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Review

Re-adopting classical nuclear receptors by cholesterol metabolites

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ABSTRACT

Since the first cloning of the human estrogen receptor (ER) α in 1986 and the subsequent cloning of human ERβ, there has been extensive investigation of the role of estrogen/ER. Estrogens/ER play important roles not only in sexual development and reproduction but also in a variety of other functions in multiple tissues. Selective Estrogen Receptor Modulators (SERMs) are ER lignds that act as agonists or antagonists depending on the target genes and tissues, and until recently, only synthetic SERMs have been recognized. However, the discovery of the first endogenous SERM, 27-hydroxycholesterol (27HC), opened a new dimension of ER action in health and disease. In addition to the identification of 27HC as a SERM, oxysterols have been recently demonstrated as indirect modulators of ER through interaction with the nuclear receptor Liver X Receptor (LXR) β. In this review, the recent progress on these novel roles of oxysterols in ER modulation is summarized.

Contents

1. Estrogen receptors, estrogen and SERM

Estrogen plays critical roles in reproduction, development, bone mineralization, and metabolism as well as cardiovascular, immune system and brain function. It is also an important factor in breast tumor progression. Its receptor, the estrogen receptor (ER), is a member of the nuclear hormone receptor superfamily, and it consists of the following domains: animo-terminal ligand-independent activation function-1 (AF-1), DNA binding domain, hinge region, and ligand-binding domain, which contains the carboxyl-terminal activation function 2 (AF-2). There are two subtypes of ER, ERα and ERβ, and they share 96% homology at the amino acid level in the DNA binding domain and 59% homology in the ligand-binding domain in humans. ERα and ERβ have distinct tissue expression patterns, and together with differences in their ligand affinity, the abundance of the two subtypes in cells and tissues define the physiological function of estrogen [1]. The relatively large ligand-binding pockets of ERs allow many compounds other than steroid structures to bind and differentially alter ER structure [2–4]. In contrast to estrogens, which have various levels of agonistic activity in all tissues, Selective Estrogen Receptor Modulators (SERMs), which are diverse ER ligands with non-steroidal structures, act as agonists or antagonists depending on the target genes and tissues. Although the exact mechanism of the tissue-selective effects of SERMs is still incompletely understood, these ligands exert agonistic/antagonistic properties mainly based upon the amount of ER in the tissue, ligand-dependent ER conformational changes, and differential interaction with various coactivators and corepressors. Clomiphene was the first SERM used

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as a pituitary gonadotropin inhibitor in 1967, and tamoxifen was the first SERM to be clinically developed and marketed for the treatment of breast cancer. SERMs are classified into several groups according to their core structure, including triphenylethylenes such as tamoxifen, benzothiophenes such as raloxifene, indoles such as bazedoxifene (BZA), benzopyrans and tetrahydronaphthalenes [5]. The ideal SERM for clinical use would have estrogenic effects in some tissues such as bone and the cardiovascular system, but have anti-estrogenic or neutral effects in other tissues, such as the breast and endometrium. Many classical SERMs show limited ER subtype selectivity; however, a growing number of novel ER subtype-selective ligands have been developed [6]. In addition, the combination of a SERM with estrogens as a tissue-selective estrogen complex (TSEC) has been tested for the potential to achieve a more favorable clinical profile in postmenopausal women. This approach is expected to combine the desired ER agonist activities of estrogens with the tissue selectivity of a SERM. BZA paired with conjugated estrogens (CE) is the most advanced TSEC for the treatment of menopausal symptoms, and BZA/CE has shown a significant improvement of said symptoms in clinical trials [7]. There is increasing evidence that in addition to its transcriptional activity in the nucleus, ER also has a nonnuclear action in the plasma membrane caveolae/lipid rafts, where it participates in kinase-mediated signaling pathways [8]. In contrast to our understanding of the mechanisms of action of SERMs on the transcriptional activity of ER, the impact of SERMs on the nonnuclear action of ER still remains unclear.

2. 27HC as a novel endogenous SERM

Through screening oxysterols that exist in the human body for an effect on the transcriptional activity of ER, we discovered that certain oxysterols modulate ER activity [9]. Among such oxysterols, 27-hydroxycholesterol (27HC) is the most abundant circulating oxysterol, and its plasma concentration correlates with that of total cholesterol [10]. Using combinatorial peptide phage display, we found that 27HC induces a unique active conformational change in ERα [11]. In addition, while 27HC shows an anti-estrogenic effect in vascular endothelial cells (ECs), it shows a pro-estrogenic effect in hepatoma and colon cancer cells [9]. These findings identified 27HC as the first naturally occurring SERM and revealed that it has distinct functions in various tissues as described below.

27HC is generated and metabolized by the P450 enzymes CYP27A1 and CYP7B1, respectively [12]. These enzymes are involved in the conversion of cholesterol to bile acids in the liver. There are two (classical and alternative) pathways of cholesterol-bile acid conversion in liver; CYP27A1 is involved in both pathways, but CYP7B1 is only involved in the alternative pathway. Both enzymes are not very responsive to negative feedback by bile acids [13], and dietary manipulation, such as a high cholesterol diet, does not alter the expression of the enzymes [14]. Instead, these enzymes are regulated by many factors other than cholesterol metabolism (Tables 1 and 2), suggesting that 27HC has important actions other than cholesterol metabolism.

Table 1
Factors studied with the respect to the regulation of CYP27A1 expression.

Factors	↑/↓	Tissue (in vivo)/cell line	Species	References
Estrogen	↑	LNCaP	Human	[57]
Estrogen	↓	Hep G2, RWPE-1	Human	[57]
Estrogen	→	Liver	Mouse	[58]
Testosterone	↑	Hep G2	Human	[57]
Testosterone	↓	RWPE-1	Human	[57]
Testosterone	→	LNCaP	Human	[57]
Thyroid hormone	↑	Liver	Mouse	[59]
Thyroid hormone	↓	Hep G2	Human	[60]
Glucocorticoid	↑	Huh7, HepG2	Human	[60,61]
Glucocorticoid	↑	Liver	Rat	[62]
Vitamin D3	↑	RWPE-1, RWPE2-W99, 3T3-L1	Human	[63,64]
GH	↑	Hep G2	Human	[60]
IGF-1	↑	Hep G2	Human	[60]
TNFα	↓	HepG2	Human	[65]
TNFα	→	THP-1, HAEC	Human	[66]
IL-1β	↓	Liver	Hamster	[65]
IL-1β	↓	HepG2	Human	[65]
IL-1β	→	THP-1, HAEC	Human	[66]
LPS	↓	Liver	Hamster, mouse	[65]
LPS	↓	HepG2	Human	[65]
LPS	→	BM-derived macrophage	Mouse	[67]
IFNγ	↓	THP-1, HAEC	Human	[66]
PMA	↓	Hep G2	Human	[60]
Bile acids	↓	Huh7, HepG2, HEK293	Human	[61,68,69]
Bile acids	→	Hepatocyte	Human	[70]
Bile acids	↓	Liver	Rat	[61,68,69]
Bile acids	→	Liver	Human, rat	[71–73]
PPARγ	↑	THP-1, monocyte-derived macrophage	Human	[74,75]
RAR	↑	monocyte-derived macrophage	Human	[75,76]
LXR	↑	Astrocyte	Rat	[77]
LXR	→	THP-1, monocyte-derived macrophage, microglia	Human, rat	[74,77]
RXR	↑	THP-1, monocyte-derived macrophage	Human	[74,75]
Atheroscrelotic lesion	↑	Aorta, carotid artery	Human	[75,78,79]
High cholesterol diet feeding	→	Liver	Mouse	[14]
Monocyte to macrophage differentiation	↑	Monocyte	Human	[75,80,81]
Aging	→	Liver	Swine	[82]

GH, growth hormone; IGF-1, insulin-like growth factor-1; TNFα, tumor necrosis factor α; IL-1β, interleukin-1β; LPS, lipopolysaccharide; IFNγ, interferon γ; PMA, phorbol 12-myristate 13-acetate; PPARγ, peroxisome proliferator-activated receptor γ; RAR, retinoic acid receptor; RXR, retinoid X receptor.