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Review

Estrogen metabolism and autoimmunity

Maurizio Cutolo [a,*], Alberto Sulli [a,1], Rainer H. Straub [b,2]

[a] Research Laboratory and Academic Unit of Clinical Rheumatology, Dept. Internal Medicine, University of Genova Italy, Viale Benedetto XV, 6-16132 Genova, Italy
[b] Laboratory of NeuroEndocrino-Immunology, Division of Rheumatology, Department of Internal Medicine I, University Hospital, D-93042 Regensburg, Germany

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ABSTRACT

Epidemiological and experimental immunological evidence suggest that estrogens enhance the humoral immune response, and at the same time, seem to play important roles in pathophysiology of autoimmune rheumatic diseases. Estrogens in human subjects are generally considered as enhancers of cell proliferation (anti-apoptotic), however, rather than through their serum levels (that may exert opposite dose-related effects), they play important roles through their peripheral metabolites especially in autoimmune rheumatic diseases. Several investigations strongly support an accelerated aromatase-mediated peripheral metabolic conversion of upstream androgen precursors to estrogen metabolites in peripheral tissues affected by immune/inflammatory reactions, both, in male and female patients. In RA synovial tissue, biological effects of these metabolites as a consequence of altered peripheral sex hormone synthesis (intracrine, e.g., at the level of macrophages and fibroblasts) mainly results in stimulation of cell proliferation and cytokine production (i.e. TNF). It was shown that RA synovial cells mainly produce the cell proproliferative 16alpha-hydroxyestrone which, in addition to 16alpha-hydroxy-17beta-estradiol, is the downstream estrogen metabolite that interferes with monocyte proliferation. Therefore, a preponderance of 16alpha-hydroxylated estrogens is an unfavorable sign, at least, in synovial inflammation and possibly related synovial tissue hyperplasia. Interestingly, urinary concentration and total urinary loss of 2-hydroxyestrogens was found 10 times higher in healthy subjects compared to RA or SLE patients irrespective of prior prednisolone treatment or sex. The intracrine synthesis of active estrogen metabolites at the level of cells involved in the immune response (e.g. macrophages and fibroblasts) represents a common pathway that characterizes a similar final immune reactivity in both male and female patients.

Contents

1. Introduction

The majority of hormones involved in pathogenesis/treatment of rheumatic diseases are cholesterol derivatives and are steroid hormones modulating a broad range of signaling mechanisms mainly linked to the immune response [1,2]. Cholesterol is precursor for six steroid hormone classes: progestagens (i.e. progesterone), glucocorticoids (i.e. cortisol), mineralcorticoids (i.e. aldosterone), androgens (i.e. testosterone), estrogens (i.e. 17beta estradiol) and finally D hormone (vitamin D). During its metabolism, cholesterol is hydroxylated and shortened to the C21 intermediates pregnenolone and progestagen that act also as precursors for the male and female sex hormones androgens (C19) and estrogens (C18), respectively [1].

2. Estrogens and the immune response

Based on epidemiological and immunological evaluations, estrogens in normal conditions enhance the humoral B cell immune response in humans, and at the same time seem to play important

* Corresponding author. Tel.: +39 010 353 7994, +39 010 353 8885 (Secretary), +39 335 233621 (Mobile); fax: +39 010 353 8885.
E-mail addresses: mcutolo@unige.it (M. Cutolo), albertosulli@unige.it (A. Sulli), rainer.straub@klinik.uni-regensburg.de (R.H. Straub).
[1] Tel.: +39 010 353 7779.
[2] Fax: +49 941 944 7121.

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roles in pathophysiology of autoimmune rheumatic diseases [1]. As a matter of fact, clinical evidences show that menstrual cycle, pregnancy, and menopausal status that are characterized by fluctuations of endogenous estrogens significantly influence the course of autoimmune diseases [2,3].

On the other hand, different concentrations used in vitro or in vivo testing, might render estrogens friend or foe in immuno-inflammatory conditions and different cells involved in the immune system react in an opposite manner to different estrogen concentrations [1,2]. In addition, the efficiency of the functional estrogen receptors (ER-alpha or ER-beta) found in macrophages and lymphocytes might be quite different under inflammatory conditions depending on the microenvironment and the type of disease [1,4–6] (Fig. 1). Generally, estrogens enhance cell proliferation and reduce cell apoptosis [2,7]. For example, 17β-estradiol was found to induce in dendritic cells via p38 and MAPKs the expression of CD40 which is a costimulatory molecule and plays a crucial role in modulating the immune response of effector cells [8].

Interestingly, different downstream estrogen metabolites (especially hydroxylated) interfere with monocyte proliferation and generally might modulate the immune response (see next paragraphs) [9]. Differently, estrogen treatment was found to protect isolated primary B cells from B cell receptor-mediated apoptosis [10]. These latter studies suggested that estrogen induces a genetic program that alters survival and activation of B cells in a B cell-autonomous fashion and thus skews the naive immune system toward autoreactivity and proliferation [10] (Fig. 1). In summary, if a disease is based on B cell-driven pathophysiology, estrogens can be harmful, while T cell-driven disease might be inhibited by estrogens.

2.1. Proliferative effects of peripherally synthesized estrogens — what we learn from tumors

The role of peripheral metabolism of estrogens is crucial in disease progression. Important perspectives arise from the observation that the production of estrogens from androgens is peripherally mediated by the aromatase enzyme complex, the aberrant expression of which plays a critical role in the development of malignancy in a number of tissues such as the prostate [11]. In fact, the altered promoter utilization can lead to an altered testosterone:estrogen ratio that is associated with the development of disease. Increased tissue estrogens on the basis of elevated endogenous estrogens due to aromatase overexpression cause initial prostatic inflammation [12]. Stimulation of estrogen receptors (ERalpha) leads to aberrant proliferation, inflammation and pre-malignant pathology [12]. Interestingly, inhibition of estrogen receptor-positive breast cancer (BCa) cell growth/proliferation has been reported which was mediated by calcitriol-dependent downregulation of aromatase transcription suggesting that calcitriol has a potential benefit for BCa therapy [13].

As a matter of fact, aromatase inhibitors can also be used for neoadjuvant therapy of BCa in which they have achieved better therapeutic efficacy than tamoxifen since local aromatase produces sufficient estrogen for its proliferation [14].

2.2. The peripheral estrogen metabolism and the local inflammatory influence

Several investigations strongly support an accelerated peripheral metabolic conversion of upstream androgen precursors to estrogen metabolites in peripheral tissues affected by immune/inflammatory reactions both in male and female patients [15]. High estrogen concentrations have been found particularly in synovial fluids of RA patients of both sexes and the most acceptable explanation might originate from recent studies showing that inflammatory cytokines (i.e. TNF, IL-6, IL-1), particularly increased in RA synovitis, are able to markedly stimulate aromatase activity [15–17] (Fig. 2).

A significant correlation was found between aromatase activity and IL-6 production in tissues rich in macrophages, and aromatase has also been found in fibroblast synoviocytes [18]. Therefore, the increased aromatase activity induced by locally produced inflammatory cytokines (i.e. TNF, IL-1, IL-6) might explain the altered balance resulting in lower androgens and higher estrogens in synovial fluid of active RA patients [4,17].

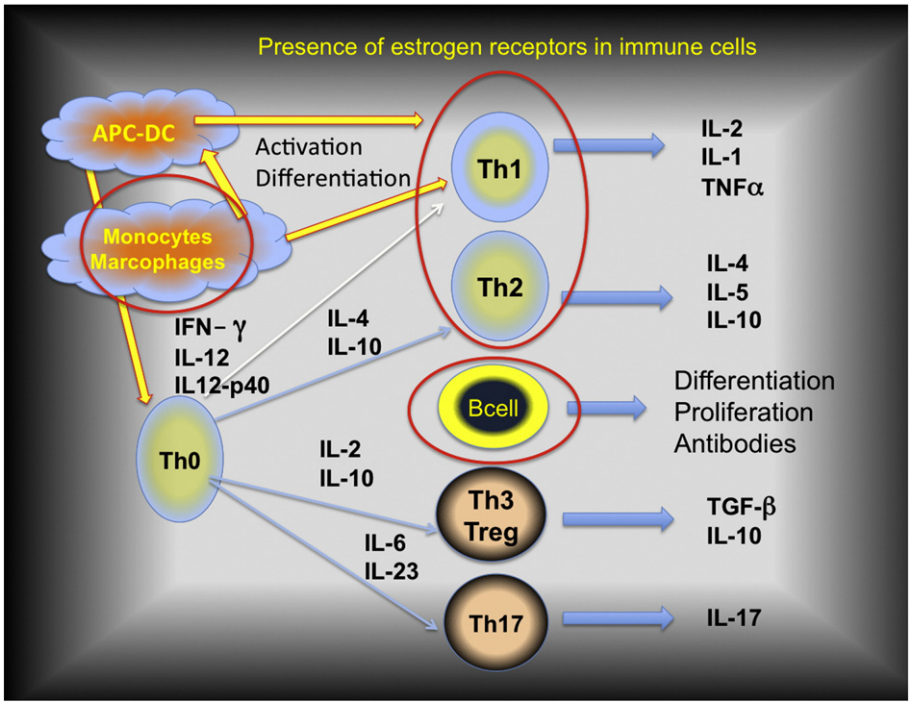

Fig. 1. Presence of estrogen receptors in cells involved in the immune response. Functional receptors have been found at the level of macrophages, T and B cells (see red circles).