Advanced Drug Delivery Reviews 62 (2010) 1265–1276

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Selectively targeting estrogen receptors for cancer treatment ☆

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ARTICLE INFO

Article history:
Received 25 February 2010
Accepted 4 August 2010
Available online 10 August 2010

Keywords:
Estrogen receptor alpha
Estrogen receptor beta
SERMs
SERDs
Selective agonist
Antagonist
Breast cancer
Prostate cancer
Colon cancer
Ovarian cancer

ABSTRACT

Estrogens regulate growth and development through the action of two distinct estrogen receptors (ERs), ERα and ERβ, which mediate proliferation and differentiation of cells. For decades, ERα mediated estrogen signaling has been therapeutically targeted to treat breast cancer, most notably with the selective estrogen receptor modulator (SERM) tamoxifen. Selectively targeting ERs occurs at two levels: tissue selectivity and receptor subtype selectivity. SERMs have been developed with emphasis on tissue selectivity to target ER signaling for breast cancer treatment. Additionally, new approaches to selectively target the action of ERα going beyond ligand-dependent activity are under current investigation. As evidence of the anti-proliferative role of ERβ accumulates, selectively targeting ERβ is an attractive approach for designing new cancer therapies with the emphasis shifted to designing ligands with subtype selectivity. This review will present the mechanistic and structural features of ERs that determine tissue and subtype selectivity with an emphasis on current approaches to selectively target ERα and ERβ for cancer treatment.

Published by Elsevier B.V.

Contents

Abbreviations: ER, estrogen receptor; SERM, selective estrogen receptor modulator; SERD, selective estrogen receptor down-regulator; ERKO, estrogen receptor knockout; PPT, propyl pyrazole triol; DPN, diarylpropionitrile; ARKO, aromatase inhibitor knockout; AOM, azoxymethane; ERE, estrogen response element; DBD, DNA binding domain; LBD, ligand binding domain; DES, diethylstilbestrol; CBI, coactivator binding inhibitor; BRET, bioluminescence resonance energy transfer.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Development of Novel Therapeutic Strategy by Regulating the Nuclear Hormone Receptors".

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0169-409X/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.addr.2010.08.001

1. Introduction

Two distinct estrogen receptors (ERs), ERα and ERβ, mediate estrogen signaling and distinctly regulate transcription driving growth, proliferation, and differentiation, among many cellular processes. ERα is well characterized as a mediator of cell proliferation, especially in breast cancer cells, driving proliferation in the presence of estrogen [1]. ERβ opposes ERα and inhibits ERα mediated proliferation in many cells [2–8]. Because ERs can regulate cell proliferation, they can be targeted therapeutically to inhibit cancer growth. ERα specifically has been implicated as a key factor in breast cancer growth and has been effectively targeted in breast cancer with the development of selective estrogen receptor modulators (SERMs) such as tamoxifen or raloxifene [1,9]. SERMs function to target ER signaling in a tissue specific manner and the tissue selectivity of SERMs is determined by structural features induced by SERM binding to the receptors and cell type specific factors. Approximately 30% of breast cancers develop resistance after extended exposure to SERMs [10]. SERMs target the ligand dependent activation of ER but alternative methods of targeting ER activity are emerging to overcome resistance. Selective estrogen receptor down-regulators (SERDs) have been developed to inhibit ER signaling through degradation of the receptor. Alternative approaches to inhibit ERα activity go beyond the ligand binding domain and target ER-DNA or ER-cofactor interactions. In this review we will present current methods of targeting ERα for cancer treatment and discuss the mechanistic and structural components that contribute to the tissue selectivity of SERMs.

Additionally, we will discuss the development of ER subtype selective ligands. With the identification of a second estrogen receptor subtype, ERβ, the design of compounds which selectively target ERs has shifted towards subtype selectivity. Ligands with selectivity for ERβ show promise as cancer treatments given the anti-proliferative role of ERβ in many tissues. ERβ is not yet targeted clinically for cancer treatment, but ERβ selective ligands hold therapeutic promise in breast cancer, as well as prostate, ovarian, and colon cancers. Such compounds could promote ERβ mediated growth inhibition while avoiding proliferative side affects mediated by ERα. Here, we will discuss known ERβ selective compounds with an emphasis on structural features that contribute to subtype selectivity. We will also present recent approaches to identifying novel ERβ selective ligands and discuss future directions for identifying ERβ selective compounds with therapeutic potential. Selectively targeting ERs can provide effective cancer treatments and new techniques to inhibit ERα and selectively activate ERβ are emerging to improve the effectiveness of identifying tissue and subtype selective ER ligands for cancer therapy.

2. Estrogen receptor action in normal and cancerous tissues

2.1. Estrogen receptors and normal development

ERs have important roles in normal development and function of reproductive tissues as well as non-reproductive tissues including the lungs, colon, prostate, and cardiovascular system. ERα and ERβ show overlapping and distinct tissue distributions suggesting the receptors have distinct biological roles. Both receptors are expressed in the uterus, breast, lung, heart, intestine, and brain. ERα is expressed in the absence of ERβ in hepatocytes and the hippocampus while ERβ shows unique expression patterns in the prostate, vagina, and cerebellum [11]. Much of our understanding regarding the developmental roles of ERs has been gleaned from observations of ERα and ERβ knockout mice (αERKO, βERKO, and α/βERKO mice). It is necessary to briefly discuss the functional roles of ERα and ERβ in normal development in order to understand the contributions of ER signaling in cancerous tissues. We will present a brief overview of the roles of ERs as demonstrated by αERKO and βERKO mice with a narrowed focus on tissues that may develop cancers which could benefit from selective ER therapies such as reproductive tissues, breast, prostate, and colon. The phenotypes of ERKO mice have been reviewed extensively elsewhere [12–14].

2.1.1. Reproductive development

ERα and ERβ are important mediators of normal ovarian and uterine development and function; the most obvious developmental impairment in αERKO and βERKO mice is found in reproductive structures including the ovary and uterus. ERα is required for normal reproductive development and both male and female αERKO mice are infertile [15,16]. In normal development, estrogen stimulates proliferation of the uterine epithelium. αERKO females develop rudimentary estrogen insensitive uteri demonstrating the role for ERα in mediating estrogen induced proliferation in the uterus. In the ovaries, both ERα and ERβ are expressed though their distributions among cell types are markedly different. ERα is primarily expressed in thecal and interstitial cells whereas ERβ is primarily expressed in granulosa cells. ERα is critical for normal ovary function and αERKO mice develop abnormal ovaries in which the follicles remain immature [15,16].

βERKO mice generated in different laboratories do not have consistent phenotypes and conflicting evidence for the role of ERβ in reproductive development is present in the literature (reviewed in [14]). In some models, βERKO females are subfertile suggesting ERβ has a less critical role in reproductive and ovarian development [16,17]. More recently, ERβ null mice have been generated using Cre/LoxP mediated disruption of the ERβ gene past exon 3, and both males and females are infertile [18]. In these mice, follicle development proceeds normally but does not completely proceed to ovulation due to high rates of termination during atresia demonstrating a critical role for ERβ in development of functional ovaries. Unlike αERKO mice, estrogen responsiveness in the uterus and ovaries appears normal in βERKO mice. In α/βERKO mice, in which both ERα and ERβ are null, reproductive development is similar to that observed in αERKO mice demonstrating the dominant role of ERα [16].

2.1.2. Mammary gland development

Mammary gland development is also dependent on functional estrogen signaling. The mammary gland grows during puberty and completely differentiates during pregnancy and lactation. In the mammary gland, ERα is a key regulator of proliferation in response to

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