Trends in Genetics

CellPress
REVIEWS

Opinion

The Pregnancy Pickle: Evolved Immune Compensation Due to Pregnancy Underlies Sex Differences in Human Diseases

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We hypothesize that, ancestrally, sex-specific immune modulation evolved to facilitate survival of the pregnant person in the presence of an invasive placenta and an immunologically challenging pregnancy – an idea we term the 'pregnancy compensation hypothesis' (PCH). Further, we propose that sex differences in immune function are mediated, at least in part, by the evolution of gene content and dosage on the sex chromosomes, and are regulated by reproductive hormones. Finally, we propose that changes in reproductive ecology in industrialized environments exacerbate these evolved sex differences, resulting in the increasing risk of autoimmune disease observed in females, and a counteracting reduction in diseases such as cancer that can be combated by heightened immune surveillance. The PCH generates a series of expectations that can be tested empirically and that may help to identify the mechanisms underlying sex differences in modern human diseases.

Highlights

There are major sex differences in human disease that cannot be explained by reproductive hormones or environmental exposures alone.

Genes on the sex chromosomes exhibit differences in expression that are independent of reproductive hormones, and could contribute to sex differences in disease.

We propose that the ancestral immune system was strongly shaped by the requirement to compensate for unique immune regulation during pregnancy.

Dimorphism in immune function in response to placentation and pregnancy occurs via direct impact of reproductive hormones on immune function, as well as through heritable variation in sex chromosome dosage.

Although evolution has shaped sex differences in immune function over millions of years, industrialized urban populations experience both exacerbated sex differences in hormonal composition as well as reduced pregnancies compared with nonindustrialized populations.

Pregnancy Compensation Hypothesis: An Explanation for Sex Differences in Human Disease Risk

Sex differences exist across a range of human diseases, but these remain understudied and largely unexplained [1]. For example, females in **industrialized populations** (see Glossary) exhibit a higher prevalence of most autoimmune diseases than do males (Table 1) [2]. By contrast, females have a lower risk of developing cancer, with nearly all nonreproductive cancers showing a higher incidence in males (Table 1) [3]. We present here the **pregnancy compensation hypothesis (PCH)**, which explains both the proximate and ultimate (evolutionary) mechanisms that are responsible for the sexual dimorphism observed in human disease, as mediated by selection on the immune system by pregnancy and placentation (Figure 1, Key Figure; and Figure 2). We propose that sex differences in diseases are a consequence of evolution shaping the human immune system differently in males and females, and this – in conjunction with changing conditions that accompanied industrialization – explains why sexual dimorphism in some diseases is more pronounced in urban, industrialized contexts.

Specifically, under the PCH, we propose that the evolution of eutherian placentation exerted significant sex-specific selection on immune function to tolerate fetal antigens while still defending the pregnant individual against parasites and pathogens [4]. We theorize that this process is regulated proximately via hormones, and is mediated genetically by gene dosage on the sex chromosomes, and that the mismatch between an ancestral environment (being pregnant or lactating for the majority of adult reproductive years) and the urban industrial environment (where common contraceptive use results in reduced pregnancies) interacts with this evolved compensatory immune regulation, and results in the observed sex

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Table 1. The Occurrence of Common Autoimmune Diseases and Cancers of Nonreproductive Tissues[a]

Disease	F:M ratio	Tissue	Refs
Immune diseases			
Sjögren's syndrome	16:1	Systemic	[69]
Hashimoto's thyroiditis	9:1	Thyroid	[2]
Primary biliary cirrhosis	8:1	Bile ducts	[70]
Systemic lupus erythematosus	8:1	Systemic, connective tissue	[2]
Grave's disease	7:1	Thyroid	[2]
Rheumatoid arthritis	7:1	Spine, joints	[2]
Multiple sclerosis	3:1	Myelin	[71]
Addison's disease	2.5:1	Adrenal glands	[72]
Alzheimer's disease	2.34:1	Neurons	[73]
Celiac disease	1.8:1	Small intestine	[74]
Myasthenia gravis	1.5:1	Neuromuscular receptors	[75]
Crohn's disease	~1:1	Digestive tract	[2]
Guillain–Barré syndrome	~1:1	Myelin	[2]
Psoriasis	~1:1	Skin	[76]
Psoriatic arthritis	~1:1	Joints	[77]
Type 1 diabetes	~1:1	Pancreas	[78]
Ulcerative colitis	~1:1	Digestive tract	[2]
Ankylosing spondylitis	0.8:1	Spine, joints	[79]
Cancers			
Thyroid cancer	2.9:1	Thyroid	NIH SEER 2018
Colorectal cancer	1:1.3	Colon, rectum	NIH SEER 2018
Lung and bronchus cancer	1:1.3	Lung, bronchus	NIH SEER 2018
Myeloma	1:1.6	Plasma cells	NIH SEER 2018
Melanoma	1:1.7	Melanocytes	NIH SEER 2018
Kidney and renal pelvis cancer	1:2	Kidney	NIH SEER 2018
Liver and intrahepatic bile duct cancer	1:2.9	Liver	NIH SEER 2018
Bladder cancer	1:4.1	Bladder	NIH SEER 2018
Esophageal cancer	1:4.2	Esophagus	NIH SEER 2018

[a]Disease occurrence and the sex ratio within any category vary across human populations. We report here overall female to male (F:M) ratios in disease occurrence from the literature for immune diseases. F:M ratios of cancer types were estimated from the numbers of new cases across all ethnicities in 2018 in the NIH Surveillance, Epidemiology, and End Results Program (SEER) statistics (https://seer.cancer.gov/).

differences in disease risk (Figure 2). Finally, a sedentary lifestyle that affects **reproductive hormone** levels exacerbates these differences.

We focus here on two disease classes with documented immune components that also show sex differences in incidence and etiology: autoimmune diseases and cancer. We anticipate that the sex differences in immune function will, to some extent, contribute to sex differences in all human diseases. However, our rationale for focusing on these particular classes of disease is twofold. First, our hypothesis intersects factors related to shifting reproductive states, parasite loads, and energy availability, which are particularly relevant for these disease classes. Second, we believe that it is important to narrow the scope and to effectively use empirical studies to

Glossary

Eutherian mammal: a classification of mammals that includes those that have fully formed placentas, often referred to as 'placental' mammals.
Hygiene hypothesis: this proposes that the decreasing incidence of infections in western countries is the origin of the increasing incidence of both autoimmune and allergic diseases as a result of insufficient immunomodulation caused by the lack of early exposure to parasites and pathogens.
Industrialized population: middle to high development index countries with labor- and/or technology-driven economies that enable mass food production, with a high capacity for division of labor, and advanced infrastructure, sanitation systems, and access to national or global economies. These populations tend to be more sedentary, have access to modern medical care and vaccines, low parasite and pathogen loads, and have a higher-calorie diet that is rich in high-carbohydrate, low-protein, and processed foods.
Karyotypic: the karyotype is the chromosomal complement and structure of an individual. We use karyotypic to refer to the typical karyotype observed in genetic females (46, XX) and genetic males (46, XY).
Nonindustrialized population: low development index populations that rely on traditional subsistence activities or a mix of subsistence and wage-labor to acquire food and material goods, and where there tends to be less infrastructure for basic sanitation (leading to a higher prevalence of parasites and pathogens), and little access to medical care. Individuals in nonindustrial populations tend to lead more active lifestyles, necessitated by subsistence activities, and tend to have lower-calorie diets with little or no industrial processed foods.
Pregnancy compensation hypothesis (PCH): this proposes that the maternal immune system evolved to compensate to tolerate the pregnancy while still protecting the pregnant person against parasites and pathogens: the mismatch with industrialized environments results in increased incidence of autoimmune disorders and decreased risk of cancer in females relative to males.
Reproductive hormones: hormones typically produced by the reproductive

Key Figure

Pregnancy Compensation Hypothesis (PCH): Pregnancy, Pathogens, and Parity

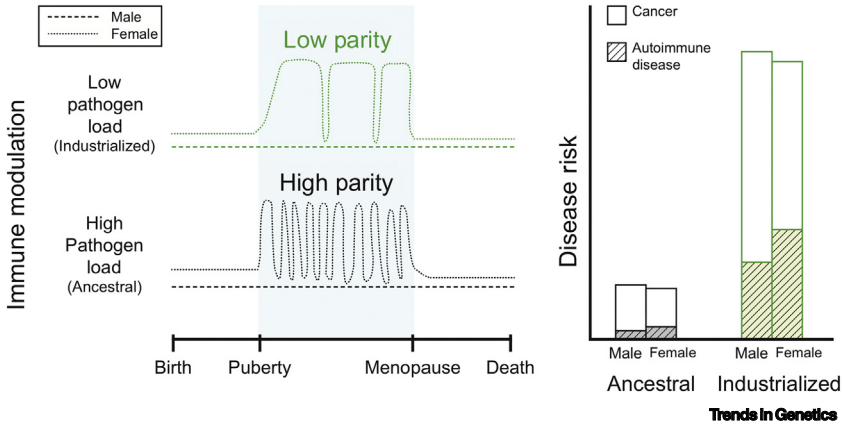

Figure 1. In this figure we illustrate the expected immune differences between high and low parity (layered on top of high/low pathogen load). In particular, we suggest that low pathogen load (hygiene hypothesis) affects immune function in both men and women (green lines), making everyone more susceptible to autoimmune disease, whereas low parity will only affect the immune system in women, exacerbating the immune compensation that evolved in response to tolerating an internal pregnancy, further increasing the immune risk for women in industrialized regions.

illustrate evidence for specific aspects of our hypothesis. In the following we unpack the interrelated components of the PCH, and how each relates to either proximate or evolutionary underpinnings of differences in disease risk (Figure 2). For the purposes of this manuscript, we

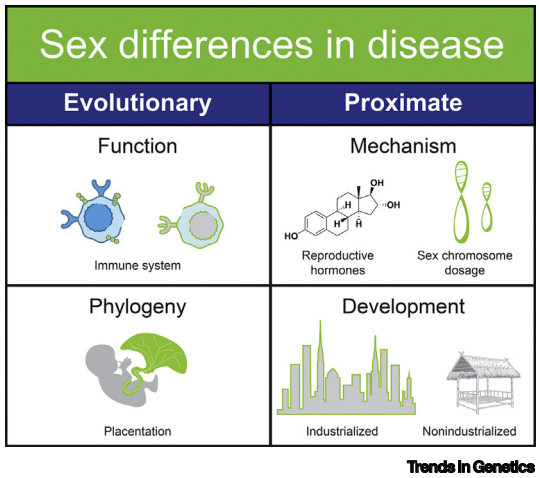

Figure 2. Explanations for Sex Differences in Autoimmune Disease and Cancer. There are longer-term evolutionary explanations and more immediate proximate explanations for sexual dimorphism in immune function. The female immune system must compensate for the unique DNA of the placenta and immune-modulation during pregnancy. The placenta is phylogenetically shared across therian mammals, but with additional unique evolutionary pressures including invasive hemochorial placentas in eutherian mammals. Dimorphism in immune function in response to placentation and pregnancy occurs via the direct impact of reproductive hormones on immune function, as well as through heritable variation in sex chromosome gene content and dosage. Although evolution has shaped these sex differences over millions of years, industrialized urban populations experience exacerbated sex differences in hormone mechanisms as well as reduced pregnancies compared with nonindustrialized populations.

organs: ovaries (e.g., estrogens and progesterone) and testes (e.g., testosterone). Reproductive hormones are known to impact on immune function and contribute to the development of reproductive cancers.

X-inactivation: the process by which one of the two X chromosomes (or indeed every X chromosome in excess of one) is inactivated and most genes on that X chromosome are silenced.

refer to **karyotypic** males and females, both across species and when discussing humans, unless otherwise noted. Although not often explicitly stated, where possible we emphasize differences between genetic sex, gonadal/**reproductive hormones**, and gender in the research discussed here.

Sex Differences in Autoimmune Disease and Cancer Incidence

Sexual dimorphism in immune function appears to be a general feature of many species, and differences are documented across vertebrates and invertebrates, although at varying magnitudes [5]. Across several vertebrate species, there is evidence of female bias in the peripheral abundance of markers of innate and adaptive immunity [5,6]. Autoimmunity is characterized by the presence of an increased level of autoantibodies, as well as of inflammatory and mediatory cells, resulting in chronic inflammation [7] that affects females more than males (Table 1). In mammals in particular, both the sex chromosome complement and hormone levels have been implicated in the female bias in autoimmune disease prevalence, including in systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes [8]. By contrast, females have reduced rates of nearly all nonreproductive tissue cancers relative to males (Table 1). Sex differences in environmental exposure alone do not explain the sex differences in cancer [3]. Further, there are sex differences in response to cancer immunotherapy [9], perhaps suggesting that the sex differences in immune function that underlie autoimmune disease may also contribute to the sex difference in cancer incidence and response to therapy. Consistent with this, clinical and epidemiological studies have demonstrated more robust innate and adaptive immune responses in females compared with males; females exhibit better outcomes and survival from infections, injuries, and sepsis [10,11]. Females also develop higher antibody responses to vaccinations than do males [12].

Industrialization Explains Increases in Autoimmunity and Cancer, but not Sex Differences

Most research on cancer and autoimmunity is conducted in urban populations, but most of human evolution took place in small-scale subsistence populations; sedentary industrialized life has resulted in major changes in human reproductive ecology and lifetime fertility [13]. There is a documented increase in the incidence of autoimmune disorders over recent decades in urban and industrialized populations [14]. The 'old friends' or **hygiene hypothesis** suggests that, because humans coevolved with helminths and other pathogens, the human immune system has an 'evolved dependency' on parasites, and is specifically tailored to expect these infections for effective immunomodulation [15–18]. The absence of these parasites and pathogens is cited as an explanation for the increasing rates of asthma and immune-related diseases in industrialized populations, but cannot explain why there is sexual dimorphism in disease risk.

Curiously, the shift in the immunological profile that occurs during pregnancy is not unlike that which occurs as a result of chronic infection by a helminthic parasite such as the hookworm. Although no single extant **nonindustrialized population** is an exemplar of the mosaic of environments in which humans evolved, evidence from existing hunter-gatherer and forager-horticultural populations suggests that most of the female reproductive career throughout human history was spent either pregnant or lactating [19,20]. This sustained reproductive state would have led to chronic readjustments of components of the maternal immune system. For the pregnant person, maintaining a pathogen-competent immune system while regulating the immune response to pregnancy (which may be considered 'foreign' to the maternal immune system) is a balancing act that involves numerous immunoregulatory mechanisms driven by both maternal and fetal signals. To accommodate these dual needs, the maternal immune system is not uniformly downregulated during pregnancy. Instead, it is differentially modulated throughout the gestational period. Described as 'maternal–fetal immune tolerance', the maternal immune

system is primed to upregulate specific immunological pathways to maintain a sufficient immune response to survive pathogens and parasites, while also downregulating other pathways to tolerate the genetically distinct pregnancy [21].

The PCH proposes that the genetically distinct placenta and fetus exert pressure on the maternal immune system that modulates the 'host' immune response, thereby protecting itself from elimination while minimizing damage to the host environment (Figure 1). In both cases the immune response shifts towards an anti-inflammatory bias [22,23]. However, in contrast to the hygiene hypothesis, the PCH postulates that the maternal immune system must compensate to tolerate the pregnancy, while still protecting the mother against parasites and pathogens. The PCH, therefore, predicts sex-specific immune modulation.

In Urban Industrialized Contexts, Pregnancy Compensation Explains Dimorphism in Disease Risk

Despite caloric availability to maintain a high number of pregnancies, fertility in modern urban environments has decreased [19]. In the contemporary industrialized context, the absence of repeat pregnancies may leave the immune system of an urban industrial female prone to dysregulation. Given the role of the immune system in surveying and preventing cancer [24,25], this 'undampened' immune response should facilitate increased immune surveillance, which may be protective against some cancers in females; however, it may also trigger autoimmune diseases. Further, energy constraints that limited reproduction throughout human evolutionary history, including reduced caloric availability and high immune burden, no longer limit investment in reproductive hormone levels. As a result, people in industrialized populations can attain high, if not evolutionarily novel, levels of testosterone, estrogens, and progesterone compared with extant subsistence populations [26–29]. These high hormone levels increase the prevalence of reproductive-related conditions including benign prostatic hyperplasia and prostate cancer [29,30], as well as breast and endometrial cancers [13]. Under the PCH, these high hormone levels in industrialized populations are expected to heighten sex differences in nonreproductive cancers and contribute to the increased prevalence of autoimmune disease. Consistent with this, both the incidence and prevalence of autoimmune diseases are increasing [31]. The diminished immunomodulation consequent from reduced pregnancy and lactation further leaves the immune system primed for overactivation.

Pregnancy, and Related Hormonal Shifts, Are Directly Linked to Changes in the Maternal Immune System and the Incidence/Onset of Autoimmune Disease

The maternal immune system is alternately dampened and recalibrated throughout gestation and lactation during a successful pregnancy. Such immunomodulation is facilitated by the highly invasive nature of the eutherian placenta, that is primarily composed of fetal tissue, and is accomplished through coordinated signaling between the fetus and the mother. Early implantation by the fetal trophoblast is facilitated by innate inflammatory processes at the maternal–fetal interface [32], followed by a progressive shift in maternal immunity from a proinflammatory bias towards a systemic anti-inflammatory phenotype during the last two trimesters of pregnancy [32]. These anti-inflammatory processes, facilitated by actions by the fetal unit, modulate the maternal immune response, decreasing some aspects of both humoral and cell-mediated immunity, while increasing levels of regulatory immune cells, which together foster a stable tolerant immune profile (reviewed in [33–35]). As the fetus develops, tolerance is further established through biosynthesis of the maternal hormone estriol, and its positive effect on the continued production of regulatory immunity. This 'tit-for-tat' maternal–fetal conflict would have imposed additional selective pressures for a highly plastic immune response at different periods over the life course (e.g., pregnant versus cycling females) that is dissimilar from males, and is manifest in distinct immune regulation in males, cycling females, and pregnant females (Figure 1 and Table 2).

Table 2. Immunological Differences between Human Males, Cycling Females, and Pregnant Females[a]

Main cell types	Finding	Direction	Refs
Eosinophils, lymphocytes, monocytes	Cycling females have higher levels of all cells compared with males	F > M	[5]
$CD4^+$ cells	Cycling females have higher levels of $CD4^+$ than males	F > M	[6]
CRP	Females have generally higher levels than males	F > M	[80]
TLR[b] pathways, TLR6, dendritic cells, B cells, immunoglobulins	Cycling females have higher levels than men	F > M	[8]
Tregs, natural killer (NK) cells, $CD8^+$ cells	Males have higher levels than cycling females	M > F	[8]
Macrophages, monocytes, dendritic cells	Females have higher expression than males	F > M	[81]
NK cells	Males have higher levels than females	M > F	[82]
Tregs	Compared with cycling females, pregnant females have higher levels of Tregs	PF > CF	[6]
Eosinophils	Cycling females have higher levels of eosinophils than pregnant females	CF > PF	[83]
Neutrophils, lymphocytes	Pregnant females have higher levels of neutrophils and lymphocytes than cycling	PF > CF	[83]
TNF-α, IL-6, IL-2	Compared with cycling females, pregnant females have higher levels of IL-2, IL-6, and TNF-α	PF > CF	[84]

[a]Markers of immune function show differences in overall levels in gonadal males and females. Notably, however, there are many immunological differences between gonadal females who are cycling versus those who are pregnant. The table catalogs a variety of cell types and reported results of differences in each of these cell types between healthy human males (M), cycling females (CF), and pregnant females (PF).
[b]Abbreviations: CRP, C-reactive protein; IL, interleukin; TLR, toll-like receptors; TNF-α, tumor necrosis factor alpha.

Consistent with the PCH, estrogen metabolites and their receptors also have regulatory effects on immune function in relation to autoimmunity and cancer. Importantly, estriol –which is placentally derived and produced almost exclusively during pregnancy – may have a role in generating immune tolerance during pregnancy through the production of regulatory T cells (Tregs) [36]. Estriol and the presence of its preferred receptor, ERβ, have been found to alleviate several autoimmune diseases in general [37–39], and are considered to be protective against cancer [40].

In particular, the estriol spike during pregnancy has been found to attenuate several autoimmune diseases throughout gestation [37–39]. Notably, in patients with rheumatoid arthritis who become pregnant, 75% of pregnancies are characterized by an improvement in symptoms, particularly during the second and the third trimesters [41]. Similarly, multiple sclerosis relapse rates decline during pregnancy from 0.7 relapses per person per year prepregnancy to 0.2 relapses per person per year during the third trimester of pregnancy [42]. In contrast to rheumatoid arthritis and multiple sclerosis, which are mainly mediated by T cell activation [43], systemic lupus erythematosus is associated with more complex and heterogeneous immunological abnormalities. Curiously, patients with systemic lupus erythematosus typically experience exacerbation or no changes in symptoms during pregnancy [44,45]. Under the PCH we predict that these hormonal regulators of immune function during pregnancy are encoded by genetic pathways that evolved in response to placentation, starting millions of years ago.

Evolution of the Mammalian Sex Chromosomes and Placentation Leads to Sex Differences in Immune Function

Although **eutherian mammals** are commonly termed placental mammals to contrast them with marsupials, it is now understood that the development of a placenta, if even for a short time, occurs in marsupial mammals and is important for successful pregnancy [46]. Thus, although all mammals share lactation as a trait [47], placentation evolved in the common ancestor of therian mammals, after they diverged from the egg-laying monotreme mammals (Figure 3). Further, phylogenetic comparisons have been used to suggest that the early eutherian placenta was highly invasive (hemochorial), and that this was crucial for sustaining a pregnancy, initially exerting a huge selective pressure for immune compensation at the offset, and placentas only later diverged in invasiveness across individual eutherian clades [48].

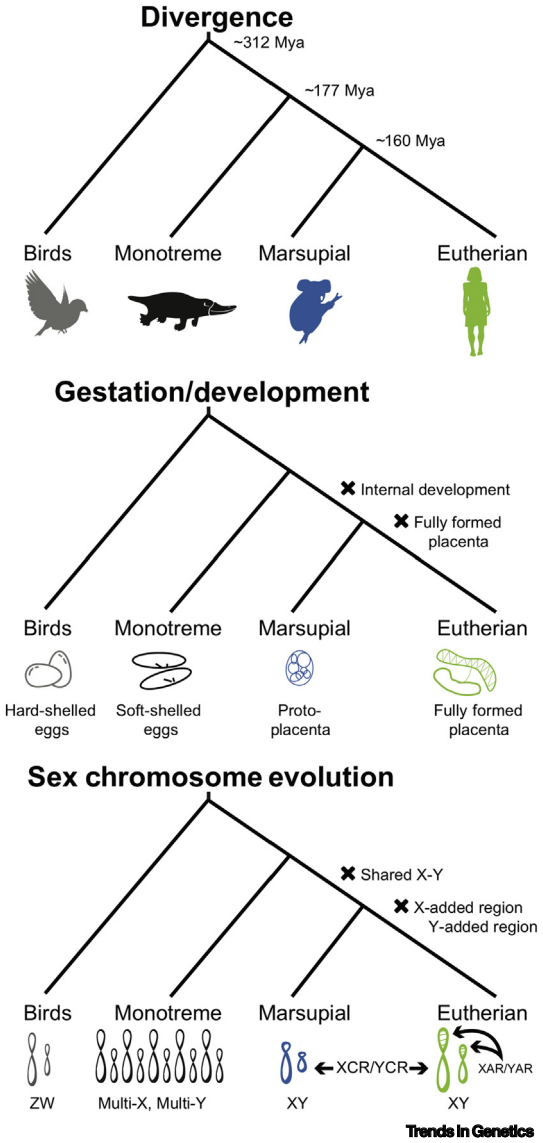

Figure 3. Evolution of Placentation and the X Chromosome. We observe that the evolution of placentation and lactation in mammals correlates with the evolution of different regions of the mammalian X chromosome. Notably, there is a shift in the mechanism of dosage compensation and the structure of the mammalian X chromosomes that correlates with the evolution of fully formed placentas. Abbreviations: Mya, million years ago; XAR, X-added region; YAR, Y-added region; XCR, X-conserved region YCR, Y-conserved region.

We propose that the evolution of mammalian sex chromosomes is one genetic alteration that could have been involved in the physiological shift of placentation that prompted significant sex-specific selection on immune function, and sets the scene for future dimorphism in disease risk. Human sex chromosomes originated from a pair of autosomes in the common ancestor of marsupial and eutherian mammals [49], concurrently with the initial evolution of the placenta in the therian common ancestor (Figure 3). Moreover, at the same time as the second major shift in placental physiology occurred in the common ancestor of eutherian mammals, the eutherian X and Y chromosomes experienced the addition of an X-added and Y-added region that comprises ~30% of the modern human sex chromosomes [50] (Figure 3).

Most Y-linked genes have been pseudogenized or deleted [51], resulting in unequal gene content between the X and Y chromosomes, providing a potential mechanism for at least some sex-specific gene regulation. To balance the dosage of X-linked genes between males and females, one of the X chromosomes in females is largely epigenetically silenced during embryogenesis, a process termed **X-inactivation** [52]. Interestingly, the additions to the sex chromosomes that coincide with invasive placentation also correspond with an apparent shift in the mechanism of dosage compensation from paternally silenced X-inactivation in marsupials to random X-inactivation, including cell-by-cell heterogeneity and gene-specific silencing that is observed in eutherian mammals, specifically humans [53,54]. In humans, notably, dosage compensation is incomplete [55]; as many as 30% of the genes on the inactive X are known to escape inactivation [54], or may never have been silenced. Although some 'escapees' show uniformity, most of these genes exhibit heterogeneity in escape from X-inactivation between individuals, tissues, and cells, and may contribute to heterogeneity in disease phenotypes [53,54] (Figure 4). We propose that the addition of these genes to the sex chromosomes, and evolution of a new dosage-compensation mechanism, is one mechanism to achieve sex-specific immunomodulation in response to invasive placentation.

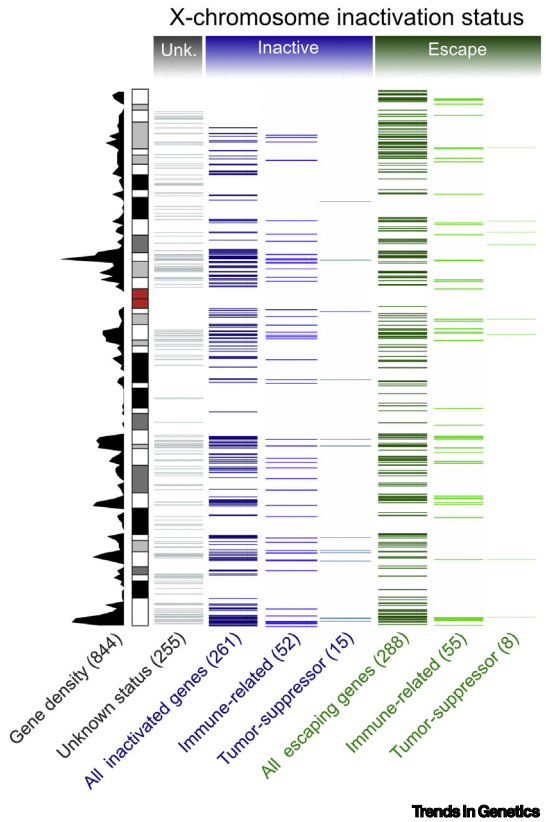

Figure 4. Inactivation Status of X-Chromosome Genes. All protein-coding X-linked genes (Gencode release 29) are presented as a density plot, and the inactivation status, as reported in recent studies [53,54], is summarized. Genes with unknown status (Unk.) are shown in grey. Genes reported to be subject to X-inactivation in all tissues and cell lines surveyed are labeled as inactive (blue). Genes found to escape X-inactivation in any of the individuals, tissues, or cell lines in any individual are labeled as escaping (green). The numbers of genes belonging to each category are shown in parentheses. The information on putative tumor-suppressor genes was obtained from the Tumor Suppressor Gene Database [67]. Immune-related genes contain genes obtained from ImmPort [68] or that belong to the Gene Ontology class 'immune response'.

Gene dosage on the X chromosome has a compounding effect on immunity, in combination with reproductive hormones, as illustrated by individuals with Klinefelter syndrome or Turner syndrome, both of which are characterized by numeric and structural variations of the X chromosome. Klinefelter syndrome occurs in males who carry two X-copies (47,XXY). Klinefelter males have higher immunoglobulin concentrations and adaptive immune cell levels compared with XY males [56], and are at an increased risk of developing autoimmune diseases, particularly systemic lupus erythematosus, than XY males [57,58]. By contrast, Turner syndrome is characterized by a single X chromosome in affected females (45,X0), sometimes with a partial X or Y. Female patients with Turner syndrome have lower immunoglobulin concentrations and adaptive immune cell levels compared with XX females [59]. Turner syndrome is associated with T cell immune alterations, suggestive of possible immune deficiency [60]. Interestingly, although females with Turner syndrome have higher reported rates of autoimmune disease than XX females, they have particularly higher rates of autoimmune diseases that are typically characterized by male-predominance [61]. Hormone therapy may reverse some of the immunological effects of Klinefelter [56] and Turner syndrome [62], emphasizing the complex interactions between endocrinological functions and the X-chromosome in regulating immunity.

Concluding Remarks

We present here the PCH to explain how evolution may have shaped both gene dosage on the X chromosome and reproductive hormones in response to placentation and pregnancy to mechanistically explain sex differences in disease, reflecting an ancestral mismatch with modern environments. There are both general trends and specific exceptions to sex differences in disease that can be explained by the PCH. For example, it is notable that a key exception to reduced female cancer incidence is thyroid cancer [63]. This is provocative because the thyroid is involved in reproduction and is crucial during pregnancy [64]. The thyroid increases in size during pregnancy and plays a vital role in iodine sufficiency, which must pass through the placenta during pregnancy [65]. Of concern and relevance here is that papillary thyroid cancer is increasing in incidence in females across all race/ethnic groups in industrialized populations, and cannot be explained by increases in surveillance alone [66]. However, under the PCH one would expect the thyroid to be primed to be active for the reproductive career of a woman. In industrialized

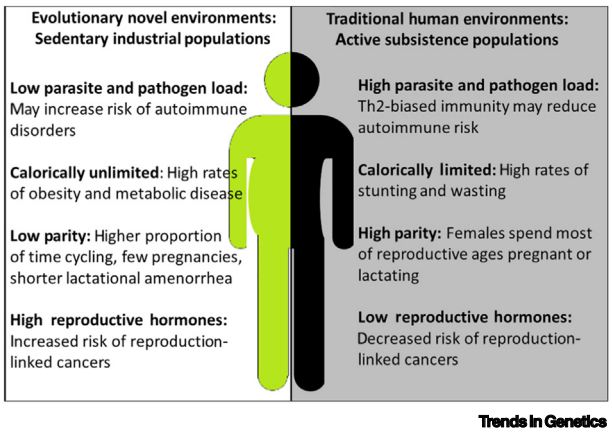

Figure 5. Comparison of Environmental Differences between Humans Living in Active Subsistence Populations versus Sedentary Industrial Populations. Although humans evolved in a mosaic of different environments, sedentary industrialized urban environments are evolutionarily novel. We predict that these shifts in the environment may contribute to mismatches between how our systems (e.g., the immune system) have been shaped by natural selection to respond to the environment and how they are now responding, resulting in human disease. Abbreviation: Th2, T helper 2 cells.

Outstanding Questions

Which genes escape inactivation during development, in which tissues, and do they show a sex difference?

Which classes of genes (oncogenes and/or immune genes) are specifically tied to sex differences?

Is the dosage of tumor-suppressor and immune-related genes altered in cancer, or does it reflect healthy system regulation?

What is the difference in disease risk between absolute dosage differences between sexes, or it is the relative heterozygous dosage? (i.e., is mosaicism afforded by X-inactivation protective in particular cases of disease risk?)

Do nonindustrialized populations show sex differences in autoimmune disease and cancer?

What is the relationship between sex-linked gene expression, reproductive hormone expression, and the immune system?

Is female-bias in autoimmune disease related to parity, or is it tied to the immune system during reproductive years?

What are the roles of innate and adaptive immune modulation in placentation, pregnancy, autoimmunity, and cancer?

Is the immune modulation of placentation and pregnancy a local or systemic process?

Does the 'protectiveness' of pregnancy differ by the type of immune response invoked by a specific autoimmune disease?

Does chronic stimulation of estriol postpone the development of symptoms for some types of autoimmune diseases?

Do animal models recapitulate the sex differences in gene content, placentation, and immune function documented in humans?

populations, and in the absence of routine pregnancy, the thyroid may be primed for constant usage and cell proliferation but instead experiences underutilization, resulting in increased susceptibility to thyroid cancer in females but not in males.

Under the synthesis presented here, a suite of new questions and testable hypotheses emerge (see Outstanding Questions) that we anticipate will push both evolutionary and clinical research forward. We propose that there is a combinatorial effect of the way evolution has differentially shaped immune function between males and females, and that the reduced amount of time spent pregnant and lactating together with the environmental effects on hormone levels, lead to the observed sexual dimorphism in disease risk in urban, industrialized societies (Figure 5). We further propose that the evolution of gene dosage on the human sex chromosomes, and primarily on the X chromosome, is a heritable mechanism by which the maternal immune system ancestrally compensated to tolerate placentation, and now may provide the explanation for the sexual dimorphism of autoimmune disease and cancer in industrialized populations.

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