The Mosaic of Autoimmunity: Hormonal and Environmental Factors Involved in Autoimmune Diseases – 2008

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Key words: hormones, autoimmunity, pregnancy, Epstein-Barr virus, stress, smoking

IMAJ 2008;10:8–12

In the previous article we summarized the genetic factors involved in the mosaic of autoimmunity. In this article we will concentrate on some of the hormonal and environmental factors contributing to this mosaic.

Nocturnal hormones and circadian rhythms in arthritis

Circadian rhythms are driven by biological clocks and are endogenous in origin [1]. Therefore, circadian changes in the metabolism or secretion of endogenous glucocorticoids are responsible, in part, for the time-dependent changes observed in the immune/inflammatory response and related clinical symptoms (e.g., arthritis).

Recently, another circadian hormone, melatonin – the secretory product of the pineal gland – was found to be implicated in the time-dependent inflammatory reaction with effects opposite to those of cortisol, and as such, generates immune-potentiating activities. Interestingly, cortisol and melatonin show an opposite response to light [2]. The light conditions in the early morning have a strong impact on the morning cortisol peak, whereas melatonin is synthesized in a strictly nocturnal pattern. Reduced daily light exposure in northern Europe, at least during the winter, might explain the higher and more prolonged melatonin concentrations, as well as some epidemiological features concerning the prevalence of autoimmune diseases such as rheumatoid arthritis, that are observed in northern Europeans versus southern Europeans [3].

A diurnal rhythmicity in healthy humans between cellular (Th1 type) and humoral (Th2 type) immune responses was recently found and was related to the immunomodulatory actions of cortisol (decrease) and melatonin (increase) [4]. The interferon-gamma/interleukin-10 ratio peaks during the early morning and correlates negatively with plasma cortisol and positively with plasma melatonin. Accordingly, the intensity of arthritic pain varies consistently as a function of the hour of the day: pain is

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greater after waking up in the morning than in the afternoon or evening.

The reduced cortisol and adrenal androgen secretion observed during testing in rheumatoid arthritis patients not treated with glucocoticoids should be considered as a "relative adrenal insufficiency" in the presence of a sustained inflammatory process; it allows Th1 type cytokines to be produced in higher amounts after midnight. The clinical conclusion is that the right timing (early morning) for the glucocorticoid "replacement" therapy in arthritis is fundamental and well justified by the circadian rhythms of the inflammatory mechanisms.

Estrogen, autoimmunity and systemic lupus erythematosus

The impact of estrogens on the immune system is momentous. Not only natural hormones, but also endocrine disruptors, such as environmental estrogens, act in conjunction with other factors to override immune tolerance to self-antigens [5].

Murine experimental studies demonstrated that the gender bias in the prototypical autoimmune disease systemic lupus erythematosus may be influenced by sex hormones and genetic factors. The female hormones estrogen and prolactin act as immunostimulators, accelerating onset of the disease and causing early mortality in the NZB/W F1 murine model of lupus [5]. Also, both estrogen and prolactin induced lupus in mice, which are not spontaneously autoimmune, by impairing the deletion of autoreactive B cells. Estrogen leads to the survival and activation of autoreactive B cells by eliciting T cell-independent autoreactive marginal zone B cells [6]. An elevation in serum levels of estradiol facilitates the maturation of a pathogenic naive autoreactive B cell repertoire and hampers the maturation of a potentially protective autoreactive B cell repertoire [7].

Blockade of estrogen and inhibition of prolactin secretion with selective estrogen receptor modulators and bromocriptine, respectively, provides a therapeutic effect in lupus-prone mice, as well as in mice with estrogen- or prolactin-induced lupus. Tamoxifen prevents the development of estrogen-induced murine lupus by deterring DNA-reactive B cells from becoming marginal zone B cells, which are known to harbor autoreactivity in this hormone-induced model of lupus. Raloxifene increases survival in MRL/lpr lupus-prone mice by mitigating the progression of lupus nephritis.

Estrogen receptor-beta activation plays the predominant and immunostimulatory role in the estrogen-mediated modulation of lupus, but at the same time appears to have a slightly immunosuppressive effect on this disease, as shown in ovariectomized NZB/NZW F1 mice treated with specific estrogen receptor antagonists [8]. In addition to the inhibitory effect on the production of Th1 cytokines (IL-12, tumor necrosis factor-alpha, IFNγ), estrogen stimulates the production of Th2 cytokines (Il-10, IL-4, transforming growth factor-beta) [9].

The effects of the hormones are genetically determined, and it has been established that certain genetic factors (e.g., lupus susceptibility locus Sle3) synergize with prolactin to allow the development of lupus. In contrast to female sex hormones, androgens have an ameliorative effect on disease activity in lupus-prone mice [10].

Alterations of specific gender-associated genetic factors are linked to murine lupus. The Yaa mutation on the Y chromosome of lupus-prone BXSB male mice contains a duplication of a set of genes from the X chromosome. One of these duplicated genes encodes for TLR7, and the extra copy of this gene leads to a doubling of the RNA receptor and renders the BXSB mice predisposed to an autoimmune response to the body's own RNA [5].

Hyperprolactinemia was observed in 15–33% of SLE patients. The activity of the disease is related, most probably, to the 23 kD prolactin (little prolactin). In two studies bromocriptine treatment for mild to moderate SLE significantly improved disease activity and reduced the flare rate. Discontinuation of bromocriptine was followed by a flare of disease activity [11].

Exposure of the immune system to estrogens may be endogenous or exogenous, the latter by introduction for therapeutic purposes. Artificial hyper-estrogenic states can affect SLE disease activity: ingestion of oral contraceptives high in estrogen content by young women and hormone replacement therapy for post-menopausal women may be associated with mild disease flare-up. Ovarian stimulation may lead to the development of SLE or induction of SLE flares [5].

A hormonal dysequilibrium can also influence the development of lupus. Injection of a pathogenic idiotype, human anti-DNA (16/6 Id+) antibody to BALB/c female mice and orchiectomized male mice treated with estrogen caused a rapid outburst of the disease 3 months after immunization, while non-estrogen-treated mice developed the disease 5 months after immunization. The sex steroid metabolism of patients with Klinefelter's syndrome and SLE is similar to that of women with SLE. Hyper-estrogenic states in transgender males may lead to the development of lupus.

The mechanisms by which potential sources of environmental estrogens – such as plastic bottles, pesticides, industrial chemicals, and phytoestrogens – could alter the immune system (oral, aerosol, or dermal routes) by mimicking natural hormones, blocking hormonal binding to estrogen receptors, or altering the metabolism of natural estrogens are yet to be established [5].

Pregnancy and autoimmunity

Pregnancy is a condition in which profound immune-endocrine changes occur in order to achieve immunosuppression and tolerance by the immune system to paternal and fetal antigens [12]. Steroid hormones play an important role because of their strong modulating effects on the immune system. Hormones account for the higher immune reactivity and susceptibility to autoimmunity in females compared to males during the reproductive age. Estrogens seem to be mainly implicated as major enhancers

IL = interleukin
IFN = interferon

SLE = systemic lupus erythematosus

of the immune response, whereas cortisol and androgens seem to act as natural suppressors [12]. It is well known that estrogens progressively increase in maternal circulation during pregnancy, particularly in the third trimester. Although less markedly, an increase in cortisol and progesterone was also observed during pregnancy.

Progesterone is the crucial hormone during the first part of pregnancy and the precursor of some fetal hormones. It also has other functions, some of which are still partially unknown. Its origin is placental since it is secreted by the corpus luteum during the first 6–8 weeks of gestation. During normal pregnancy progesterone levels are four to six times higher than non-pregnancy levels. Deoxicorticosterone, one of its metabolites, is found in concentrations 1000 times higher than that in the non-pregnant state, but the physiologic role of this hormone is still not known [12].

Estrogen concentration is also significantly increased during pregnancy, reaching levels three to eight times higher than normal levels [13]. This increase is the result of a unique interchange between mother and fetus. The fetus uses the pregnenolone produced by the placenta in order to produce adrenal dehydroepiandrosterone and dehydroepiandrosterone sulphate. These hormones are metabolized to androstenedione and testosterone at the level of the placenta. Finally, they are rapidly converted to estrone and estradiol and released into the maternal circulation.

The physiological increase of cortisol, progesterone, estradiol and testosterone during the third trimester of pregnancy seems to lead to Th2 cytokine polarization both at the systemic level and at the fetomaternal interface [14]. Therefore, the suppression of the immune response mediated by Th1 cytokines seems to be essential for fetal survival.

Elevated levels of Th2 cytokines, such as IL-10, have been found in the placenta and amniotic fluid during the third trimester of pregnancy [12]. It has also been demonstrated that during pregnancy IL-6 serum levels gradually increase in the maternal circulation and even more so during labor [1]. TNFα serum levels do not vary during pregnancy, whereas those of the TNFα soluble receptors increase – probably to protect the fetus from the dangerous effects of TNFα [12].

It is known that glucocorticoids inhibit IL-1, TNFα, IFNγ and IL-2 production and stimulate IL-10, IL-4 and IL-13 synthesis, confirming a modulatory effect on the balance between anti-inflammatory/immunosuppressive responses during pregnancy. At physiological concentrations progesterone stimulates IL-4 (Th2 cytokine) synthesis, whereas estradiol stimulates TNFα production (Th1 cytokine). In contrast, at pharmacological levels, such as those observed during the second part of pregnancy, progesterone inhibits TNFα secretion and stimulates IL-10 production in T lymphocyte clones, leading to an increased humoral immune response [12].

Autoimmune rheumatic diseases affect young females in their childbearing years. Over the last few decades the improvement in survival as well as in quality of life in patients affected with autoimmune diseases has led to an increased number of pregnancies during the course of such diseases.

It is noteworthy that some autoimmune diseases (such as SLE), which are mainly mediated by Th2 cytokines, tend to occur or relapse during pregnancy [15], whereas Th1-mediated diseases (such as rheumatoid arthritis) tend to improve. In both cases there is a flare or onset of disease during the postpartum period, when the anti-inflammatory Th2 cytokines collapse due to a modification in the balance between estrogens and androgens and to an increase in prolactin levels [12].

Data on pregnancy outcome in other autoimmune diseases such as ankylosing spondylitis, Sjögren's syndrome, undifferentiated connective tissue diseases, systemic sclerosis, polymyositis dermatomyositis and systemic vasculitis, are limited mainly because most of them are rare and their onset occurs after the age of 40 [16].

EBV infection represents the relationship between infection and autoimmunity

When discussing the mosaic of autoimmunity we must consider environmental factors as contributors to the development of autoimmune diseases. Of all, most probably the most important environmental factor is infection by a microbial agent. Briefly, there are five main mechanisms by which such an infection can lead to an autoimmune disease. The first is molecular mimicry where the infecting agent may incorporate an epitope that is structurally similar to that of a self-antigen. The second is a phenomenon known as "epitope spreading," where an exaggerated local activation of antigen-presenting cells due to an inflammatory state may cause over-processing and over-presentation of antigens that may cause the priming of large numbers of T cells with broad specificities, thus encouraging the development of the autoimmune disease. The third refers to polyclonal activation, a mechanism where an infection of B cells results in B cell proliferation, enhanced antibody production, and the generation of circulating immune complexes which may cause damage to self-tissues. Bystander activation, the fourth mechanism, describes a situation where enhanced cytokine production induces the expansion of autoreactive T cells whose prior number was insufficient to produce an overt disease. Finally, viral and bacterial super-antigens possess the ability to bind to the variable domain of the T cell receptor beta chain along with the ability to bind to a wide variety of major histocompatibility complex class 2 molecules, thereby allowing them to bind to a wide variety of T cells, irrespective of their specificity, and to induce an autoimmune reaction.

EBV infection is, to date, the most well-established relationship between a viral infection and the development of an autoimmune disease. The best understood relationship is that of EBV and SLE. Several explanations have been offered for this interesting association, yet molecular mimicry between EBV nuclear antigen-1 and lupus-specific antibodies such as anti-dsDNA, anti-Ro and anti-La, is considered the most profound.

TNF = tumor necrosis factor

EBV = Epstein-Barr virus

As previously reviewed [17], EBV has been associated with many chronic autoimmune diseases, including SLE, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, autoimmune thyroiditis, autoimmune hepatitis and Kawasaki disease. Recently, we observed a higher prevalence of EBV antibodies in polymyositis patients when compared to controls, thus raising the possibility that EBV plays a role in the pathogenesis of polymyositis as well [18].

Vaccines and adjuvants in the mosaic of autoimmunity

Since 1796, when Edward Jenner inoculated cowpox material and prevented smallpox in 12 people, vaccination has been used as an indispensable tool against infectious diseases. In fact, it may be considered one of the greatest medical discoveries since it succeeded in totally eradicating some diseases around the world (plague and smallpox) and consequently improved the quality of life and survival of entire populations [19].

However, several adverse effects can ensue from the vaccination, ranging from local reactions to systemic side effects, such as fever, flu-like symptoms, gastrointestinal disorders and, in the last two to three decades, the most serious – autoimmune diseases [20]. Considerable data have recently been gathered with regard to involvement of the immune system following vaccination, although its precise role has not been fully elucidated [21]. Several authors have postulated that the autoimmunity process could be triggered or enhanced by vaccine immunogen content as well as by adjuvants, which are used to increase the immune reaction [19].

A common target for the occurrence of autoimmune complications is the central nervous system, with the appearance of demyelinating disorders such as multiple sclerosis, and other neurological conditions, e.g., Guillain-Barré syndrome and autism.

Other autoimmune diseases that may occur after vaccination include arthritis, rheumatoid arthritis, reactive arthritis, SLE, diabetes mellitus, thrombocytopenia, vasculitis, Reiter's syndrome, dermatomyositis, and polyarteritis nodosa. Other vaccines reported to be associated with the onset of autoimmune disorders are the following: rubella, mumps and measles; influenza; diphtheria, pertussis and toxoid; typhoid; hepatitis A and B; tetanus; Meningococcus; Bacillus Calmette-Guerin; rabies; smallpox; and poliovirus vaccines (practically all types).

The relationship between vaccines and autoimmunity is bi-directional. On the one hand, vaccines prevent infectious conditions, and in turn prevent the development of an overt autoimmune disease which in some individuals is triggered by infections. On the other hand, many case reports and series that describe autoimmune diseases post-vaccination strongly suggest that vaccines can trigger autoimmunity.

It is important to emphasize that a temporal relationship between autoimmunity and a specific vaccine is not always apparent. This matter is complicated by the fact that one vaccine may cause more than one autoimmune phenomenon and, likewise, a particular immune process may be caused by more than one vaccine [20].

Appropriate epidemiological studies should be undertaken to confirm the case reports or series where familial or genetic risk factors for autoimmune conditions were found in many of the patients who developed autoimmune disturbances after vaccination. In this way, vaccination should be considered part of the mosaic of autoimmunity, in which abrogation of an infectious disease could concomitantly induce another autoimmune disease. In summary, throughout our lifetime the normal immune system walks a fine line between preserving normalcy and the development of autoimmune disease [21].

Stress as a trigger for autoimmune disease [22,23]

Physical and psychological stresses have also been implicated in the development of autoimmune disease, as evidenced by numerous animal and human studies demonstrating the effect of sundry stressors on immune function. Moreover, many retrospective studies found that a high proportion (up to 80%) of patients reported uncommon emotional stress before disease onset. Several studies suggest that stress is not only a participating factor but may also be a cause of disease exacerbations. Unfortunately, it is a vicious circle because not only does stress cause disease, the disease itself causes considerable stress in patients.

Hans Selye defined stress as "a non-specific response of the body to any demand made upon it." Selye's theory about the effects of stress has been shown to be applicable to any sort of stress. However, the word "stress" has been oversimplified and manipulated in public usage. It is worth repeating that the stress system orchestrates body and brain responses to the environment. Stress may be related to work (internal), community (external), or family; it may be cumulative or related to a particular critical incident. The possible role of psychological stress and the major stress-related hormones as etiologic factors in the pathogenesis of autoimmune disease were discussed in recent reviews. It was presumed that neuroendocrine hormones triggered during stress may lead to immune dysregulation or altered or amplified cytokine production, resulting in autoimmune diseases. Various types of transmitter substances of the neuroendocrine-immune network include epinephrine, norepinephrine, acetylcholine, substance P, vasoactive intestinal peptide, glucagon, insulin, cytokines, growth factors, and numerous other mediators. The stress response and induction of a dysregulation of cytokine balance can trigger the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. In addition, the multiple roles of Th2 cells in maintaining allergic inflammation and altering the balance between Th1 and Th2 responses are important mechanisms for allergic inflammation and tissue damage. These new concepts of neuroendocrine immunology are necessary to better understand the role of stress in the pathogenesis of autoimmune diseases and to improve the treatment. Therefore, the treatment for autoimmune diseases should include stress management and behavioral intervention to prevent stress-related immune imbalances. Different stress reactions should be discussed in patients with autoimmune diseases, and questionnaires on trigger factors

should include questions on psychological stress, in addition to infection, trauma and other common "triggers."

Smoking and autoimmune diseases [24]

Tobacco smoking is one of the most potent environmental factors that influence autoimmune diseases. It has been shown to modify many inflammatory and autoimmune diseases through various mechanisms including immunomodulation and chemical exposure. Smoking has been associated with SLE; the incidence rate ratios for current and past smoking for development of the disease were found to be 1.6. In addition, in a meta-analysis of studies from 1966 to 2002 on the role of smoking as a risk factor for the development of SLE, the odds of SLE in current smokers versus never-smokers was 1.5. Regarding clinical manifestations, SLE patients who were current smokers were found to suffer more from pleuritis and peritonitis and expressed more neuropsychiatric symptoms and lupus headaches compared to non-smoking patients.

The association of smoking with rheumatoid arthritis is even more established. Smoking was found to be associated with the incidence of seropositive rheumatoid arthritis. Relative risks for ex-smokers and current smokers compared to non-smokers were 2.6 and 3.8 respectively. Smoking has been determined to be associated with an increased risk of rheumatoid arthritis, an effect that was more pronounced in male compared to female patients, and in seropositive compared to seronegative patients [24]. Smoking interacts with genetic risk factors such as specific HLA-DR alleles, creating up to a 21-fold risk of disease. Moreover, smoking has been demonstrated to be associated with increased disease activity and a decreased response to anti-TNFα therapy [24].

Smoking can contribute to autoimmunity by diverse mechanisms [25]. It induces tissue damage and increases apoptosis through generation of free radicals, release of metalloproteinases, and the induction of Fas expression on lymphocytes. In addition, smoking induces inflammation as it causes elevation of fibrinogen levels, induces leukocytosis, and elevates levels of C-reactive protein, intercellular adhesion molecule-1 and E-selectin [25]. These findings support non-smoking as a possible preventive measure for autoimmune diseases.

Thus, new hormones and diverse environmental factors are currently being added to the mosaic of autoimmunity.

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