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## Review

# Estrogens, osteoarthritis and inflammation

Marta Martín-Millán<sup>a,\*</sup>, Santos Castañeda<sup>b</sup>

<sup>a</sup> Department of Internal Medicine, IFIMAV, Hospital Universitario Marqués de Valdecilla, Avenida de Valdecilla s/n, 39008 Santander, Cantabria, Spain

<sup>b</sup> Department of Rheumatology, IIS-Princesa, Hospital Universitario de La Princesa, c/Diego de León 62, 28006 Madrid, Spain

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## ABSTRACT

Estrogens participate in several biological processes through different molecular mechanisms. Their final actions consist of a combination of both direct and indirect effects on different organ and tissues. Estrogen may have pro- and anti-inflammatory properties depending on the situation and the involved tissue. In general, acute loss of estrogens increases the levels of reactive oxygen species and activates nuclear factor- $\kappa$ B and pro-inflammatory cytokine production, indicating their predominant anti-inflammatory properties. Furthermore, pro-inflammatory cytokine expression has been shown to be attenuated by estrogen replacement. Osteoarthritis and cardiovascular disease are two of the more prevalent diseases once menopause is established, which has suggested the link between estrogens and both processes. In addition, deletion of estrogen receptors in female mice results in cartilage damage, osteophytosis and changes in the subchondral bone of the joints suggesting that estrogens have a protective role on the maintenance of joint homeostasis. Furthermore, in spite of the negative effect of estrogen replacement reported in 2002 by the Women's Health Initiative study, several works published afterwards have explored the potential protective effect of estrogen supplementation in animal models and have postulated that these actions may justify a beneficial role of estrogens in different diseases where inflammation is the major feature. In this review, we will analyze the effects of estrogens on certain pathological situations such as osteoarthritis, some autoimmune diseases and coronary heart disease, especially in postmenopausal women.

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## 1. Introduction

Estrogens regulate many physiological processes, including normal cell growth, development, and tissue-specific gene regulation in the reproductive tract, the brain, the immune system, and in the cardiovascular and skeletal systems [1,2]. Estrogen was originally thought to be exclusively a sexual hormone implicated mainly in the development of the reproductive system. However, the understanding of its physiological functions has considerably improved in last years.

Epidemiological evidences suggest that female sex hormones play an important role in the etiology and pathophysiology of chronic inflammatory and degenerative diseases. However, whether estrogens are friends or not in inflammatory and immune-mediated diseases is still a matter of debate [3,4]. Several significant factors generate confusion in evaluating the role of estrogens in inflammatory or immune diseases. However, as supported by the higher prevalence of autoimmune diseases in women, estrogens are generally considered as enhancers of cell proliferation and immune

response. As an example, in systemic lupus erythematosus (SLE), female to male ratio ranges from 10:1 to 15:1 [5].

Osteoarthritis (OA) is another disease commonly seen in postmenopausal women. The prevalence of OA is higher among women than men, and this prevalence is associated with menopause. In fact, a nationwide population survey showed that radiographic OA is three times more common among women aged 45–64 years compared to their male peers [6,7]. In the EPISER study, the estimated prevalence of symptomatic knee OA in subjects aged 20 years or above was 10.2% (5.8% in men vs. 14% in women). The prevalence of symptomatic hand OA in the same population was 2.3% in male and 9.5% in female [8].

In this review, we update the relationship between estrogens, OA and inflammation and the main mechanisms by which estrogens mediate their pathologic effects in inflammatory and degenerative joint diseases.

## 2. Estrogen receptor structure and characteristics

The biological actions of estrogens are mediated by binding to one of two specific estrogen receptors (ERs), ER $\alpha$  or ER $\beta$ , which belong to the superfamily of nuclear receptors, a family of ligand-regulated transcription factors, located mainly in the cytoplasm

\* Corresponding author. Tel.: +34 942 201990.

E-mail addresses: [martinmma@unican.es](mailto:martinmma@unican.es), [mmmillan1974@hotmail.com](mailto:mmmillan1974@hotmail.com) (M. Martín-Millán).

**Table 1**  
Tissues in which estrogen receptor subtypes (ERs) are expressed.

| Type of ER              | Tissues in which they are expressed                                                                                                                                                                    |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ER $\alpha$             | Uterus, placenta, pituitary and cardiovascular system                                                                                                                                                  |
| ER $\beta$              | Ventral prostate, urogenital tract, ovarian follicles, lung and immune system                                                                                                                          |
| ER $\alpha$ and $\beta$ | Mammary gland, bone, brain and joint tissues: growth plate chondrocytes, articular chondrocytes; subchondral osteoclasts, osteoblasts and osteocytes; synoviocytes, ligament fibroblasts and myoblasts |

ER $\alpha$ : estrogen receptor alpha; ER $\beta$ : estrogen receptor beta.

[1]. ER $\alpha$  is located at chromosomal locus 6q25.1 [9], whereas ER $\beta$  is found at position 14q22–24 [10]. Several ER $\alpha$  and ER $\beta$  splicing variants have been described, but whether all transcripts are expressed as functional proteins and have biological functions remains unclear.

Both receptors are expressed in a variety of tissues throughout the body, but in different proportions in each tissue. ER $\alpha$  is highly expressed in classical estrogen target tissues such as the uterus, placenta, pituitary and cardiovascular system, whereas ER $\beta$  is more abundant in the ventral prostate, urogenital tract, ovarian follicles, lungs and immune system (Table 1). However, both ERs are co-expressed in the mammary gland, bone, and certain regions of the brain [11] (Table 1). Although both ER subtypes can be expressed in the same tissue, they may not be expressed in the same cell type.

In joint tissues, both ER types are expressed by the chondrocytes [12], subchondral bone cells [13], synoviocytes [14], ligament fibroblasts [15] and myoblasts [16] in humans and other species. However, ER $\alpha$  is predominant in cortical bone and ER $\beta$  predominates in cartilage, cancellous bone and synovium [17].

The two receptors have the typical structure of the nuclear receptor family, which consists of six regions designated by letters from A to F (Fig. 1). The central C domain is a highly conserved region also known as the DNA-binding domain (DBD). This region contains two “zinc fingers” which recognize sequences of 13 bp (5'-GGTCAnnnTGACC3'), called the estrogen response element (ERE). The ERE is located in the promoter of target genes, which is where the ER interacts with the DNA [18]. After the DBD domain, we can find the D domain, a less conserved region, whose flexibility allows the protein to fold up easily. The C-terminal domain includes the ligand-binding domain (LBD), which is where the ligand binds to its receptor. The LBD contains a nuclear localization, a dimerization and a ligand-dependent transactivation region. This latter domain is also called AF-2, and is responsible for recruiting co-activators or repressors depending on the ligand bonded [19]. The F

domain varies in length depending on the species. It is not directly involved in ligand-binding or transcriptional activation, but modulates receptor activity [20].

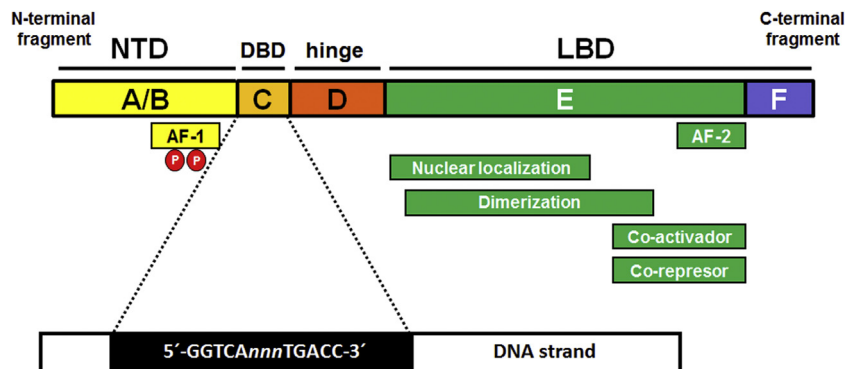
The amino-terminal region is the most variable among family members, both in size and amino acid sequences. It contains a transactivation region, called AF-1, which unlike the AF-2 it is ligand-independent. Both AF-1 and AF-2 regions can activate transcription independently or synergistically. In addition, the N-terminus contains 14 serine residues that can be phosphorylated by a variety of protein kinases [21–23].

The resulting conformation obtained once the ligand has bonded to the ER will determine the type of regulator that will be recruited. Binding of agonists promotes interaction with co-activators, while binding of antagonists induces the interaction with co-repressors. On the other hand, it is important to remember that not only do different cell types have different proportions of ERs, but also different proportions of transcription factors, which will establish the final transcriptional effect.

Estrogens are essentials in the development of the reproductive system. However, estrogens have other important functions. Thus, estrogens contribute also to promote both skeleton mineralization and epiphyseal maturation. As a matter of fact, the description of a 28-year-old man with estrogen resistance due to truncated estrogen receptor unable to bind the DNA-binding and hormone-binding domains revealed the importance of estrogens in growth plate closure eighteen years ago [24]. The most remarkable phenotypic finding of the human estrogen resistance was tall stature due to a continued slow linear growth determined by unfused epiphyses. As well as this, this man had low bone mass with biochemical evidence of increased bone resorption. These observations highlighted the importance of estrogen signals via its ER $\alpha$  to promote not only skeletal maturation, but also, epiphysis maturation, since without them the final adult length limbs are disproportionally increased.

Estrogens, through direct and indirect mechanisms on different cell types, exert a broad spectrum of pleiotropic effect on non-sexual tissues, and that loss of estrogen is involved in many age-related conditions. Yet, its precise molecular mechanism is still not fully understood.

It has been developed estrogen receptor analogues, such as the Selective Estrogen Receptor Modulators, which as their name says, SERMs are “selective” – this means that a SERM that blocks estrogen's action in some tissues, such as breast cells, can activate estrogen's action in other cell types, such as bone, liver, and uterine cells. This tissue-specificity makes them very useful drugs in clinic, since they allow us to dissect the positive effects of estrogens on non-sexual tissues from the deleterious effects on breast, when they are used for long periods of time.



**Fig. 1.** Nuclear estrogen receptor structure. Estrogen receptors have four functional domains, which harbor a DNA-binding domain (DBD), a ligand-binding domain (LBD), an N-terminal domain (NTD) and two transcriptional activation functions (AF-1 and AF-2). At the AF-1 there are several phosphorylation sites that can be activated by different growth factors regardless of the ligand.

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