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Review

Estrogen receptors regulate an inflammatory pathway of dendritic cell differentiation: Mechanisms and implications for immunity

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ABSTRACT

This article is part of a Special Issue "Neuroendocrine-Immune Axis in Health and Disease."

Immune cells and hematopoietic progenitors express estrogen receptors (ER). As ligand-activated transcription factors that modulate chromatin structure, ER regulate transcriptional programs that direct the development or functional responses of immune cells. ER-regulated immune responses likely contribute to significant sex biases in infection, autoimmunity and other inflammatory diseases, and changes in immune function during the female hormonal cycle and pregnancy. Here we summarize our own and others' studies showing that ERα signaling regulates the development of dendritic cells (DCs), antigen-presenting cells crucial for initiation of innate and adaptive immunity. During inflammation, elevated GM-CSF directs the development of new DCs from monocytes or other precursors that infiltrate tissues and lymphoid organs, and these *de novo* populations of inflammatory DCs have critical roles in programming T cell-mediated responses during infection and autoimmunity. Estradiol acting via ERα, but not ERβ, promotes the GM-CSF-mediated inflammatory pathway of DC differentiation, leading to the development of DCs with increased functional capacity. Estradiol/ERα signaling acts directly in GM-CSF-stimulated myeloid progenitors to induce elevated levels of IRF4, a transcription factor that directs a developmental program underlying $CD11b^+$ DC differentiation. In contrast, during homeostatic Flt3 Ligand-driven DC development, ERα signaling decreases numbers of myeloid progenitors and differentiated DCs, yet promotes more functionally competent DCs. Thus ERα signaling regulates the response of DC progenitors to the external cytokine environment, thereby altering the strength or integrity of DC developmental pathways. The development of increased numbers of DCs during inflammation will likely increase the magnitude of DC-mediated functional responses including cytokine production, processing and MHC-mediated presentation of antigens, and activation and polarization of T and B lymphocytes; these functions also may be regulated directly by ERα signaling. In sum, via profound effects on DC development and ensuing functional responses, ERα signaling can regulate the quality of the adaptive immune responses and influence the resolution of infection or chronic inflammatory diseases.

Contents

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Introduction

Novel roles of nuclear hormone receptors in immune cell biology have been elucidated in recent years. Through their action as ligand-activated transcription factors, nuclear receptors (e.g., for estrogen, androgen, vitamin D, retinoic acid) regulate gene expression programs that direct immune cell development or function (Moro et al., 2008; Olsen and Kovacs, 1996; Fish, 2008). Immune cells and their progenitors in females and males express estrogen receptors (ERs). Accordingly, effects of estrogens or ERα on normal or pathological immune responses, or immune cell development, have been identified (Straub, 2007; Kovats and Carreras, 2008). An understanding of how ER signaling regulates immunity is clinically important. Autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis are strongly female-biased and modulated by sex steroid levels and pregnancy, yet the cellular and molecular basis for this is not completely understood (Whitacre, 2001). Furthermore, sex differences including sex hormone levels are one crucial factor that modulates susceptibility and immune responses to virus infection (Klein et al., 2011). Thus the study of mechanisms of ER-regulated immunity will lay the foundation for new therapeutic approaches to these sex-biased immune diseases. Here, I begin with a description of ER signaling mechanisms and an overview of DC development and function, followed by a review of studies that provide evidence for the ER-mediated regulation of the development and function of dendritic cells (DCs) in rodents and humans.

ER signaling mechanisms

ER are ligand-dependent transcription factors that regulate chromatin structure and gene expression by forming complexes with chromatin-modifying coregulators and other transcription factors (Mann et al., 2011). Estrogens also elicit rapid (within minutes) changes in cell signaling pathways, and although currently there is no consensus as to whether these rapid responses involve the classical ER, the signaling pathways activated can lead to histone modifications and altered chromatin structure near estrogen-regulated genes (Mann et al., 2011; Heldring et al., 2007). Thus a complete understanding of how estrogens modulate immune responses will ultimately stem from investigation of mechanisms by which ligand-bound ER modulate gene expression programs in immune cells or their precursors.

ER α and β proteins are members of the nuclear receptor super family; single ER chains form αα, ββ and αβ dimers, each of which may be functionally distinct (Heldring et al., 2007). ERα, and in some cases ERβ, expression by mature immune cells in murine lymphoid organs and human blood has been reported [reviewed in (Kovats et al., 2010)]. ERα appears to be ubiquitously expressed by immune cells, based on reports of expression in T and B lymphocytes, DCs, macrophages, monocytes, natural killer cells and mast cells. ERβ is less universally expressed. Within human peripheral blood mononuclear cells (PBMC), $CD4^+$ T cells express higher amounts of ERα than ERβ, $CD8^+$ T cells express low amounts of both ER, and B cells express more ERβ than ERα (Phiel et al., 2005). Human monocytes and monocyte-derived DCs, and blood myeloid and plasmacytoid DCs, express ER and respond to estrogens (Mor et al., 2003; Escribese et al., 2008; Seillet et al., 2012). In mice, splenic DCs and peritoneal macrophages express ERα but not ERβ. However, some populations of DCs *in vivo*, such as DCs infiltrating the central nervous system during experimental autoimmune encephalomyelitis (EAE), do express ERβ (Du et al., 2011).

Hematopoietic progenitors in human and murine bone marrow also express ER. $CD34^+$ hematopoietic progenitors in human adult bone marrow, but not cord blood, express both ERα and ERβ (Igarashi et al., 2001). In mice, ERα is expressed by adult bone marrow hematopoietic progenitors, but not by fetal liver progenitors (Igarashi et al., 2001; Carreras et al., 2008). These data suggest that ER expression in hematopoietic progenitors coincides with development of the mature immune system in neonatal life.

Blood and tissues contain variable levels of both endogenous and exogenous ER ligands, which are likely to impact DC differentiation and function during homeostasis and inflammation. Endogenous estrogens include 17-β-estradiol, the major form present in adult females and males, and estriol, which is produced at high levels during pregnancy. The K_D of the ER for estradiol is 0.1–1.0 nM (27–272 pg/ml). This is consistent with serum levels of estradiol in cycling female mice: ~25–35 pg/ml during diestrus and ~70–200 pg/ml during estrus, and in male mice: ~8–15 pg/ml (Foster et al., 1983). Serum estradiol levels in humans peak at 200–500 pg/ml, while levels at the term of pregnancy reach 16,000–30,000 pg/ml (Askanase and Buyon, 2002). The body also is exposed to ill-defined amounts of exogenous ER ligands, including phytoestrogens and environmental endocrine disruptors such as bisphenol A. A class of pharmaceuticals termed selective ER modulators (SERM), such as tamoxifen and raloxifene, also may modulate immune function. SERM have tissue-specific agonist or antagonist properties and are used to treat breast cancer and osteoporosis, and contemplated for treatment of autoimmune disease (Dutertre and Smith, 2000). Recently identified estrogen receptor subtype agonists are a new class of drugs planned for treatment of clinical conditions secondary to menopause, but also may be useful for immune modulation (Leitman et al., 2010).

Upon ligand binding, cytosolic ER dimers are released from stabilizing heat shock proteins and translocate to the nucleus. Nuclear ER directly bind estrogen response sequence elements proximal to genes, or are tethered indirectly to DNA by forming complexes with other transcription factors that bind DNA via their own consensus sequences (O'Lone et al., 2004). ER often bind to DNA associated with transcription factors (e.g. NF-κB, Sp1, AP-1, C/EBPβ) that are important for immune cell function (Leitman et al., 2010). Each structurally distinct ligand imparts a specific unique conformation to ER dimers, which then dictates recruitment of distinct profiles of coregulators and histone-modifying enzymes into multi-protein transcription complexes (Heldring et al., 2007). The complex of ligand-bound ERα, coregulators and histone-modifying enzymes leads to post-translational histone modifications (acetylation, phosphorylation, methylation) that alter chromatin structure (Mann et al., 2011). Transcriptional coregulators may act as coactivators or corepressors (or both), remodeling chromatin in configurations that are permissive or inhibitory for transcription. For example, some ER coactivators have histone acetyltransferase activity (e.g. SRC1), or they can interact with acetyltransferases such as p300/CBP, leading to transcriptional activation. ER corepressors such as NCOR can complex with histone deacetylases, leading to gene repression. Although cell type