Modulation of immune functions by oestrogens. Part I

Immunomodulacyjna rola estrogenów. Część I

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Summary

One of the most important functions of oestrogens is modulation of the immune system. By interactions with specific oestrogen receptors ERα and ERβ these sex steroid hormones are capable of regulating many aspects of both natural and adaptive immunity. Aging and the hypoestrogenic state can therefore influence immunological functions. Use of drugs belonging to SERM or isoflavones could also modify the immune response in post-menopausal women. All these phenomena might influence the risk of cancer initiation and the natural course of tumour growth.

Key words: immunology, oestrogens.

Streszczenie

Jedną z najważniejszych funkcji estrogenów jest zdolność modulowania działania układu immunologicznego. Poprzez interakcje ze swoistymi receptorami estrogenowymi ERα i ERβ estrogeny są zdolne do regulowania zarówno elementów odporności naturalnej, jak i swoistej. Dlatego starzenie się i towarzyszący mu stan hipoestrogenizmu mogą wpływać na funkcje immunologiczne. Podobnie zastosowanie u kobiet po menopauzie leków z grup SERM i izoflawonów może modyfikować odpowiedź immunologiczną. Zjawiska powyższe mogłyby stanowić mechanizm wpływający zarówno na ryzyko powstania, jak i na charakter wzrostu nowotworów.

Słowa kluczowe: immunologia, estrogeny.

Introduction

It is a commonly accepted fact that the biological functions of oestrogens are not limited to breast and reproductive organs, but that these hormones also influence body metabolism and function of the cardiovascular system, brain and bones. However, one of the most important beneficiaries of oestrogen regulatory capabilities is the immune system. The biological action of oestrogens is mediated through specific high-affinity oestrogen receptors (ERα and ERβ) which are ligand-dependent transcription factors [1, 2]. The genes subjected to oestrogen regulation include those responsible for cell differentiation, growth and survival [3]. The interaction of oestrogens with ER can occur directly, through oestrogen response elements (EREs), or indirectly through mediation of other transcription factors such as activator protein 1 (AP1), factor SP1 or nuclear factor κB (NF-κB) [4]. The receptor ERβ activates the same genes in the response to oestradiol stimulation; however, its efficacy is less than that of ERα. Generally, ERβ plays the role of an inhibitor of ERα in cells where both types of ER are present [5]. The final effect of oestrogen depends on its concentration, the relative cellular density of both ER, and co-activation by different factors [6]. Besides, oestrogens show probably ER-independent abilities of direct modulation of intracellular signalling pathways, through stimulation of kinases, phosphatases, and calcium channels [7]. At least one of the ER is expressed inside lymphoid organs, on the surface of haematopoietic progenitors in bone marrow, as well as on peripheral lymphocytes, natural killer cells (NK), neutrophils, dendritic cells (DC), monocytes and macrophages [8-13].

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Influence of oestrogens on immune function

Observations of immune functions in both females and males indicate the existence of gender-based differences. Compared to men, women have increased immunity towards infections caused by both extra- and intracellular pathogens, and generate stronger responses after vaccinations, but unfortunately show a predisposition to autoimmune reactions [14-16]. However, during the reproductive period women have better control over excessive inflammation, and thus are less prone to septic complications [17, 18]. Those gender-based differences indicated that sex steroid hormones, including oestrogens, could modify the immune response. The results of many studies performed on both mice and humans show that oestrogens enhance especially the humoral response, but the influence of cellular immunity seems to be more complex, and is either stimulatory or suppressive dependent on dose of oestrogen, duration of action and immune cell population [19-22].

Oestrogens and innate immunity

Animal studies clearly indicate that oestrogens can modulate the immune response in the reproductive tract of studied mice. The concentration of molecules of known antimicrobial activity present in cervical and uterine fluids such as lactoferrin and lysozyme is regulated by oestradiol concentrations [23, 24]. Oestradiol administered into mice caused an increase in uterine vascular permeability, which resulted in an increase of extravasated C1q, C2, C3, C4, and C6 components of the complement system in uterine tissues and luminal fluid [25]. During oestrus, characterized by the highest concentration of oestrogens, recruitment of neutrophils, macrophages and DC into the endometrium and uterine stroma was significantly increased [26-28]. Ovariectomized animals did not show such changes, unless they were given hormonal supplementation [29]. The number and function of uterine NK cells infiltrating the endometrium are also oestradiol dependent [30]. Exposure to oestrogens enhances cytotoxicity of peripheral blood NK cells and increases IFNγ secretion [31, 32]. Human studies support these results, and indicate that postmenopausal women show decreased NK activity, which returns to the premenopausal level during hormonal therapy [33]. Oestrogens indicate functional ambiguity towards innate immunity, as depending on their concentration and time of action, they are capable of down-regulation of an exaggerated immune response inside genital tracts by reduction of neutrophil infiltration and decrease of tumour necrosis factor-α (TNFα) production [34-36].

Oestrogens are also modulators of DC function, decreasing their migration, maturation and capacity for antigen presentation. Mouse studies indicated that oestradiol negatively regulated secretion of TNFα, interferon-γ (IFNγ) and interleukin (IL)-12 by DC, thus shifting cytokine production towards the Th2 profile (IL-4, IL-10) [37]. Inside reproductive organs oestrogens were able to disturb antigen presentation of both professional antigen-presenting cells (APC), such as DC and macrophages, and of epithelial cells functioning as non-classical APC [38, 39]. The above-mentioned mechanisms seem to be regulated by oestrogen-dependent secretion of transforming growth factor-β (TGFβ), inhibitory cytokine produced by immature DC [40, 41]. Oestrogens also promote DC survival, as administration of oestradiol immediately after trauma-haemorrhage prevented splenic DC apoptosis and dysfunction observed normally in these cases [42]. However, some investigations have put more criticism into our understanding of oestrogen-regulated DC function, because it was found that the regulatory capacity of oestrogens depends on their dose and time of action. Supra-physiological doses of oestradiol caused opposite effects than those described above. A short time exposure to higher oestradiol doses stimulated secretion of pro-inflammatory Th1 cytokines, while a long time exposure increased splenic DC antigen presentation capacity [43, 44]. Oestrogens could also have different influence on particular DC subpopulations (Langerhans cells, myeloid, splenic and IFN-producing killer DC) [45, 46], and exert opposing effects on DC bone marrow differentiation mediated by granulocyte-macrophage colony stimulating factor (GM-CSF) and Flt3 ligand [47]. As the Flt3-mediated pathway is used mainly in normal circumstances, while the GM-CSF-mediated pathway is used during inflammation, oestrogens seem to affect DC differentiation dependent on the status of homeostasis or pathology, as well as on cytokine milieu [48].

The influence of oestrogens on macrophage function consists of enhancement of expression of inducible nitric oxide synthase (iNOS) and proinflammatory IL-1, IL-6, IFNγ and TNFα cytokines [49, 50]. This oestrogen action was also confirmed in a mouse model of encephalitis. In this model microglial cells (macrophage homologues) of ovariectomized mice were unable to produce TNFα and IL-12 during brain infection [51]. However, as in the case of DC, the precise oestrogen action depends on its dose and differentiation state of monocytes and macrophages [52, 53]. Oestrogen induced Fas/FasL-dependent apoptosis in monocytes expressing ERβ, but not in macrophages expressing ERα [54]. It was found in "in vitro" studies that low concentrations of oestrogen induced iNOS activity in resting macrophages, but at higher concentrations oestrogen appeared to reduce iNOS activity [54-56]. According to some authors [57] even in the presence of physiological oestradiol concentrations activation of macrophages by lipopolysaccharide (LPS) was

ineffective, due to inhibitory effects of oestrogen on NK-κB function, and induction of macrophage apoptosis. These observations support the thesis of anti-inflammatory oestrogen function in high/normal dose and suggest that it affects the activation of macrophages by toll-like receptor (TLR) ligands [58].

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