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Review

The emerging roles of orphan nuclear receptors in prostate cancer

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ABSTRACT

Orphan nuclear receptors are members of the nuclear receptor (NR) superfamily and are so named because their endogenous physiological ligands are either unknown or may not exist. Because of their important regulatory roles in many key physiological processes, dysregulation of signalings controlled by these receptors is associated with many diseases including cancer. Over years, studies of orphan NRs have become an area of great interest because their specific physiological and pathological roles have not been well-defined, and some of them are promising drug targets for diseases. The recently identified synthetic small molecule ligands, acting as agonists or antagonists, to these orphan NRs not only help to understand better their functional roles but also highlight that the signalings mediated by these ligand-independent NRs in diseases could be therapeutically intervened. This review is a summary of the recent advances in elucidating the emerging functional roles of orphan NRs in cancers, especially prostate cancer. In particular, some orphan NRs, RORγ, TR2, TR4, COUP-IFII, ERRα, DAX1 and SHP, exhibit crosstalk or interference with androgen receptor (AR) signaling in either normal or malignant prostatic cells, highlighting their involvement in prostate cancer progression as androgen and AR signaling pathway play critical roles in this process. We also propose that a better understanding of the mechanism of actions of these orphan NRs in prostate gland or prostate cancer could help to evaluate their potential value as therapeutic targets for prostate cancer.

Contents

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1. Introduction

Prostate cancer is the most frequently diagnosed cancer among males in most economically developed countries. The American Cancer Society estimates that in 2016, there will be 180,890 newly diagnosed cases and 26,120 deaths due to prostate cancer in the United States, making it the second leading cause of cancer death in men [1]. Recent statistics indicates that its incidence rate is also rapidly increasing in China [2]. The majority of newly diagnosed (about 85%) prostate cancers are localized to prostate gland and treatment options for primary cancers include active surveillance, radical prostatectomy and external beam radiotherapy. However, the natural history of prostate cancer is threatening once it progresses to the fatal invasive or metastatic disease. Patients with metastatic or high-risk localized disease are commonly treated with hormone therapy (androgen-deprivation therapy ADT or androgen receptor/AR-axis-targeted therapy) targeting to AR signaling. Suppression of AR signaling can be achieved by means of surgical or chemical castration to reduce androgen levels using luteinizing hormone-releasing hormone agonists (LHRHa) or androgen biosynthesis inhibitor, and blocking of AR activity using antiandrogens. Although initial responses to ADT are highly favorable for most patients, it can only last for an average of 18–20 months after treatments. The disease inevitably becomes unresponsive to androgen blockade and progresses to the fatal metastatic castration-resistant prostate cancer (CRPC). Patients with metastatic CRPC have only a median survival period of about 1–2 years [3].

2. Nuclear receptors and orphan nuclear receptors

Nuclear receptors (NRs) constitute a superfamily of DNA-binding transcription factors, comprising the ligand-regulated (or hormone NRs) and ligand-independent members (orphan NRs), which can both activate and repress target gene expression by directly binding to specific genomic DNA sequences or indirectly via protein-protein interaction with other DNA-bound transcription factors, such as specificity proteins (Sp) and activating protein-1 (AP-1) [4]. Among the total 48 members of human NRs, 25 receptors are classified as orphan NRs or orphan receptors either because their endogenous physiological ligands have not been identified so far or their transactivation is ligand-independent. Some members originally classified as orphan NRs, including retinoid X receptors (RXRs) and peroxisome proliferator-activated receptors (PPARs), are re-classified as "adopted orphan NRs" since some cellular metabolites or biomolecules have been identified as weak ligands to these NRs [5] (Fig. 1).

In general, all NRs share a common conserved modular structure: activation domain AF-1 at the N-terminus, central DNA-binding domain (DBD), C-terminal ligand-binding domain (LBD) and the second activation domain AF-2. DBD is the most conserved domain with two zinc fingers that allow the binding of NRs to specific DNA responsive elements. NRs bind to these responsive elements, which are usually composed of hexameric sequence AGAACA-like or AGGTCA-like motifs, as monomer, homodimer or heterodimer. The LBD and AF-2 domains mediate functions including ligand-dependent transcriptional activation, coregulator binding and subcellular localization. Three-dimensional structural study reveals that the LBD consists of 12 α-helices with a hydrophobic pocket into which the ligand fits. The last C-terminal helical segment, helix-12 (H12) serves as a lid to the ligand-binding pocket and repositions for coregulator binding when there is ligand engagement. For the constitutively activated and ligand-independent orphan NRs, H12 also undergoes specific repositioning, determines the interaction between these NRs and their coactivators.

NRs play important regulatory roles virtually in all biological processes including development, embryogenesis, differentiation and maintenance of homeostasis. Dysregulation of signaling pathways controlled by NRs are involved in many diseases, including diabetes and cancer. Accruing evidences in recent years strongly suggest that orphan NRs play important roles in cancer development and progression as shown by their altered expressions and dysregulated signaling pathways involved in multiple cancers [6,7]. Although these orphan NRs are constitutively active and independent of any physiological ligands, there are increasing studies showing that orphan NRs are druggable and regarded as prospective novel cancer drug targets [8], as evidenced by some synthetic or natural compounds which can directly bind to these orphan NRs and modulate their activities. In this review, we summarized the emerging roles of orphan NRs in prostate cancer.

3. Orphan NRs in prostate cancer

Within the orphan NR subgroup, half of the members have been studied so far in prostate cancer.

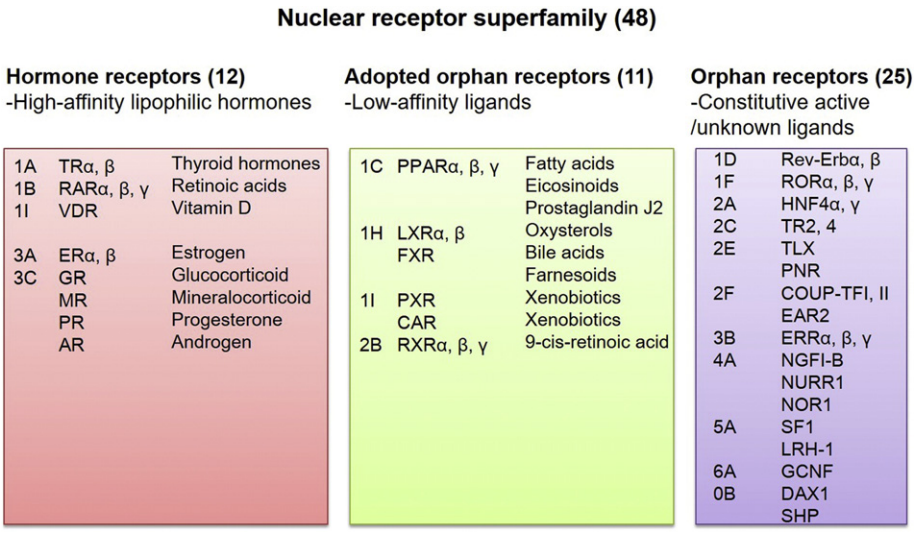

Fig. 1. Classification of NRs. According to their ligand dependence, nuclear receptors are classified as hormone receptors, adopted orphan receptors and orphan receptors.