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Estrogen Receptors in Leukocytes - Possible Impact on Inflammatory Processes in the Female Reproductive System

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1. Introduction

Estrogens carry out various reproductive and non-reproductive functions. Traditionally, estrogen action was thought to be solely mediated through its nuclear receptors - estrogen receptor (ER) α and ER β (Deroo & Korach, 2006). However, recently a membrane bound G protein-coupled receptor-30, now designated as G protein-coupled estrogen receptor-1(GPER), has been described as a receptor for estrogen (Prossnitz et al., 2007). ER α and ER β belong to the nuclear receptor superfamily and functions as ligand activated transcriptional factors. The classical mechanism of nuclear ER action involves ligand binding to receptors, dimerization and binding to specific response elements of the target genes to elicit a transcriptional response. Although estrogen action is mostly targeted towards reproductive tissues, they also act via ERs in non-reproductive target tissues (Diel, 2002; Manolagas & Kousteni, 2001; Walker & Korach, 2004). Estrogens can also act rapidly through non-genomic mechanisms by binding to membrane bound ERs (Deroo & Korach, 2006; Prossnitz et al., 2007). GPER is a member of the G protein-coupled receptor superfamily containing seven transmembrane helices and mediates estrogen-dependent kinase activation as well as transcriptional responses (Prossnitz et al., 2007). Receptors for estrogens are present in leukocytes and perform various functions. ERs and several of their splice variants have been identified in polymorphonuclear and mononuclear leukocytes isolated from peripheral blood of both men and women (Stygar et al., 2006). ERs are present in a variety of leukocytes like myeloid progenitor cells, neutrophils, lymphocytes, natural killer cells, macrophages, monocytes, mast cells etc. This chapter will summarize the publications on the role of estrogen in leukocytes and its implications in female reproduction.

2. Estrogen receptors in leukocytes

Leukocytes play a key role in several physiologically important processes like immunity, inflammation, extracellular matrix remodeling, wound healing, cardiovascular disorders, autoimmune diseases, menstruation, embryo implantation, cervical ripening, labor etc. They are involved in various functions during normal as well as pathological conditions. Estrogens act on leukocytes and influence their number and function (Bouman et al., 2005). In recent years, several investigations have focused on the action of estrogens in the immune

system and inflammation. Clinical, epidemiological and immunological studies have shown that women are more prone to autoimmune disorders in comparison to men. Studies have shown that the incidence of cardiovascular disease is higher in men than in women and the incidence in women increases towards the level of men after menopause. There is clear sex bias in the disease presentation. Estrogens have been suggested to be responsible for these differences (Cutolo et al., 2010; Druckmann, 2001; Nalbandian & Kovats, 2005). These diseases are often associated with leukocyte infiltration and immune dysfunction. It has been hypothesized that estrogens alter the course of these disorders by modulating leukocyte function in various tissues. Although the exact mechanism by which estrogens modulates the immune cell function is not completely understood, these observations clearly show that leukocytes are estrogen targets.

2.1 Neutrophils

Neutrophils are the most abundant type of leukocytes and form an essential part of the immune system. Klebanoff demonstrated that estrogens specifically bind to neutrophils using ligand binding experiments (Klebanoff, 1977). It was further shown that estrogens influence the neutrophil count and women have a higher neutrophil count than men (Bain & England, 1975a). In women, the neutrophil number varies during the menstrual cycle (Bain & England, 1975b; Smith et al., 2007). Higher levels of neutrophil counts correlate to the elevated levels of estradiol in peripheral blood (Mathur et al., 1979). Recent studies showed that ERs are present in neutrophils and execute various direct or indirect functions. It was shown that polymorphonuclear cells express both ER α and ER β and their various splice variants (Molero et al., 2002; Stygar et al., 2007). Molero et al, demonstrated that estradiol up-regulated both ER α and ER β in women but only ER α in men (Molero et al., 2002). The functional signaling of ERs in neutrophils was further established by the induction of nNOS by estradiol (Garcia-Duran et al., 1999). Further, estradiol and ER specific agonists regulated physiologically relevant genes in polymorphonuclear cells in rats (Stygar et al., 2007). Recently, we have identified the presence of GPER in terminally differentiated neutrophil like HL-60 cells. The GPER agonist G1 could stimulate a transcriptional response indicating that GPER is functionally active in these cells (Blesson and Sahlin, unpublished). Neutrophils have a very short life span and they stay in circulation for 6 to 18 hours before undergoing apoptosis. Estradiol along with progesterone increases neutrophil survival by delaying apoptosis via decreasing the activities of caspases 3 and 9 (Molloy et al., 2003). Estrogens may also have a vital role in the regulation of genes that are associated with the immune and inflammatory response, like chemokines and cytokines. These genes are responsible for neutrophil recruitment and activation during normal as well as pathological conditions (Jabbour et al., 2009; Straub, 2007).

2.2 Lymphocytes

Lymphocytes express nuclear as well as membrane estrogen receptors. Studies on human peripheral blood lymphocytes showed the presence of ER α and ER β in various lymphocyte subsets including natural killer (NK) cells (Curran et al., 2001). A smaller variant of ER α called ER α 46 appears to be the most abundant isoform of ERs in lymphocytes. This variant was localized to the cell surface and mediates estrogen induced proliferation of T lymphocytes and NK cells but not B lymphocytes (Pierdominici et al.,

2010). ER β is expressed predominantly in secondary lymphoid tissues and plays an important role in the peripheral immune system (Shim et al., 2006). Both ER α and ER β are expressed in the NK cells of mice and humans (Curran et al., 2001). In mice, estrogens act via ER β to suppress NK cell activity by altering their ability to lyse target cells (Curran et al., 2001). Estradiol induces the proliferation of splenic NK cells and suppresses the cytotoxicity of these cells (Hao et al., 2007). However, *in vitro* studies on murine NK cells showed that estradiol reduces NK cell proliferative capacity and reduces cytotoxicity by influencing cytokine expressions (Hao et al., 2008). In humans, the number of NK cells was significantly altered during the different phases of menstrual cycle. The NK cell population in the periovulatory phase when the estrogen level is high was twice that in other phases indicating a positive effect on its number (Yovel et al., 2001). The ER β 1 variant could be localized to uterine NK (uNK) cells (Henderson et al., 2003). Hence, estrogens could act directly on uNK cells via the ER β 1 receptor.

2.3 Other mononuclear leukocytes

ERs are also expressed in monocytes, macrophages, dendritic cells and mast cells. Both ER α and ER β are present in monocytes and are able to regulate the expression of CD16 (Kramer et al., 2007). Estrogens can act on monocytes to modulate apoptosis and cell cycle progression (Thongngarm et al., 2003). Monocytes are responsive to estrogens and may be important in modulating the immune response (Scariano et al., 2008). These cells are recruited into damaged tissue and undergo differentiation to become macrophages or dendritic cells. In macrophages derived from a human primary monocyte culture, ER α and ER β mRNA were detected. However, only the ER β protein could be seen (Kramer & Wray, 2002). Stygar and co-workers showed the presence of mRNA and protein of wild type ER α and ER β and their splice variants in mononuclear cells purified from peripheral blood (Stygar et al., 2006). Recent reports have shown the presence of ER α and ER β localized to the membrane and cytoplasm of macrophages derives from THP-1 cells (Subramanian & Shaha, 2009). Estradiol was shown to regulate the expression of several genes related to macrophage activation and apoptosis (Kramer & Wray, 2002; Subramanian & Shaha, 2009). Further, plasma membrane associated ER α and cytosolic ER β oppose the function of each other thereby promoting cell survival suggesting the importance of both receptors (Kramer & Wray, 2002; Subramanian & Shaha, 2009). A recent study showed that estradiol suppresses LPS induced NF κ B activation in primary human macrophages (Murphy et al., 2010). These reports indicate that estrogen dependent ER signaling is necessary to perform various important activities in monocytes and macrophages. Estrogens act via ER α on myeloid progenitor cells to regulate their differentiation into dendritic cells by increasing expression of the transcription factor IRF4 (Carreras et al., 2010). It has also been reported that estradiol may strengthen innate immunity by enhancing interferon- γ production in dendritic cell suggesting an active role played by ER in these cells (Siracusa et al., 2008). ERs have also been localized in mast cells (Zhao et al., 2001). In mast cells, estradiol acts via a membrane bound ER α and regulates calcium influx, which is a non-genomic signaling mechanism (Zaitsu et al., 2007). Estradiol also enhances IgE-dependent mast cell activation, resulting in a shift of the allergen dose response (Zaitsu et al., 2007).

These observations clearly show that in addition to their role in reproduction, estrogens appear to influence the immune system by targeting leukocytes. The presence of ERs

indicates that estrogens could act directly on these cells regulating cellular functions. It could also explain the sexual dimorphism in the immune and inflammatory response.

3. Leukocyte mediated estrogen action in reproduction

Many normal female reproductive processes show classical signs of inflammation. It is now widely accepted that ovulation, menstruation, implantation, pregnancy, cervical ripening and parturition are governed by inflammatory processes. These events are often associated with expression of an array of inflammatory mediators including various cytokines and chemokines (Jabbour et al., 2009). Leukocytes are present in substantial numbers in the female reproductive tract and sex hormones directly or indirectly play a role in the recruitment and activation of these cells (Wira et al., 2010). Abnormal activation of inflammatory pathways leads to various pathological conditions like menstrual disorders, infertility, pregnancy loss, complicated labor, unripe cervix, reproductive tract cancers etc. (Jabbour et al., 2009). It appears that there is a coordinated attempt by the immune system to protect, maintain and repair the reproductive organs to perform its normal functions.

3.1 Reproductive cycle

The female reproductive cycle is highly controlled by reproductive hormones from hypothalamus, pituitary and ovary. The ovarian steroids not only perform their primary reproductive functions but are also involved in various functions related to immunity and inflammation. Innate and adaptive immunity are active throughout the menstrual cycle and ovarian estrogens act on epithelial cells and leukocytes of the female reproductive tract to offer protection against infection (Wira et al., 2010). Infiltration of leukocytes into the ovary is essential for ovulation. The invading leukocytes secrete proteases to weaken the follicular wall and thus aiding ovulation (Oakley et al., 2010). These leukocytes include macrophages and lymphocytes (Oakley et al., 2010). Leukocytes are present in great numbers and diversity in the reproductive tract throughout the reproductive cycle. The human endometrium undergoes constant remodeling during the course of the menstrual cycle and is infiltrated by leukocytes. A variety of leukocytes including uNK cells, neutrophils, eosinophils, lymphocytes, macrophages and mast cells invade endometrium (Salamonsen & Lathbury, 2000). Endometrial remodeling involves inflammatory factors like cytokines, chemokines and prostanoids (Jabbour et al., 2009). Estrogens regulate the inflammatory process in the endometrium which involves influx of leukocytes (King & Critchley, 2010). Infiltrating leukocytes not only provide protection against pathogens but also actively participate in the degradation and subsequent regeneration of endometrial tissue by secreting various proteases, cytokines and chemokines (Guo et al., 2011; Lathbury & Salamonsen, 2000). Various proteases like tryptase, chymase, chymotrypsin plasminogen activator, elastase, heparanase, cathepsin G, β -glucuronidase, aryl sulphatase, metalloelastase and several metalloproteases are secreted and regulated by leukocytes, thereby playing an active role in tissue degradation prior to menstruation (Salamonsen & Lathbury, 2000). Leukocytes also participate during the process of regeneration of the endometrium. Endometrial regeneration is an estrogen dependent process and the repair begins with the restoration of glands, stroma and epithelium along with endometrial angiogenesis. Leukocytes are abundantly present and could participate in the endometrial

rebuilding process (Salamonsen & Lathbury, 2000). Neutrophils are present in large numbers during endometrial repair and play an important role. In a mouse model designed to mimic the events of menstruation, it was observed that when neutrophils were depleted, endometrial regeneration was severely affected suggesting that neutrophils along with the regulatory factors they produce contribute to the tissue repair (Kaitu'u-Lino et al., 2007). Macrophages, eosinophils and lymphocytes could also contribute in this process (Salamonsen & Lathbury, 2000). In humans, different subpopulations of leukocytes are present during the menstrual, proliferative, mid-secretory, and late-secretory phases (Jones et al., 2004). Certain chemokines like MDC, MCP-3, and FKN are abundant throughout the cycle. During the menstrual phase, IL-8 and HCC-4 mRNAs are up-regulated. In the proliferative phase, MIP-1 β , HCC-4, and eotaxin are up-regulated in glands and vessels of endometrium, whereas MIP-1 β , HCC-1, HCC-4 and 6Ckine were up-regulated during in the mid-secretory phase followed by the upregulation of HCC-1 and 6Ckine in the late secretory phase (Jones et al., 2004). It was also noticed that neutrophils, eosinophils and macrophages are present during menstrual phase, macrophages during proliferative phase, uNK cells, macrophages and T cells during mid-secretary phase and neutrophils, eosinophils and macrophages during late-secretory phase of the menstrual cycle (Jones et al., 2004).

3.2 Implantation and decidualization

A large number of leukocytes especially monocytes, macrophages and uNK cells infiltrate the implantation site, believed to be important modulators of trophoblast invasion and decidualization (Drake et al., 2001; Jones et al., 2004). If pregnancy does not occur another sub-population of leukocytes like neutrophils, eosinophils, and macrophages infiltrate and facilitate endometrial destruction (Jones et al., 2004). Decidualization is the process by which stromal cells differentiate into decidual cells. It involves an inflammatory type of reaction including leukocyte infiltration and cytokine production (Hess et al., 2007). Leukocytes are present in large amounts during decidualization indicating their participation in the process (Guo et al., 2011). Studies in mice showed that uNK cells promote uterine vascular cell remodeling that assist decidual growth (Blois et al., 2011). Certain uNK cell derived chemokines and cytokines can influence the gene expression profile of human endometrial fibroblasts *in vitro* suggesting that a similar mechanism could operate in the endometrium (Germeyer et al., 2009). uNK cells express ER β and it may exert control over trophoblast invasion (Henderson et al., 2003; Kwak-Kim & Gilman-Sachs, 2008). They also promote uterine vascular modifications assisting decidual growth during early pregnancy (Blois et al., 2011). Regulation of inflammation during implantation may follow a sequential model in which pro-inflammation is followed by anti-inflammation or there may be a continuous balance between the pro- and anti-inflammatory environments (Jabbour et al., 2009). These observations imply that there are interactions between different types of invading leukocytes and the factors that they secrete in the endometrium are important in order to bring about a successful implantation.

3.3 Pregnancy

The level of serum estrogens peaks during pregnancy and may reach more than a hundred fold to that of normal non-pregnant levels (Tulchinsky & Hobel, 1973). At these high levels, estrogens can suppress many cytotoxic and innate immune responses, but stimulate

antibody production, neo-angiogenesis and growth (Straub, 2007). Several chemokines and cytokines like TPO, VEGF, IL1 α , ENA-78, IL-8, GM-CSF and GRO- α are upregulated in the first-trimester decidua (Segerer et al., 2009). These factors perform various functions including attracting a variety of leukocytes. Estrogens along with progesterone can regulate leukocyte number and activity. Studies indicate that neutrophils from women at term pregnancy have a significant delay in apoptosis inducing physiologic neutrophilia (Watson et al., 1999). This delay in apoptosis could be induced by estradiol and progesterone (Molloy et al., 2003). Along with the increase in neutrophil count, several metabolic changes including accumulation of myeloperoxidase take place in neutrophils to enhance cell metabolism and oxidant release during pregnancy (Kindzelskii et al., 2006; Muller et al., 2009). The symbiosis between mother and fetus during pregnancy is not due to immunological ignorance, but a complex transient modulation of the maternal immune response where the adaptive immunity is down-modulated and the innate immune response is enhanced (Muller et al., 2009). It has been reported that there is a temporary suppression of maternal T cell responses by arginase secreted by polymorphonuclear leukocytes in normal pregnancies (Kropf et al., 2007). Thus, there is interplay between the different types of leukocytes to protect the fetus from the maternal immune system. Early pregnancy also involves the action of dendritic cells. They control stromal cell proliferation, angiogenesis and the homing and maturation of NK cell precursors in the pregnant uterus (Blois et al., 2011). The number of uNK cells increase drastically during pregnancy. Precursors of uNK appear to be recruited from blood and this is promoted by rising levels of plasma estrogens and luteinizing hormone and limited by increasing progesterone (van den Heuvel et al., 2005). uNK cells promote vascular modifications during gestation which is vital for the formation of the placenta (Blois et al., 2011). Further, placenta and trophoblasts produce chemokines that may also recruit NK cells into the decidua during pregnancy (Chantakru et al., 2002; Drake et al., 2001).

3.4 Cervical ripening and parturition

Cervical ripening is an important event prior to parturition. It has been suggested that leukocytes could be responsible for the ripening of the cervix at term and these leukocytes express ERs (Junqueira et al., 1980; Osmers et al., 1992; Sahlin et al., 2008; Wang et al., 2001). Cervical ripening includes an inflammatory type of process and thus there is an infiltration of leukocytes. Both polymorphonuclear and macrophages migrate from blood vessels and accumulate in cervix before the onset of parturition (Osman et al., 2003; Stygar et al., 2001). The quantum of infiltrating leukocytes is modulated by inflammatory mediators like IL-8 and prostaglandins (Chwalisz et al., 1994; Luo et al., 2000). Cervical extracellular matrix is remodeled by the degradation of collagens and proteoglycans. Proteases like matrixmetalloprotease (MMP)-2 and MMP-9 were expressed during cervical ripening (Stygar et al., 2002). Cervical stromal fibroblasts and smooth muscle cells were identified as main sources of MMP-2, but MMP-9 protein was localized exclusively in invading leukocytes (Stygar et al., 2002). There are also reports showing that migrating leukocytes secrete collagenases that could play an important role in tissue remodeling during cervical ripening (Osmers et al., 1992). These data indicate the involvement of invading leukocytes in the cervical ripening process. It was observed that the influx of leukocytes were impaired in cervix of women post term not responding to prostaglandin priming, indicating that

leukocytes are important for normal cervical ripening (Sahlin et al., 2008). Infiltrating leukocytes express ERs where estrogen may also act directly. ER β expression in human cervix was significantly increased at term pregnancy when compared to non-pregnant controls, implying a role for ER β in cervical ripening (Wang et al., 2001). Further, it was later shown that ER β is expressed in invading leukocytes including macrophages (Stygar et al., 2001). In rats, estradiol and selective agonists regulate a number of genes related to inflammation and extra cellular matrix remodeling (Stygar et al., 2007). Thus ER β might mediate the estrogen action leading to the activation of leukocytes facilitating cervical ripening. Leukocytes also infiltrate myometrium prior to parturition. Macrophages and neutrophils massively infiltrate the upper and lower segment of myometrium at term, suggesting that parturition is an inflammatory event (Thomson et al., 1999). Inflammatory genes are significantly regulated in human endometrium and cervix in association with parturition (Bollapragada et al., 2009). The inflammatory events are not limited to uterus and cervix but there are indications that peripheral blood leukocytes also actively participate in this process for a successful labor (Yuan et al., 2009). It has been suggested that inflammatory stimulus upregulate pro-inflammatory cytokines which may further upregulate prostaglandins, MMPs and attract leukocytes leading to myometrial contractility, rupture of membranes and cervical ripening (Challis et al., 2009).

4. Inflammatory pathologies regulated by estrogen

Abnormal regulation of the immune system could lead to various complications in female reproduction. Various autoimmune and inflammatory disorders have been reported (Cutolo et al., 2010; Deroo & Korach, 2006; Jabbour et al., 2009; Straub, 2007). Estrogens have been implicated directly in diseases like arthritis, osteoporosis, systemic lupus erythematosus, multiple sclerosis, preeclampsia, complications in fertility, pregnancy loss, post-term labor, labor complications, cancers of breast and reproductive tract. Estrogens also play a vital role in the pathophysiology of female reproduction mediated by leukocytes. There are ample evidences to indicate that aberrant inflammatory pathways are directly or indirectly regulated by estrogens, contributing to the cause of various diseases.

5. Conclusion

Estrogens act through ERs and regulate various aspects of the immune system directly or indirectly acting through various downstream mediators. ERs have been found on diverse types of leukocytes. Estrogens act directly via its different receptors and regulate various inflammatory functions mediated through different types of leukocytes. Estrogens are also able to regulate the number, migration and function of leukocytes involving complex mechanisms. There are several clues and confirmations; however the exact nature, timing and interactions are still to be explored. Considering the recent findings of the function of estrogens in various aspects of immune regulation and inflammation, it is difficult to consider estrogens just as a 'female reproductive hormone' anymore. The role of estrogens in various inflammatory processes and its significance is well accepted. Estrogens regulate normal and pathological inflammatory events in reproduction. However, the molecular mechanisms of these events are still being worked out and demand more attention.

Understanding the molecular mechanisms will enable us to know more about the normal and aberrant regulation of these reproductive events involving inflammation and their mediators. Both ER α and ER β have several splice variants lacking different domains with possible different functions. The expression of these variants in different types of leukocytes is not known and warrants further investigation. With the identification of the new membrane bound GPER, the signaling mechanism has yet another layer of complexity and its presence or role in most of the leukocytes are yet to be established. Insights into the function and regulation of ERs in leukocytes could open up new possibilities for treatments for various diseases involving inflammation.

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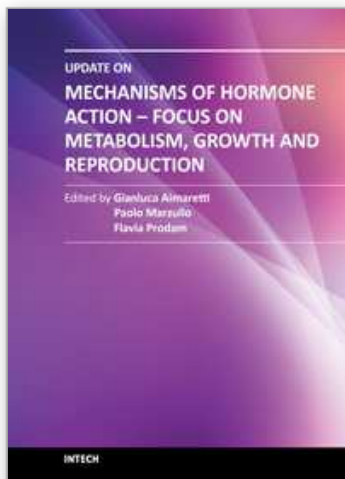
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The purpose of the present volume is to focus on more recent aspects of the complex regulation of hormonal action, in particular in 3 different hot fields: metabolism, growth and reproduction. Modern approaches to the physiology and pathology of endocrine glands are based on cellular and molecular investigation of genes, peptide, hormones, protein cascade at different levels. In all of the chapters in the book all, or at least some, of these aspects are described in order to increase the endocrine knowledge.

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