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Immune response and auto-immune diseases: gender does matter and makes the difference

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Summary. Women produce a more robust immune response to infection and this fact has been suggested as a tool to explain why women usually live longer than men; however, this increased immune reactivity may be responsible for the higher risk of developing autoimmune diseases (AID). Indeed, a female to male predominance occurs in AID and about 65% of all patients are women. Different factors have been implicated in underlie this striking gender difference, sex hormones being the mostly investigated. Gonadal hormones affect both the phenotype and the function of immune cells through interaction with specific receptors that are expressed in these cells. As a general rule, estrogens enhance the immune reactions, while progesterone and testosterone may exert an immunosuppressive role; however, the mechanisms involved in this complex scenario are not yet completely identified. In addition to sex hormones, genetic and environmental factors, innate and adaptive immune cells, fetal microchimerism, X chromosome inactivation and abnormalities have been proposed as key players in the development of AID and female gender bias, but their relative value is not yet fully appreciated. This review will try to critically describe the most important elements involved in the women's predominance in AID.

Key words: gender, immune response, autoimmune diseases, sex hormones, genetic factors, environmental factors.

Risposta immunitaria e malattie auto-immuni: il genere conta e fa la differenza

Riassunto. Le donne producono una più intensa risposta immunitaria e ciò contribuisce a spiegare perché le donne vivano più a lungo degli uomini; tuttavia, questa aumentata reattività immunitaria predispone le donne a un aumentato rischio di sviluppare malattie autoimmuni (AID). Infatti, nelle AID, c'è una chiara predominanza del genere femminile e circa il 65% di tutti i pazienti sono donne. Tra i fattori implicati quali responsabili di questo bias di genere, gli ormoni sessuali sono sicuramente i più studiati. Gli steroidi sessuali modulano sia il fenotipo che la funzionalità delle cellule immunitarie interagendo con specifici recettori, che sono espressi nelle varie popolazioni cellulari. In linea generale, gli estrogeni potenziano le risposte immuni, mentre il progesterone e il testosterone possono esercitare un effetto di immunosoppressione; tuttavia, i meccanismi coinvolti in questo complesso scenario non sono ancora completamente identificati. Oltre agli ormoni sessuali, altri fattori (quali, ad es., alcuni determinanti genetici e ambientali, l'attività delle cellule della risposta immunitaria, il microchimerismo fetale, l'inattivazione del cromosoma X e le anomalie cromosomiali) possono giocare un ruolo chiave nello sviluppo delle malattie autoimmuni e nel determinare il bias di genere, anche se il loro peso non è ancora completamente apprezzato. Questa review cercherà di descrivere in maniera critica i più importanti elementi che sottendono la predominanza femminile nelle malattie autoimmuni.

Parole chiave: genere, risposta immunitaria, malattie autoimmuni, ormoni sessuali, fattori genetici, fattori ambientali.

Introduction

Autoimmune diseases (AID) represent an important cause of morbidity and mortality, affecting 8.5 million people in USA[1,2] and about 6% of the population in industrialized countries[3,4].

In spite of ethnic and geographic differences in the incidence of selected AID, some groups being at higher risk for some diseases and lower risk for others[4], and, despite a large variability in the age of onset, clinical setting and drug responses, most AID share a common characteristic: the prevalence of female sex.

Indeed, about 65% of all AID patients are women and this percentage is even higher in Sjogren's syndrome, systemic lupus erythematosus (SLE) and primary biliary cirrhosis[4,5].

In spite of this well-known sex bias and multiple efforts to elucidate this situation, the reasons for the female predominance are still unknown. Genetic and environmental factors, innate and adaptive immune cells, sexual hormones, fetal microchimerism, X chromosome inactivation and abnormalities, have been proposed as key elements[6,7], but the precise cause is still lacking.

This review will try to critically describe the most important elements involved in the women's predominance in AID.

The immune response

As known, the immune response, a complex and tightly regulated one, is orchestrated by the immune system in order to protect the body from pathogens or other foreign damaging elements. When functioning properly, the immune system identifies a variety of threats, including viruses, bacteria and parasites, and

distinguishes them from the body's own healthy tissues. While the innate immune system represents the evolutionarily oldest defense mechanism and provides an early first line of defense against invading pathogens, the adaptive immune system allows for a stronger immune response as well as immunological memory, each pathogen being "remembered" by a signature antigen.

The components of nonspecific immune responses are monocytes, macrophages, natural killer (NK) cells, dendritic cells and granulocytes (neutrophils, eosinophils and basophils). These cells phagocyte bacteria and produce oxy-radicals (neutrophils, monocytes and macrophages), lyse infected cells (NK cells), produce cytokines to enhance nonspecific and specific immune responses. Dendritic cells, as well as monocytes and macrophages, act as antigen presenting cells (APC): they take up foreign antigens, process them and present on their surface antigen peptides for the specific immune system, mainly helper T lymphocytes.

The specific immune response comprises the humoral immune response (that is, B lymphocytes producing antibodies) and the cell-mediated immune response (that includes phagocytes, specific T lymphocytes and various cytokines).

T lymphocytes are divided into 3 distinct populations: a) cytotoxic T lymphocytes (Tc cells) that kill foreign or infected cells, b) helper T lymphocytes (Th cells) that produce cytokines and are further sub-divided into Th1 cells (producing IFN-γ that promotes cellular immune responses), Th2 cells (producing IL-4, IL-13 and IL-5 to help humoral immune responses) and Th17 cells (producing IL-17 that plays a key role in autoimmunity and allergen-specific responses), and c) regulatory T lymphocytes (Treg cells) that exert immunoregulation and can suppress both Th1- and Th2-mediated responses[8].

The most relevant functions (as well as the major cell types involved; see also below) of innate and adaptive immunity are reported in Table 1.

Disorders of the immune system can result in immunodeficiency (when the immune system is less active than normal; chronic granulomatous disease represents a congenital, inherited immunodeficiency, whereas AIDS/HIV or immunosuppressive medications are examples of acquired immunodeficiency) or autoimmune diseases. AID represent a condition of hyperactive immune system and occur when the immune system, failing to properly distinguish between self and non-self, attacks and destroys tissues and organs of its own host.

Cells involved in immune responses and differences between males and females

Gender differences in autoimmunity can be attributed, at least partly, to differences between male and female immune systems, women presenting stronger cellular and humoral immune reactions than men[7].

Table 1. Major functions and relevant cell types of the innate and adaptive immune systems.

	Innate immune system	Adaptive immune system
Functions	- Cell recruitment to sites of infection - Production of chemical mediators, including cytokines - Phagocytosis - Immune cells' activation - Activation of the complement cascade - Removal of foreign substances present in the body (by specialized cells) - Clearance of antibody complexes or cell debris - Activation of the adaptive immune system (antigen presentation) - Anatomical barrier (e.g., saliva, mucus, tears, sweat etc)	- Humoral immune response - Cell-mediated immune response - Recognition of specific "non-self" antigens, during the process of antigen presentation - Immune cells' activation - Generation of responses "tailored" to eliminate specific pathogens or infected cells - Development of immunological memory (to "remember" specific pathogens; memory B cells and memory T cells)
Cell types	- Phagocytes (neutrophils, monocytes, macrophages, dendritic cells) - Natural killer (NK) cells - Mast cells - Eosinophils - Basophils - Helper T cells	- B lymphocytes (humoral response-antibody production) - T lymphocytes (cell response) - CD8+ T cells (cytotoxic lymphocytes) - CD4+ T cells (helper or regulatory lymphocytes) - Th1 and Th2 response - Treg (Regulatory T) cells (control aberrant immune responses to self-antigens; autoimmune diseases) - Gamma delta T cells

Sex differences in infectious diseases are common, but often neglected, at any age[9,10], males being more susceptible than females[11]. This male bias has been documented for bacterial, parasitic and viral infections such as tuberculosis, leishmaniasis, leprosy, leptospirosis, HIV[12,13].

Response to vaccination, too, differs, either in childhood than in adult life, between sexes: healthy females present a more robust protective antibody response to the influenza and the measles-mumps-rubella vaccines[13-16] and it has been also demonstrated that women could be given half dosage of the vaccine[17]. Thus, the enhanced female immune response to vaccination can ensure a more effective and long lasting protection but can also cause a greater prevalence of adverse effects in women[14-16,18]. Indeed, following monovalent 2009 pandemic influenza A (H1N1) vaccines, the female:male ratio of adverse effects was > 4:1 for healthy people aged 20-59 years[18].

Sex hormones (see below) exert potent effects on immune cell subsets, estrogen and androgen receptors being present in the majority of immune cells; the "reproductive function" (including pre-puberty, puberty, pregnancy and menopause) deeply affects immune responses and AID.

As known, T lymphocytes secrete cytokines that underlie cell-mediated adaptive immunity, while B lymphocytes produce IgG and IgM antibodies.

Men and women have the same total number of lymphocytes, but males present a lower number of T cells[19] and post-menopausal women present less Th cells[20]. The overall number of B lymphocytes does not change between men and women; nevertheless, females aged > 6 years have increased IgM levels, secrete higher amounts of IL-4, IFN-γ and IL-1, present higher $CD4^+$ T lymphocytes and higher plasma IgM levels than men[7] and this has been associated to the female susceptibility to AID[1].

Upon antigen challenge, men's T-helper lymphocytes produce a milder "anti-inflammatory" mix of cytokines – the Th2 response, in which antibody production predominates. On the contrary, female lymphocytes tend to generate a more "pro-inflammatory" mix of cytokine, the Th1 response, in which production of cytotoxic T cells predominate, except during pregnancy. In fact, in pregnancy, women's immune system shifts towards the milder Th2 response: this may explain why some women with multiple sclerosis or rheumatoid arthritis ameliorate, especially during the third semester, while a few weeks after delivery, the disease rebounds[2]. Indeed, IFN-γ production, that is the paradigm of Th1 response, is regulated by estrogens[21] and is secreted at higher levels after menopause and decreased over the years after reaching a plateau[22]. On the contrary, no difference in IL-10 production has been documented between males and females[19] and at different moments of the menstrual cycle[23].

Higher numbers of NK cells are more often observed in women than in men[24,25], their activity being modulated by estrogens in a biphasic manner: high dosage suppresses NK activity, whereas low dosage has no effect[26].

Monocyte and macrophage activity is also regulated by sex steroids: estrogens stimulate TNF-α secretion from monocytes[27] whereas testosterone has no effect[28]. Male monocytes have been reported to produce more IL-1β than female ones[19]; this cytokine is also regulated by estrogens in a biphasic manner[26]. Indeed, 17 beta-estradiol modulates cytokine release through modulation of CD16 expression in human monocytes and macrophages and inhibits the release of pro-inflammatory cytokines[29].

Gender differences have been observed also in polymorphonuclear leukocytes, females showing a decreased neutrophil apoptosis, as compared to males[30]. Moreover, chemotaxis is enhanced by progesterone, inhibited by estrogens and unaffected by testosterone[31]. As far as the respiratory burst is concerned, contrasting and unconclusive results have been reported[26].

Gender differences have been reported also in autophagy[32].

Auto-immune diseases (AID)

Autoimmune diseases (AID) include more than 70 chronic disorders, affecting about 5% of population in the United States (with a cost of about 100 billion US dollars per year[33]) and presenting a large variability in terms of age of onset, targeted organs and response to therapy, but sharing a common feature: the female predominance[6,11,34-36].

Indeed, as shown in Table 2, the most striking sex differences are detected in Sjogren disease, systemic lupus erythematosus (SLE), systemic sclerosis, primary biliary cirrhosis and autoimmune thyroid diseases (Graves' disease and Hashimoto's thyroiditis)[4,5,34,37-39]. A female to male predominance also occurs for multiple sclerosis (MS), rheumatoid arthritis (RA), dermatomyositis and myasthenia gravis[37,40]. On the contrary, type 1 diabetes, idiopathic pulmonary fibrosis and myocarditis are more frequent in men than in women[37,41] (Table2).

Also the severity of AID may vary between males and females, even if this is not so clearly defined as in the case of gender prevalence. As an example, psoriasis, SLE and disability progression in MS are more severe in males[42-44] and men present autoimmune hepatitis at a younger age and have high relapse rates than women[45]; on the contrary, Crohn's disease is more severe in girls[46]. Moreover, MS women have poorer survival outcomes[47] and relative mortality for type 1 diabetes is higher in females than in males, at least in Finland[48]. Increased mortality in SLE patients has been also associated with female sex[49,50].

Despite the female susceptibility to AID has long been recognized, the precise cause of this bias is still

unknown and both genetic and environmental factors have been suggested as major determinants. A susceptible genetic background is necessary but does not explain by itself both AID onset and female predominance, while environmental factors act as additional players in tolerance breakdown[6,51].

The most reputed mechanisms include sex hormones, fetal microchimerism, sex chromosomes and their major defects; however, none of these determinants has gathered till now enough convincing data and conflicting results are often present.

Environmental factors

Increasing evidence supports a role for the environment in the development of AID[52] and at least two well-defined environmentally-associated diseases - i.e., the toxic oil syndrome that occurred after oleic anilide and 1,2-di-oleyl ester (DEPAP) addition to rapeseed oil[53] and the eosinophilia myalgia syndrome, occurring after ingestion of tryptophan that had been produced by an alternative manufacturing procedure[54] - have been described.

Infections, tobacco smoke, sun exposure, stress situations, diet and drugs have been all implicated in the development of AID[3,35].

Various AID have been linked to microorganisms, e.g., *Streptococcus pyogenes* for rheumatic heart disease, *Enterovirus* for type 1 diabetes[55,56]; tobacco smoke has been found to play a relevant role in some AID, as it may trigger the development of autoantibodies and act on pathogenic mechanism possibly related with an imbalance of the immune system[57].

Sun exposure (i.e., ultraviolet radiation) is reported to play a role in systemic sclerosis, RA, SLE and phospholipid syndrome[35] and a varied sunlight exposure may occur between males and females, depending on lifestyle and/or occupation.

Cosmetics (especially hair dyes and nail polish) may also trigger primary biliary cirrhosis, an AID with a striking female predominance that affects middle-aged women, mainly[58]. Food intake and food composition affect immunity and auto-immunity, as vitamins and micronutrients are necessary for immune cells' development and functioning[26,35]. As an example, low levels of vitamin D are associated with an increased risk for MS, SLE, autoimmune thyroid diseases and others[59-61].

Differences in the exposure to chemicals in the workplace between males and females are well documented and may contribute to the gender bias. As a general rule, exposure to pesticides results in anti-nuclear antibody formation[62], while exposure to organic solvents is a risk factor for systemic sclerosis, primary systemic vasculitis and MS[63].

Table 2. Female or male predominance in autoimmune diseases.

Autoimmune disease	Female : male ratio
Hashimoto's thyroiditis	19:1
Sjogren's syndrome	16:1
Systemic sclerosis	12:1
Primary biliary cirrhosis	10:1
Systemic lupus erythematosus	9:1
Graves' disease	7:1
Multiple sclerosis	3:1
Rheumatoid arthritis	3:1
Dermatomyositis	2:1
Myasthenia gravis	2:1
Type 1 diabetes	1:1.2
Myocarditis	1:2
Idiopathic pulmonary fibrosis	1:11

Genetic factors

Genetic polymorphisms largely contribute to AID susceptibility and may form the basis of ethnic differences in disease presentation and/or severity; as an example, in the United States, the black population presents a higher risk for SLE than whites[64]. Genome wide association studies (GWAS) are available for the commonest AID[3,65]; however, multiple genes are involved in disease susceptibility and the genetic patterns vary largely, so that most of the associations disclosed by GWAS are relatively modest[3]. Genetic factors may contribute to the sexual dimorphism of AID; several studies have focused on the interactions between gender and genes that affect antigen processing and presentation, lymphocyte proliferation and differentiation or encode immunoglobulins[3,35].

Human leukocyte antigen (HLA) genes are located in a region that includes many genes regulating the immune response, and there is a close association between HLA genes and AID such as Graves' thyroiditis[66], MS[67], RA[68] and SLE[35,69].

The majority of these associations are with HLA-DR and HLA-DQ genes, which encode for proteins that are mandatory for antigen presentation to $CD4^+$ T cells[35]. The association between HLA genes and AID usually presents a gender bias towards female[35], with the excep-

tion of SLE, where a higher HLA associated genetic risk is present in men[70].

Also non-HLA genes have been associated with AID susceptibility. For instance, polymorphisms in IL-10 are associated with disease severity in RA (an AA-1087 IL-10 genotype being more frequent in females[71,72]) and Sjogren's syndrome[73], while polymorphisms in acid phosphatase locus 1 (ACP1) and discs large homolog 5 (DLG5) have been linked to Crohn's disease[74,75].

Polymorphisms in apolipoprotein E (APOE) have been related to Sjogren's syndrome (women carrying APOE epsilon 4 allele presenting an earlier onset of disease than non-carriers[76]), and MS[77]. Indeed, in this latter disease, females who have the APOE epsilon2 allele present a less severe disease[78], while men carrying the APOE epsilon 4 allele experience the highest cognitive impairment[79].

Due to their pivotal role in innate immunity, toll-like receptors 7 (TLR7) and 8 (TLR8), too, have been intensively investigated. As an example, following TLR7 ligation, women responded with a significantly enhanced interferon (IFN)-alpha (but not TNF-alpha) production as compared to men[80].

Moreover, gender-specific association between TLR7 and TLR8 polymorphisms and TNF-alpha response after ligand stimulation were observed in measles virus and vaccine[81] (please, see also below).

Sex hormones and their role in the incidence of AID

Sex hormones, as well as genes encoded on the sex chromosomes and gender-specific behavior, largely contribute to AID and influence the different immune cells by modulating their responses. The role of sex hormones and gender disparity in immunity and autoimmunity has been reviewed in a previous issue of this journal[82]; therefore, in the present work, I'll provide just a few examples relative to some AID.

As known, estrogens stimulate B cell production of specific antibodies in response to infection, vaccination or autoantigens[41,82] and may further increase the risk of AID. However, estrogen therapy in MS[83] and RA[84] may be beneficial, as well as the use of contraceptives, at least in the case of RA women < 35 years of age[85]. On the contrary, estrogen worsens disease severity in SLE and, in this case, blockade of ER may be beneficial[86]. As with the contraceptive pill, diverging results are present in the literature concerning AID[35].

At high gestational levels, by inhibiting Th1 and Th17 pathways[82], progesterone significantly ameliorates RA and MS[87,88]. Consistently, RA, which was remitted during pregnancy, usually worsens post-partum[87,88]. Moreover, combined estrogen and progesterone hormone replacement therapy may induce lupus flares in post-menopausal women[89].

As far as androgens are concerned, Klinefelter's patients (that is, males with XXY karyotype) have an increased risk to develop SLE and androgen therapy reduces immunogloblulin levels[90].

One-year transdermal testosterone treatment was beneficial in MS male patients, even if it did not affect the number of lesions[91], while skin patches with testosterone did not mitigate disease severity in SLE females[92]. In this condition, conflicting results were also reported with oral dehydroepiandrosterone, a precursor of both androgens and estrogens[35]. Moreover, men with RA present low testosterone levels[93], men with low cortisol and androgen levels have an increased risk to develop RA[94] and androgen therapy in RA patients has provided some benefits[90].

While mostly secreted in the anterior pituitary gland, prolactin is also produced by human lymphocytes and binds the prolactin receptor (a member of the cytokine receptor superfamily) that is located on monocytes, T and B lymphocytes[35,95].

Activation of the prolactin receptor results in gene transcription, T cell proliferation and antibody secretion[96]. Thus, prolactin may potentiate AID, while hyperprolactinemia is often documented during different AID[97]. Moreover, antipsychotics-induced hyperprolactinemia is often associated with increased levels of thyroid autoantibodies[98]. It has been repetitively reported that bromocriptine reduces disease flares in SLE patients[99-102]; therefore, the issue of bromocriptine and prolactin antagonists for AID therapy warrants further investigations.

Fetal microchimerism in autoimmunity

Microchimerism (i.e, cells' trafficking from mother to fetus and vice-versa) occurs during pregnancy and usually persists for years after delivery, fetal microchimerism being the presence of fetal cells in the maternal circulation, whereas maternal microchimerism is the persistence of maternal cells into adult life[35,51,103].

A possible protective role has been proposed for fetal microchimerism, as fetal stem cells represent a potential source of cells for tissue repair, regeneration and immune suppression, but other evidences suggest that fetal microchimerism may favour neoplastic progression[35,104-106]. Fetal microchimerism was first evidenced in peripheral blood mononuclear cells from women with scleroderma who presented an increased level of male DNA, as compared to controls[107], but this finding was not confirmed by others[108].

Maternal microchimerism might result in detrimental effects, given that maternal cells are a possible source of graft vs host responses; however, it was recently shown to protect against asthma[35,109].

Despite microchimerism has been observed in autoimmune thyroid diseases, type 1 diabetes, RA and other AID[51,105-107,110], its role in autoimmunity and AID seems to be modest.

Sex chromosomes, especially X chromosome

Sex determination in mammals is mediated by the Sry gene on the Y chromosome, which induces the male developmental program11. Mice with the Sry gene deleted from the Y chromosome or trans-located to an autosomal region have been used to assess the role of sex chromosomes apart from the gonadal sex[11].

The X chromosome encodes about 1100 genes (that are distinct from the fewer than 100 genes on the Y chromosome)[90] and carries a large number of immune-related genes, including CD40L, CXCR3, OGT, FOXP3, TLR7, TLR8, IL12RG[51,111-113]. This is partly responsible for the female immune advantage[117] as, in general, women produce a more vigorous immune response to infection and this fact has been suggested as a tool to explain why women usually live longer than men[2].

In females, one copy of the X chromosome is inactivated to allow equal gene expression dosage between XX females and XY males. At early development, one of the X chromosomes is silenced, resulting in a mosaic expression of either the maternal or paternal X chromosome; therefore, each X-linked gene mutation is potentially expressed in 50% cells in females but in 100% cells in males. The loss of mosaicism hypothesis states that alterations in the random X chromosome inactivation may result in autoimmunity and has been proposed to explain the female predominance in AID[51,114-116].

The first support to this hypothesis came from the non-specific, polyclonal T cell activation that activated B cells presenting the same endogenous X-chromosome self antigen in females with SLE[51,116-117]. Indeed, the frequency of Klinefelter's syndrome (males with XXY karyotype) is 14-fold higher in men with SLE than normal men[118] and is comparable to the risk in females, while women with a particular X chromosome deletion (as found in the Turner's syndrome) are at lower risk for SLE[119]. Moreover, enhanced frequency of X monosomy has been found in women with primary biliary cirrhosis and autoimmune thyroid diseases, but not SLE[120,121].

It has also been estimated that about 10% of the X chromosome escapes inactivation[122]: this may determine the over-expression of some gene products in females, potentially positive or negative effects depending on the gene. Over-expression and/or hypomethylation of CD40L, CXCR3 and OGT have been reported in female, but not male, SLE patients[123,124]. FOXP3, a gene that localizes in the short arm of the X chromosome, is essential for Treg cells and its deficiency or mutation leads to aggressive and often fatal multi-organ AID[125].

Small non-coding microRNAs (miRNAs) regulate post-transcriptional gene expression by targeting mRNAs and are emerging as new players in AID. The X chromosome (but not the Y chromosome) is highly enriched for miRNAs, whose expression can be regulated by estrogens: an altered miRNA expression has been documented in some AID, including MS, RA, SLE[126,127].

In relation to autoimmunity, poor attention has been dedicated to the Y chromosome. It has been suggested to play a role in the inheritance of coronary artery disease[128] and has been demonstrated to undergo an age-dependent loss is some AID, including thyroid autoimmune diseases and primary biliary cirrhosis[129,130].

Conclusions

Gender differences in immunity, affecting both the innate and the adaptive immune responses, contribute to differences, between males and females, in the pathogenesis of infectious diseases, the response to vaccination and the prevalence of AID. Women have a lower burden of infections, most evident during their fertile years, but experience a higher incidence of AID. The gonadal hormones contribute to this clear gender bias, but alone are not enough. Other main players, e.g., genetic and environmental factors, sex chromosomes and their flaws, participate in such complex scenario, even if none of them has so far obtained a series of incontrovertible data, discrepant results being often reported.

Further investigation is needed to broaden our knowledge on sex and gender differences in immunity and AID; anyway, the differences so far highlighted are sufficient to suggest the need for gender-oriented therapeutic strategies in AID.

Key messages

- Gender differences in immune responses are well documented.
- Most auto-immune diseases share a common feature: the prevalence of the female sex.
- Immune cells express receptors for steroid sex hormones.
- Sex hormones modulate the immune responses and play a role in the onset and progression of autoimmune diseases.
- Besides sex hormones, genetic and epigenetic factors can influence the susceptibility to autoimmune diseases.

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