Modulation of immune functions by oestrogens. Part II

Immunomodulacyjna rola estrogenów. Część II

Jacek R. Wilczyński

Department of Gynecological Surgery, "Polish Mother's Memorial Hospital" Research Institute, Lodz, Poland,
Head of Department: Prof. Marian Szpakowski MD PhD
Department of Gynecology, Chair of Obstetrics & Surgical Gynecology, Medical University of Lodz, Poland,
Head of Department: Prof. Jacek R. Wilczyński MD PhD

Przegląd Menopauzalny 2010; 3: 128–131

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 isoflavons could also modify immune response in post-menopausal women. All those phenomena might influence the risk of cancer initiation and the natural course of tumour growth.

Key words: oestrogens, immunology

Streszczenie

Jedną z najważniejszych funkcji estrogenów jest zdolność modulowania działania układu immunologicznego. Estrogeny, poprzez interakcje ze swoistymi receptorami estrogenowymi ERα i ERβ, 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 grupy selektywnych modulatorów receptora estrogenowego (*selective estrogen receptor modulator* – 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: estrogeny, immunologia

Influence of oestrogens on the immune function

Oestrogens and adaptive immunity

Generally oestrogens stimulate adaptive immunity, but in detail their function is multidirectional and depends on hormone concentration [1]. Cytotoxic activity of T lymphocytes inside reproductive organs is oestrogen-dependent [2]. However, a high level of oestrogens is capable of suppressing both IL-2 secretion and IL-2 receptor expression in peripheral blood T CD4+ lymphocytes. This would prevent IL-2 mediated T cell expansion following antigen- or mitogen-induced activation [3]. From another point of view, oestrogens preserve proper T lymphocyte function by decreasing T lymphocyte apoptosis and Fas ligand expression, as it was shown in postmenopausal women receiving oestrogen therapy [4]. Lymphocytes T CD4+CD25+Foxp3+ are a population of natural or peripherally induced regulatory T cells (Treg), which seem to be crucial to the maintenance of tolerance, response towards transplants and pregnancy, or cancer growth [5]. Experiments performed on a mouse model indicated that estradiol increased both the number of Treg and expression of Foxp3 on their surface and that this mechanism could be responsible for protection against experimental autoimmune encephalomyelitis [6]. Not only

Address for correspondence:
Prof. **Jacek R. Wilczyński** MD, PhD, Department of Gynecological Surgery, "Polish Mother's Memorial Hospital" Research Institute, Rzgowska 281/289, 93-338 Lodz, Poland

the number and function of T cells could be modified by oestrogens, but also their circulation in the body. Females have increased expression of T cell C-C motif chemokine receptors (CCR)1 to CCR5, which influences the chemotactic responses of T cells [7].

The effects of oestrogen on Th1/Th2 cytokine balance also depend on hormone concentration. While in low doses estradiol triggers Th1 activity and IFN-γ secretion, in higher doses it appears to be a potent Th2 activity enhancer through stimulation of IL-10 secretion [8, 9]. Investigations performed *in vivo* indicated that IL-4 secretion by peripheral blood mononuclear cells correlated significantly with the oestrogen level and changed during the menstrual cycle, however, these correlations disappeared post menopause [10]. Negative influence of aging and hypoestrogenic environment on cytokine secretion was shown on mice subjected to injury. Higher serum IL-6 levels were connected with increased mortality in hypoestrogenic animals, while oestrogen substitution improved the outcome of supplemented animals [11]. Evaluation of cytokine levels in elderly women indicated the presence of hyper-inflammatory state characterized by elevated circulating levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, and prostaglandin E_2) [12]. Post-menopausal decline of oestrogens could contribute to these changes as oestrogen therapy improved the immune status of treated women [13]. This would rather suggest that physiological levels of oestrogens have anti-inflammatory functions. One of the possible explanations for the oestrogen role in immunoregulation is direct inhibiting properties of oestrogen on NK-κB transcription factor, which usually promotes pro-inflammatory cytokine secretion [14, 15]. Another possibility is increased production of ROI, which is secondary to an age-dependent oestrogen drop. Excessive concentration of ROI could inhibit NK-κB transcription factor [16]. Also age-dependent increase in visceral fat could account for increase in pro-inflammatory cytokines [17].

Oestrogens are engaged in activation and survival of B lymphocytes, and protect them from B cell receptor mediated apoptosis by regulation of Bcl-2 expression [18, 19]. It was also shown that oestrogen milieu and B cell receptor signalling shaped the differentiation pathway of B lymphocytes [20]. Oestrogens cause increase in immunoglobulins (IgG and IgA) in human uterine cervical mucous in the proliferative menstrual phase [21], as well as rise in total IgG and IgM production by human peripheral blood lymphocytes [22, 23].

Oestrogen deprivation caused either by castration or by senescence has profound adverse effects on adaptive immunity. Both aged and ovariectomized animals exhibited reduced T cell response to antigens and mitogenic stimuli, as well as disturbed IL-2 secretion and chemotaxis [24-26]. Compared to the pre-menopausal period, elderly females showed lowered numbers of T and B cells, poor anti-viral immunity, decreased proliferative response and T helper cytokine secretion [27-30].

Role of soy isoflavones and SERM in modulating the immune function

Genistein is one of the most important soy isoflavones, which due to its structural similarity to estradiol and has similar biological effects. Genistein is a ligand both for ERα and ERβ, however, unlike oestrogens, has a greater affinity for ERβ, and may act as ER modulator possessing both estrogenic and antiestrogenic effects [31-33]. Like in the case of oestrogens, the biological effects of genistein on immune functions depend on its dose. Higher concentrations of genistein indicated immunosuppressive activity, and caused decrease in T and NK cells activity, T cell proliferation and NO production in macrophages. Those changes resulted in genistein dose-dependent inhibition of both humoral and cell-mediated immunity [31, 34]. Some authors did not confirm these results and showed that genistein induced activity of cytotoxic T cells and NK cells [35]. They later showed that genistein treatment was also associated with IFN-γ secretion and a decrease in Treg CD4+CD25+ cells, which resulted in decreased susceptibility to toxin-induced carcinogenesis [36]. The most reliable study was based on genistein concentrations usually met during dietary isoflavones intake. This study indicated that genistein was able to inhibit exaggerated IFN-γ production during bacterial infection in mice [37]. *In vivo* studies performed on post-menopausal women showed that genistein caused an increase in B cell population, however, did not significantly influence IFN-γ, TNF-α or IL-2 serum concentrations [38]. A commonly accepted observation is that use of soy isoflavones in post-menopausal women lowers the risk of cardiovascular disease, osteoporosis, and cancer of the breast [39-42].

Selective oestrogen receptor modulators (SERM) like tamoxifen and raloxifene could effectively bind to ER, however their function of ER agonists or antagonists depends on the drug and type of responding tissue. Tamoxifen is used for prevention and treatment of breast cancer, but it increases the risk of endometrial hyperplasia including endometrial cancer. Raloxifen is used for treatment of osteoporosis, however it also decreases the incidence of both breast and endometrial cancer [43, 44]. Modulation of ER implies that SERM could influence immune functions. It was shown that they were able to regulate anti- and proinflammatory cytokines, decrease B cell activity and diminish intensity of autoimmune reactions [45-50]. SERM were shown to antagonize oestrogens in GM-CSF mediated differentiation of DC cells, which displayed immature phenotype [51]. This mechanism was probably based on SERM ability to modify IFN-γ, IL-12, and IL-6 production as well as STAT3 activity in monocyte cultures [44].

Possible influence of oestrogen-dependent immune changes on the risk of cancer

Oestrogens could predispose to breast, endometrial and probably ovarian cancer. The mechanisms of carcinogenesis consist of oestrogen proliferative abilities directed to target tissues, induction of growth factors, stimulation of activation-induced deaminase (AID), mutagenic properties of oestrogen metabolites or direct stimulation of ER positive tumours [52-56]. However, multidirectional influence of oestrogens on immune functions could also affect tumour development. The results of some studies seem to support this possibility, as it was shown, that oestrogen treatment of mice with grafted ER-negative tumours suppressed macrophage recruitment and pro-inflammatory cytokine secretion at the tumour site, thus lowering defence mechanisms [57]. Tumour-associated macrophages (TAM) are one of the most important immune cell populations inside tumours. According to the profile of secreted cytokines, there are two macrophage populations identified, M1 cells secreting pro-inflammatory Th1 cytokines, and M2 cells producing Th2 cytokines [58, 59]. There is a possibility that oestrogens could regulate both the proportion of M1/M2 TAM and their activity, thus influencing the tumour growth. Defective M1-type functions showed by TAMs inside tumours are probably caused by disturbed activation of NF-κB in response to pro-inflammatory stimuli present in advanced tumours [60]. It cannot be excluded that similar effects on NF-κB function might follow oestrogen activity. Progressive tumours contain immature DC having pro-tolerogenic functions, and being unable to stimulate host anti-tumour cytotoxic responses [61-63]. Regulatory function of oestrogens on DC could augment their differentiation into an immature phenotype. Moreover, oestrogen-dependent expansion of CD4+CD25+Foxp3+ Treg cells could adversely modify anti-tumour responses, as Treg cells were found to accumulate in tumour and local lymphatic nodes in cancer patients with unfavourable outcome [reviewed in 64]. Positive impact of oestrogens on B cell proliferation and function could potentially alter anti-tumour response, because B lymphocytes are able to create an inflammatory environment supporting tumour growth [65]. However, decreased T and NK cells function observed after menopause could also discriminate anti-cancer response. Thus, due to multidirectional influence of oestrogens on immunity, both their presence in the reproductive period of a woman's life, as well as their lack after menopause could in some aspects predispose to cancer growth.

Conclusion

Oestrogens are potent and multidirectional modifiers of the immune system. Our growing knowledge concerning this function could help in prophylaxis and treatment of many tumours in women. Use of selective ER agonists and antagonists in treatment of reproductive tract tumours, could be further adopted to management of other tumours met in females.

References

1. Beagley KW, Gockel CM. Regulation of innate and adaptive immunity by the female sex hormones oestradiol and progesterone. FEMS Immunol Med Microbiol 2003; 38: 13-22.
2. White HD, Crassi KM, Givan AL, et al. CD3+ CD8+ CTL activity within the human female reproductive tract: influence of stage of the menstrual cycle and menopause. J Immunol 1997; 158: 3017-27.
3. McMurray RW, Ndebele K, Hardy KJ, Jenkins JK. 17-beta-estradiol suppresses IL-2 and IL-2 receptor. Cytokine 2001; 14: 324-33.
4. Zhang J, Chen X, Zhang S, et al. Effects of transdermal estrogen therapy on expressions of estrogen receptors and T-lymphocyte apoptosis in surgically menopausal women. Cell Molecul Immunol 2009; 6: 277-83.
5. Wilczynski JR, Radwan M, Kalinka J. The characterization and role of regulatory T cells in immune reactions. Front Biosc 2008; 13: 2266-74.
6. Polańczyk MJ, Garson BD, Subramanian S, et al. Cutting edge: estrogen drives expansion of the CD4+CD25+ regulatory T cell compartment. J Immunol 2004; 173: 2227-30.
7. Mo R, Chen J, Grolleau-Julius A, et al. Estrogen regulates CCR gene expression and function in T lymphocytes. J Immunol 2005; 174: 6023-9.
8. Gilmore W, Weiner LP, Correale J. Effect of estradiol on cytokine secretion by proteolipid protein-specific T cell clones isolated from multiple sclerosis patients and normal control subjects. J Immunol 1997; 158: 446-51.
9. Correale J, Arias M, Gilmore W. Steroid hormone regulation of cytokine secretion by proteolipid protein-specific CD4+ T cell clones isolated from multiple sclerosis patients and normal control subjects. J Immunol 1998; 161: 3365-74.
10. Verthelyi D, Klinman DM. Sex hormone levels correlate with the activity of cytokine-secreting cells in vivo. Immunology 2000; 100: 384-90.
11. Gomez CR, Placketta TP, Kovacs EJ. Aging and estrogen: modulation of inflammatory responses after injury. Exp Gerontol 2007; 42: 451-6.
12. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 2000; 908: 244-54.
13. Fahlman MM, Boardley D, Flynn MG, et al. Effects of hormone replacement therapy on selected indices of immune function in postmenopausal women. Gynecol Obstet Invest 2000; 50: 189-93.
14. Kalaitzidis D, Gilmore TD. Transcription factor cross-talk: the estrogen receptor and NF-kappaB. Trends Endocrinol Metab 2005; 16: 46-52.
15. McKay LI, Cidlowski JA. Molecular control of immune/inflammatory responses: interactions between nuclear factor-kappa B and steroid receptor-signaling pathways. Endocr Rev 1999; 20: 435-59.
16. Pfeilschifter J, Köditz R, Pfohl M, et al. Changes in Proinflammatory Cytokine Activity after Menopause. Endocrine Rev 2002; 23: 90-119.
17. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. Trends Endocrinol Metab 2000; 11: 327-32.
18. Grimaldi CM, Cleary J, Dagtas AS, et al. Estrogen alters thresholds for B cell apoptosis and activation. J Clin Invest 2002; 109: 1625-33.
19. Medina KL, Strasser A, Kincade PW. Estrogen influences the differentiation, proliferation, and survival of early B-lineage precursors. Blood 2000; 95: 2059-67.
20. Venkatesh J, Peeva E, Xu X, et al. The cutting edge: hormonal milieu, not antigenic specificity, determines the mature phenotype of autoreactive B cells. J Immunol 2006; 176: 3311-14.
21. Kutteh WH, Prince SJ, Hammond KR, et al. Variations in immunoglobulins and IgA subclasses of human uterine cervical secretions around the time of ovulation. Clin Exp Immunol 1996; 104: 538-42.
22. Paavonen T, Andersson LC, Adlercreutz H. Sex hormone regulation of in vitro immune response. Estradiol enhances human B cell maturation via inhibition of suppressor T cells in pokeweed mitogen-stimulated cultures. J Exp Med 1981; 154: 1935-45.
23. Kanda N, Tamaki K. Estrogen enhances immunoglobulin production by human PBMCs. J Allergy Clin Immunol 1999; 103: 282-8.
24. Kahlke V, Angele MK, Ayala A, et al. Immune dysfunction following trauma-hemorrhage: influence of gender and age. Cytokine 2000; 12: 69-77.

25. De la Fuente M, Baeza I, Guayerbas N, et al. Changes with aging in several leukocyte functions of male and female rats. Biogerontology 2004; 5: 389-400.
26. Ku LT, Gercel-Taylor C, Nakajima ST, Taylor DD. Alterations of T cell activation signaling and cytokine production by postmenopausal estrogen levels. Immun & Ageing 2009; 6: 1-13.
27. Miller RA, Garcia G, Kirk CJ, et al. Early activation defects in T lymphocytes from aged mice. Immunol Rev 1997; 160: 79-90.
28. Giglio T, Imro MA, Filaci G, et al. Immune cell circulating subsets are affected by gonadal function. Life Sci 1994; 54: 1305-12.
29. Chakravarti B, Abraham GN. Aging and T-cell-mediated immunity. Mech Aging Dev 1999; 108: 183-206.
30. Kumru S, Godekmerdan A, Ytlmaz B. Immune effects of surgical menopause and estrogen replacement therapy in peri-menopausal women. J Reprod Immunol 2004; 63: 31-8.
31. Cooke PS, Selvaraj V, Yellayi S. Genistein, estrogen receptors, and the acquired immune response. J Nutr 2006; 136: 704-8.
32. Setchell KDR. Soy isoflavones – benefits and risks from nature's selective estrogen receptor modulators (SERMS). J Am Coll Nutr 2001; 20: 354S-62S.
33. Rotsztejn H. Znaczenie fitoestrogenów w świetle obecnej wiedzy. Prz Menopauz 2005; 4: 47-50.
34. Polkowski K, Mazurek AP. Biological properties of genistein. A review of in vitro and in vivo data. Acta Pol Pharm 2000; 57: 135-55.
35. Guo TL, McCay JA, Zhang LX, et al. Genistein modulates immune responses and increases host resistance to B16F10 tumor in adult female B6C3F1 mice. J Nutr 2001; 131: 3251-8.
36. Guo TL, Chi RP, Hernandez DM, et al. Decreased 7,12-dimethylbenz[a]-anthracene-induced carcinogenesis coincides with the induction of antitumor immunities in adult female B6C3F1 mice pretreated with genistein. Carcinogenesis 2007; 28: 2560-6.
37. Curran EM, Judy BM, Newton LG, et al. Dietary soy phytoestrogens and ERalpha signalling modulate interferon gamma production in response to bacterial infection. Clin Exp Immunol 2004; 135: 219-25.
38. Ryan-Borchers TA, Park JS, Chew BP, et al. Soy isoflavones modulate immune function in healthy postmenopausal women. Am J Clin Nutr 2006; 83: 1118-25.
39. Potter SM, Baum J, Teng H, et al. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. Am J Clin Nutr 1998; 68: 1375S-9S.
40. Steinberg FM, Guthrie NL, Villablanca AC, et al. Soy protein with isoflavones has favorable effects on endothelial function that are independent of lipid and antioxidant effects in healthy postmenopausal women. Am J Clin Nutr 2003; 78: 123-30.
41. Alekel DL, St Germain A, Peterson CT, et al. Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women. Am J Clin Nutr 2000; 72: 844-52.
42. Zheng W, Dai Q, Custer LJ, et al. Urinary excretion of isoflavonoids and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 1999; 8: 35-40.
43. Jakimiuk AJ, Bogusiewicz M. Selektywne modulatory receptora estrogenowego – przełom w terapii menopauzy? Prz Menopauz 2002; 4: 14-24.
44. Nalbandian G, Paharkova-Vatchkova V, Mao A, et al. The selective estrogen receptor modulators, tamoxifen and raloxifene, impair dendritic cell differentiation and activation. J Immunol 2005; 175: 2666-75.
45. Dayan M, Zinger H, Kalush F, et al. The beneficial effects of treatment with tamoxifen and anti-oestradiol antibody on experimental systemic lupus erythematosus are associated with cytokine modulations. Immunology 1997; 90: 101-8.
46. Colletta AA, Wakefield LM, Howell FV, et al. Anti-oestrogens induce the secretion of active transforming growth factor-beta from human fetal fibroblasts. Br J Cancer 1990; 62: 405-9.
47. Järvinen LS, Pyrhönen S, Kairemo KJ, Paavonen T. The effect of anti-oestrogens on cytokine production in vitro. Scand J Immunol 1996; 44: 15-20.
48. Teodorczyk-Injeyan J, Cembrzynska-Nowak M, Lalani S, et al. Modulation of biological responses of normal human mononuclear cells by antiestrogens. Anticancer Res 1993; 13: 279-83.
49. Wu WM, Suen JL, Lin BF, et al. Tamoxifen alleviates disease severity and decreases double negative T cells in autoimmune MRL-*lpr/lpr* mice. Immunology 2000; 100: 110-8.
50. Onoe Y, Miyaura C, Ito M, et al. Comparative effects of estrogen and raloxifene on B lymphopoiesis and bone loss induced by sex steroid deficiency in mice. J Bone Miner Res 2000; 15: 541-9.
51. Kovats S, Carreras E. Regulation of dendritic cell differentiation and function by estrogen receptor ligands. Cell Immunol 2008; 252: 81-90.
52. Clarke R. Human breast cancer cell line xenografts as models of breast cancer. The immunobiologies of recipient mice and the characteristics of several tumorigenic cell lines. Breast Cancer Res Treat 1996; 39: 69-86.
53. Engel LW, Young NA. Human breast carcinoma cells in continuous culture: a review. Cancer Res 1978; 38: 4327-39.
54. Dickson RB, Lippman ME. Growth factors in breast cancer. Endocr Rev 1995; 6: 559-89.
55. Yager JD, Liehr JG. Molecular mechanisms of estrogen carcinogenesis. Annu Rev Pharmacol Toxicol 1996; 36: 203-32.
56. Maul RW, Gearhart PJ. Women, autoimmunity, and cancer: a dangerous liaison between estrogen and activation-induced deaminase? J Exp Med 2009; 206: 11-3.
57. Curran EM, Judy BM, Duru NA, et al. Estrogenic regulation of host immunity against an estrogen receptor-negative human breast cancer. Clin Cancer Res 2006; 12: 5641-7.
58. Ostrand-Rosenberg S. Immune surveillance: a balance between protumor and antitumor immunity. Curr Opin Genet Develop 2008; 18: 11-8.
59. Sica A, Allavena P, Mantovani A. Cancer related inflammation: The macrophage connection. Cancer Lett 2008; 264: 204-15.
60. Sica A, Saccani A, Bottazzi B, et al. Autocrine production of IL-10 mediates defective IL-12 production and NF-kappa B activation in tumor-associated macrophages. J Immunol 2000; 164: 762-7.
61. Liu Y, Bi X, Xu S, et al. Tumor-infiltrating dendritic cell subsets of progressive or regressive tumors induce suppressive or protective immune responses. Cancer Res 2005; 65: 4955-62.
62. Bell D, Chomarat P, Broyles D, et al. In breast carcinoma tissue, immature dendritic cells reside within the tumor, whereas mature dendritic cells are located in peritumoral areas. J Exp Med 1999; 190: 1417-26.
63. Zou W, Machelon V, Coulomb-L'Hermin A, et al. Stromal-derived factor-1 in human tumors recruits and alters the function of plasmacytoid precursor dendritic cells. Nat Med 2001; 7: 1339-46.
64. Wilczynski JR , Kalinka J , Radwan M. The role of T-regulatory cells in pregnancy and cancer. Front Biosc 2008; 13: 2275-89.
65. de Visser KE, Korets LV, Coussens LM. De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. Cancer Cell 2005; 7: 411-23.