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·Review·

Cancer therapy using natural ligands that target estrogen receptor beta

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[ABSTRACT] Estrogen receptor beta (ERβ) is one of the two key receptors (ERα, ERβ) that facilitate biological actions of 17β-estradiol (E2). ERβ is widely expressed in many tissues, and its expression is reduced or lost during progression of many tumors. ERβ facilitates estrogen signaling by both genomic (classical and non-classical) and extra-nuclear signaling. Emerging evidence suggests that ERβ functions as a tissue-specific tumor suppressor with anti-proliferative actions. Recent studies have identified a number of naturally available selective ERβ agonists. Targeting ERβ using its naturally available ligands is an attractive approach for treating and preventing cancers. This review presents the beneficial actions of ERβ signaling and clinical utility of several natural ERβ ligands as potential cancer therapy.

[KEY WORDS] Estrogen receptor; Estrogen receptor beta; Tumor suppressor; ER beta agonists; Liquiritigenin; S-equol; Genistein

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Introduction

The biological effects of 17β-estradiol (E2) are mediated through their cognate receptors: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) [1]. These receptors (ERα and ERβ) have extensive similarities; however, ERβ has quite a different function than ERα, and ERβ functions as a tissue-specific tumor suppressor with anti-proliferative actions [2]. Several studies showed that overexpression of ERβ reduces cell proliferation and that knockdown of ERβ enhances cell proliferation in cancer cells [3-4]. ERβ expression is down regulated or lost in several tumors including those of the breast, ovary, prostate, colon and brain [5-11]. In this review, we summarize the recent evidence for the tumor suppressive role of ERβ signaling in cancer progression and discuss the possibility of using natural ERβ ligands as therapeutics for treating or preventing cancer.

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ERβ signaling leads to tumor suppression

ERβ was discovered in 1996 as the second receptor of E2 [12]. This discovery of a second estrogen receptor advanced the estrogen field and suggested more complexity in hormonal signaling. The human ERβ gene (ESR2) is located on chromosome 14q23.2, belongs to the nuclear receptor superfamily, contains three commonly conserved functional domains including an N-terminal activation function (AF1) domain, a central DNA binding domain (DBD) and a C-terminal ligand binding domain (LBD) that contains AF2 [13]. ERβ shares extensive homology with ERα (97% similarity in DBD, 59% in LBD, and 16% AF1) (Fig. 1A). ERβ functions as a transcription factor and is implicated in modulation of genes involved in multiple pathways. However, the molecular mechanism(s) through which ERβ mediates growth inhibition of cancer cells remains elusive. Accumulating evidence suggests that ERβ functions as either a homodimer (ERβ : ERβ) or heterodimer (ERα : ERβ) depending on the status of the cellular expression of ERs [1]. Expression of ER subtypes vary depending on tissue, some tissues such as uterus and mammary gland express more ERα

than ERβ, while some tissues such as lung and ovary uniquely express ERβ, and tissues such as bone express both subtypes [14]. The ratio of ER subtypes present in a cell dictates the complexity and magnitude of signaling depending on the status of mono or heterodimers (Fig. 2). Target gene studies using genome-wide approaches revealed that ERα and ERβ share many genes; however, ERβ has the potential to activate unique set of genes [15]. Genome-wide ChIP-on-ChIP studies suggested that a dynamic interplay exists between ERα and ERβ in their selection of chromatin binding sites and that the ligand subtype determines the spectrum of chromatin binding [16]. Recent genomic studies also suggested that ERα and ERβ have the potential to activate different sets of genes and that ERβ effects can be non-classical via its interactions with other transcription factors such as AP1, SP1, NF-κB and KLF5 [16-17]. Evidence suggests that ERβ is expressed as multiple isoforms, (with variations in the C-terminal domain ERβ1-5); however, much of the published data is focused primarily on ERβ1 [1]. ERβ isoforms 2 to 5 have weak ligand binding affinity due to deletions in C-terminal region and some isoforms such as ERβ4 and ERβ5 appear to respond to ligand signaling via hetero-dimerization with ERβ1 (Fig. 1B) [18]. Global gene expression studies comparing E2 and natural ERβ agonists revealed that natural ERβ agonists notably reduce the stimulation of genes promoting proliferation and preferably induce genes that are more pro-apoptotic. Further, these studies showed that each ERβ agonist has the ability to promote a unique set of genes and pathways in cancer cells. In addition, the gene expression pattern elicited by natural ERβ ligands is dependent on the status and ratio of ER subtypes present in a cell [19]. Collectively, these findings suggest that the overall action of ERβ on the genome of hormone-responsive cells appears to depend on the relative concentrations of both ERs, the status of ERβ isoforms, the repertoire of coregulators and the type of ligand in a given cell.

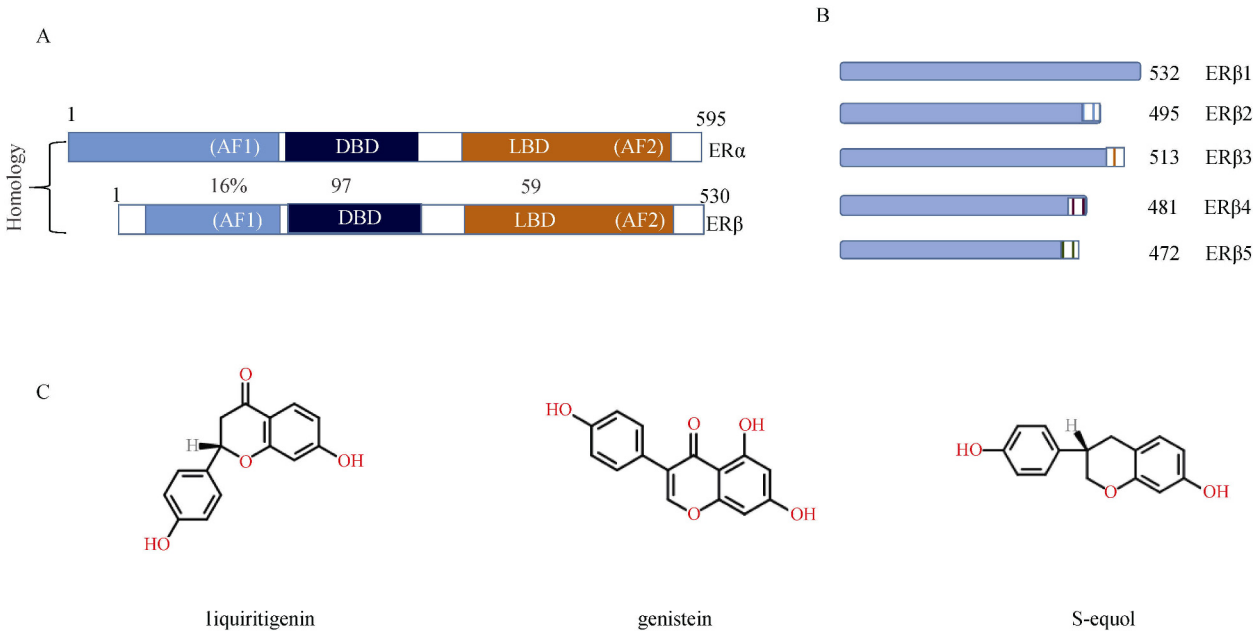

Fig. 1 A. Schematic representation of ERα and ERβ structural domains. The percentage of amino acid homologies between various domains of ERα and ERβ are also shown. AF1, N terminal activation function domain 1 that facilitate ligand independent coregulator interactions; DBD, DNA- binding domain (DBD) that facilitate interaction with ERE elements; LBD, ligand-binding domain that also harbors activation function domain 2 (AF2) which facilitate ligand dependent coregulator interactions. B. Schematic representation of ERβ beta isoforms. Isoforms 2 to 5 have variation in the C-terminal region. C. Schematic representation of structures of natural ERβ ligands

Natural ligands of ERβ

Even though ERα and ERβ are structurally similar, their ligand-binding domains differ enough to be selective for different ligands [20]. Several studies have identified a number of naturally available selective ERβ agonists that are currently being investigated for therapeutic use [2]. Identification of unique ligands that act through ERβ provides a unique therapeutic opportunity to target ERβ for tumor suppression. In this review, we focus on three naturally available ERβ ligands (liquiritigenin, S-equol, and genistein) that have preferential agonist activity for ERβ compared to ERα (Fig. 1C), and recent evidence suggests that these compounds may have potential utility in cancer prevention and/or treatment.

Liquiritigenin: The MF101 formulation that comprises 22 botanically derived active ingredients was initially found to function as a selective ERβ agonist and was originally tested for reducing the frequency and severity of menopausal hot