest that low parity causes immune dysregulation, at the individual rather than the evolutionary level, resulting in a protective effect against cancer and a deleterious effect for autoimmunity. Therefore, the PCH implies that the differences between sexes in disease rates should be correlated with parity. However, this prediction is not supported by epidemiological data, which suggests decreased risk of cancers in parous women, such as for colorectal, bladder, pancreatic, and esophageal cancers (details and references in Table S1 in the supplemental information online). Additionally, parity was found to be either unassociated or positively

associated with risk for autoimmune diseases, such as autoimmune thyroiditis, Graves' hyperthyroidism, primary biliary cirrhosis, and Sjögren's syndrome [2] (Table S2).

A second prediction generated by the PCH is that differences in disease rates between sexes should manifest only once the immune system fails to experience pregnancy, during reproductive years. Therefore, under the PCH, these differences should be observed only after reaching reproductive age, and not in children. However, this prediction is also not supported by data: studies find higher risk for cancer [3] (Table S3) and lower risks for autoimmune diseases (Table S4) in boys compared with girls.

In summary, while the second part of the PCH proposes an unlikely mechanism and is inconsistent with observations, the first part suggests an evolutionary adaptation to hemochorial placentation. The processes leading to immune sexual dimorphism need not necessarily involve modern societal trends, and may be purely evolutionary (Figure 1). The main idea is that increased placental invasiveness may have induced a selection pressure for female immune tolerance to invading fetal cells. For immune sexual dimorphism to evolve, this immune tolerance would have likely involved costs that were not incurred by males. One such cost for females could have been an increased risk for autoimmune diseases. Decreased cancer rates could have also, although not necessarily, resulted from the same evolutionary process, but may not have fully countered the costs of autoimmune diseases, under a hunter-gatherer lifestyle. While the underlying mechanisms of such immune sexual dimorphisms are unknown, future studies that would adopt an evolutionary perspective to study differences in disease rates between sexes could prove insightful.

Supplemental Information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.tig.2019.10.009.

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Letter

Evolution of Immune Sexual Dimorphism in Response to Placental Invasiveness: A Reply to Greenbaum and Greenbaum

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

While we appreciate Greenbaum and Greenbaum's intent to evaluate predictions from the Pregnancy Compensation Hypothesis (PCH) [1] within the existing literature, we disagree with their mischaracterizations of the PCH and its predictions and disagree with their interpretations of the current literature. As discussed in our original paper [1], we are not trying to explain all autoimmune diseases or all cancers, rather we are attempting to explain the sexual dimorphism in relative risk for different types of immune-related diseases. Under the PCH, we hypothesize that the patterning of sex differences in disease observed in industrialized environments can be explained, in part, by sex differences in immune function evolved due to pressures imposed by invasive placentation on the female immune system, mediated by the evolution of gene content and dosage, and regulated proximally by reproductive hormones.

When discussing immune mechanisms, Greenbaum and Greenbaum claim that because there is evidence of the immune system being primed during childhood, they do not see how there could be a mechanism for the onset of change in immune function during adulthood. However, this shift towards autoimmunity across the life course is exactly what is observed across multiple studies [2,3]. We do not dispute the accuracy of the Greenbaum and Greenbaum's description of some of the mechanisms that influence autoimmune disease during development, however, we want to point out that autoimmunity is a consequence of both genetic susceptibilities and environmental triggers that persist throughout the life course. There is evidence that differential exposure to certain environmental stimuli, both early and later in life, can trigger autoimmune diseases. Rook *et al.* [4], outline a number of studies in which a lack of exposure to environmental