Leaders between steroid hormones and cytokines in rheumatoid arthritis and systemic lupus erythematosus

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are multifactorial autoimmune diseases that originate from the patient's excessive immune and inflammatory response to a pathogenic agent (that is, an infective antigen).

The pathophysiological mechanisms are activated after the combination of several predisposing factors, which include the relations between histocompatibility epitopes and epitopes of the pathogenic antigen, the altered status of the stress response system (hypothalamic-pituitary-adrenocortical axis = HPA) and the gonadal hormone pattern (hypothalamic-pituitary-gonadal axis = HPG), with oestrogens principally implicated as enhancers of the immune response, and androgens and progesterone as natural suppressors.

An intricate balance with bidirectional interactions between soluble mediators, released by the neuroendocrine system (that is, steroid hormones and neuropeptides) and products of activated cells of the immune/inflammatory system (cytokines) maintains the homeostasis in presence of the immune/inflammatory stimulus.

Cytokine patterns and sub-patterns in RA and SLE

Cytokine secretion seems fundamental in determining the duration and intensity of an immune response, and how steroid hormones (gonadal and adrenal steroids) influence autoimmunity may entail a further balance between Th1 and Th2 lymphocyte responses.

Th1 lymphocytes produce mainly interleukin 2 (IL2) and interferon γ (IFNγ) and are primarily responsible for cell mediated immunity, while Th2 lymphocytes produce mainly IL4, IL5, IL13, and IL10, and are responsible for

Figure 1 Genetic, infectious, and dietary factors, as well as gonadal/adrenal steroid hormones, play a predisposing part in autoimmune diseases such as RA and SLE. Therefore, the involvement of the hypothalamic-pituitary-adrenocortical (HPA = adrenal steroids) and -gonadal (HPG = gonadal steroids) axis is crucial and interferes with the immune system response.

Figure 2 Role of Th1/Th2 cytokines in the regulation of cellular and humoral immunity. IL6, probably secreted by activated macrophages (Mø) is able to polarise naive CD4+ T cells (Th0) to effector Th2 cells, by inducing the initial production of IL4 in CD4+ T cells. IL12 triggers the differentiation of Th1 cells. Th1 and Th2 cells are mutually inhibitory. RA and SLE are Th1 and Th2 driven diseases, respectively.
humoral immunity, supporting the activation of immunoglobulin secreting cells (fig 2).\textsuperscript{14, 17} IL6, probably secreted by activated antigen presenting cells (macrophages), is able to polarise naïve CD4+ T cells to effector Th2 cells by inducing the initial production of IL4 in CD4+ T cells (fig 2).\textsuperscript{18} In contrast, IL12 triggers the differentiation of Th1 cells. Th1 and Th2 cells are mutually inhibitory (fig 2).

Recent data show different patterns of cytokine production (Th1 and Th2) between patients affected by RA and SLE.\textsuperscript{19, 20} In particular, based on these differences, RA is considered to be “Th1-cytokine driven” disease, whereas SLE is considered to be “Th2-cytokine dependent” disease.\textsuperscript{21, 22}

Broad differences in the clinical presentation and progression of both RA and SLE, complicate both the early diagnosis and the identification of patients in need of differentiated treatment. In fact, distinct sub-patterns of cytokine secretion characterise new onset synovitis versus chronic RA.\textsuperscript{20}

Patients with new onset synovitis, presented increased numbers of peripheral blood mononuclear cells (PBMC) secreting IL2 and IFNγ, while patients with chronic RA showed increased numbers of PBMC secreting IL6, IL10 and TNFα.\textsuperscript{20}

Correlations between joint score and number of PBMC, suggested that the number of PBMC secreting IFNγ is most relevant in new onset synovitis, while the number of PBMC secreting IL6, IL10, and TNFα is of greater relevance in chronic RA. Similarly, different serum cytokine sub-patterns have been associated with different clinical manifestations in SLE patients.\textsuperscript{19}

The serum concentrations of IL6 and IFNγ were found increased in patients with SLE associated with lymphadenopathy (LN) or nephritic syndrome (NS). In contrast, the serum concentrations of TNFα were increased in SLE patients with associated thrombocytopenia (TP) and normal in association with LN, NS or central nervous system involvement. SLE patients with associated humoral immunodeficiency disorder such as hypogammaglobulinaemia showed higher values of serum IL6.\textsuperscript{19}

Recently, a polymorphism within the IL10 gene promoter that is associated with high IL10 serum concentrations, has been described in SLE patients and has been suggested as playing a part in the development of certain clinical features in this disease.\textsuperscript{23}

Therefore, abnormal production of various cytokines in SLE, might be an intrinsic defect of PBMC and of the immune system that may explain the variety of clinical manifestations of the disease.

In conclusion, all these observations suggest that distinct cytokine secretion abnormalities may have a paramount importance in the triggering and/or maintenance of the different pathophysiological mechanisms and clinical aspects characterising RA, SLE, and probably other autoimmune disorders.\textsuperscript{24}

### Clinical relations between steroid hormones and cytokine patterns in RA and SLE

There is agreement that, the ability to make more or less of cytokine patterns in RA and SLE. Clinical relations between steroid hormones and cytokine patterns in RA and SLE and the critical immunoregulatory molecules, such as the immunodeficiency disorder such as hypogammaglobulinaemia. SLE patients with associated humoral involvement. SLE patients with associated lymphadenopathy (LN), nephritic syndrome (NS), or central nervous system involvement. SLE patients with associated humoral immunodeficiency disorder such as hypogammaglobulinaemia showed higher values of serum IL6.\textsuperscript{19}

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### Table 1 Effects of gonadal and adrenal (cortisol and DHEA) steroid hormones on macrophage, Th1-type and Th2-type cytokine production

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cortisol</th>
<th>Estradiol</th>
<th>Testosterone</th>
<th>DHEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL1</td>
<td>−</td>
<td>+*(/-)†</td>
<td>?</td>
<td>?</td>
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<tr>
<td>IL6</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
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<tr>
<td>TNFα</td>
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<td>+⋆/−⋆</td>
<td>−</td>
<td>−</td>
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<td>IL12</td>
<td>?</td>
<td>−</td>
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<td>?</td>
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<tr>
<td>Th1-type</td>
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<tr>
<td>IL10</td>
<td>?</td>
<td>?</td>
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<td>?</td>
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<tr>
<td>Th2-type</td>
<td></td>
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<td></td>
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<tr>
<td>IL4</td>
<td>?</td>
<td>?</td>
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<td>?</td>
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<tr>
<td>IL10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
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<tr>
<td>IL13</td>
<td>+</td>
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* = Physiological concentrations, † = pharmacological concentrations, + = enhancement of cytokine production, − = inhibition of cytokine production, ? = not determined.
usually results in increased systemic and local concentrations of cortisol might contribute to a polarised Th2-type cytokine milieu.

Progesterone increases IL4 production (Th2-type cytokine) by human T cells, while oestriadiol increases TNFα (Th1-type cytokine) secretion by clones at physiological concentration. However, it inhibits TNFα secretion at higher or pharmacological concentrations (late pregnancy) and increases the human IL10 production by T cell clones resulting in increased humoral immunity (table 1).35 54

Recent studies, however, have shown that testosterone also induces the immune responses towards the Th2 phenotype in the experimental autoimmune encephalomyelitis (EAE), which is a model for the human demyelinating disease multiple sclerosis.30

In fact, T lymphocytes derived from the spleen of men, during the effector phase of adoptive EAE and from dihydrotestosterone implanted EAE women, produced significantly higher concentrations of IL10 than those from women and placebo, respectively (table 1). Testosterone replacement therapy has been to improve clinical and laboratory parameters in male RA patients.30

On the basis of these steroid driven mechanisms, new explanations for the different age related incidence and behaviour of both RA and SLE might be suggested, at least in female patients.

The gradual decline of cortisol and oestrogens, observed around menopause, might explain the high incidence of RA at that time, with mechanisms similar to those realised in the postpartum period. Conversely, the same hormonal changes might explain the high incidence of SLE observed during the fertile ages and the decline around menopause.37

By acting through similar mechanisms, the increased serum oestrogen concentrations obtained by current use of oral contraceptives may protect the RA patients, but tend to exacerbate the disease in SLE patients as seen in clinical practice.34 35

Increased concentrations of oestrogens, as obtained after ovulation induction therapy, have been recently described to induce a severe or fatal exacerbation of the disease in several women with SLE, the concomitant presence of antiphospholipid antibodies being considered a further risk factor.34 35

Serum DHEA has been found decreased in premenopausal RA patients and in SLE patients, irrespective of age, sex, and disease activity.47 48

Recent double blind and open label studies of SLE patients treated with daily DHEA, showed a clinical efficacy, with the benefits sustained for at least one year in those patients who maintained treatment.49 50

When testosterone was administered to cultures of RA synovial macrophages it was metabolised and inhibited IL1 production, at least.51 52 Similar inhibition of IL1 and IL6, was found on PBMC of RA patients in presence of testosterone.54

In contrast, oestradiol was found to increase IL1 secretion in rat peritoneal macrophages and IL1 and IL6 production in human PBMC.53 54

Low serum testosterone concentrations have been observed in male RA and SLE patients and related to the aetipathogenesis of the diseases.60 67

Dihydrotestosterone (DHT), the active metabolite of testosterone, has been found to repress the expression and activity of the human IL6 gene promoter via inhibition of NFκB activity through maintenance of IkBa concentrations (fig 3).58 Human and murine macrophages exhibit functional cytoplasmic and nuclear testosterone receptors, and both site I (high affinity, low binding) and site II (low affinity, high binding) androgen receptors were found in HLA-DR positive human synovial macrophages.59 60

Therefore, in RA, synovial macrophages appear to be the “link” between the sex hormone environment (testosterone) and the immune response effectors (cytokine modulation).61

Low concentrations of plasma DHEA and DHEAS, have been found significantly correlated with early morning low cortisol concentrations and high basal concentrations of IL6 in RA patients.62 The finding of reduced DHEA production, combined with unexpected normal cortisol production during oCRH and ACTH testing, further support the concept of the presence of an adrenal hypofunction in active RA patients.63

IL6 had a strong effect on steroid release and may be one of the factors controlling the long term adrenal response to stress, because this cytokine is able to act synergistically with ACTH on the adrenal cells to stimulate the release of corticosterone.64 Therefore, the altered cortisol and adrenal androgen secretion observed during testing in RA patients not treated with corticosteroids, should be clearly regarded as an “adrenal insufficiency” in the setting of a sustained inflammatory process as shown by high IL6 concentrations.

Reduced concentrations of plasma DHEA and DHEAS, have been found significantly correlated in RA patients with high basal concentrations of IL12.62

Androgen modulation of cytokines in RA and SLE
Adrenal and gonadal androgens are considered natural immunosuppressors.41

Dehydroepiandrosterone (DHEA) is the most abundant adrenal steroid with androgenic properties and is present in about similar concentrations in both sexes. DHEA sulphate (DHEAS) is inactive and converted peripherally to DHEA, which exerts biological activity. DHEA has been found to have immunomodulatory activities. In vitro studies showed that DHEA increases secretion of IL2 by activated T lymphocytes (even in SLE patients) and decreases production of IL4, IL5, and IL6, thus stimulating Th1-type cytokines (fig 3).42 43

In particular, DHEAS has been found to repress the expression and activity of the human IL6 gene promoter, thus supporting the concept of antiinflammatory/ immunosuppressive effects exerted by androgenic steroids (table 1).44

Specific receptors for the free active adrenal androgen DHEA, have been found in T cells and particularly in activated Th1 subtype of T-cells; however, further studies are needed to elucidate their significance.35

Furthermore, DHEAS is positively correlated with the IL2 soluble receptor in SLE patients.55

Figure 3 Schematic representation of modulatory effects exerted by gonadal (testosterone) and adrenal (DHEA) steroid hormones on cytokine production, at the level of macrophages, Th1, and Th2 cells.
Recent studies, indicate that IL12 may play an important part in the perpetuation of Th1 responses in chronic RA, not only by inducing INF-Y secretion, but also by expanding Th1 cells.11 Therefore, the association of low DHEA and DHEAS and high IL12 concentrations in RA patients, might suggest their possible combined role in the Th1 responses.11

Conclusions
An intricate balance, with bidirectional interactions between steroid hormones released by the neuroendocrine system and cytokines released by activated cells of the immune/inflammatory system, maintains the homeostasis in presence of immune/inflammatory diseases, such as RA and SLE.

Pregnancy is considered the most evaluable natural and dynamic model to study the steroid hormone related changes induced on both cytokine patterns and clinical manifestations of these diseases.12 However, it is not clear whether pregnancy increases risk of the flare of disease in patients with SLE. Patients with inactive disease at conception may be have lower flare rate than controls—that is, pregnancy may be protective against a flare of the disease.13 Classically, it has been said that SLE tends to flare during the last part of pregnancy, however in most of the recent prospective studies, the percentage of flares in the third trimester falls.67 The rise of endogenous steroids and the related influences on cytokine patterns in the late pregnancy, seem to explain why the percentage of flares in the third trimester falls.67 The rise of endogenous steroids and the related influences on cytokine patterns in the late pregnancy, seem to explain why the pregnancy may be protective against a flare of the disease.13 Classically, it has been said that SLE tends to flare during the last part of pregnancy, however in most of the recent prospective studies, the percentage of flares in the third trimester falls.67 The rise of endogenous steroids and the related influences on cytokine patterns in the late pregnancy, seem to explain why the majority of SLE women can have a successful pregnancy.

Further treatment strategies, eventually as combination therapy, may be designed to shift antigen specific responses towards the desired Th0-like cytokine production in RA and SLE affected patients.

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