Cancer Treatment Reviews 40 (2014) 1137–1152

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Orphan nuclear receptors as drug targets for the treatment of prostate and breast cancers

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ARTICLE INFO

Article history:
Received 20 March 2014
Received in revised form 10 October 2014
Accepted 13 October 2014

Keywords:
Orphan nuclear receptor
Nuclear receptor
Prostate cancer
Breast cancer
Cancer therapeutics
Androgen receptor
Estrogen receptor

ABSTRACT

Nuclear receptors (NRs), a family of 48 transcriptional factors, have been studied intensively for their roles in cancer development and progression. The presence of distinctive ligand binding sites capable of interacting with small molecules has made NRs attractive targets for developing cancer therapeutics. In particular, a number of drugs have been developed over the years to target human androgen- and estrogen receptors for the treatment of prostate cancer and breast cancer. In contrast, orphan nuclear receptors (ONRs), which in many cases lack known biological functions or ligands, are still largely under investigated. This review is a summary on ONRs that have been implicated in prostate and breast cancers, specifically retinoic acid-receptor-related orphan receptors (RORs), liver X receptors (LXRs), chicken ovalbumin upstream promoter transcription factors (COUP-TFs), estrogen related receptors (ERRs), nerve growth factor 1B-like receptors, and "dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1" (DAX1). Discovery and development of small molecules that can bind at various functional sites on these ONRs will help determine their biological functions. In addition, these molecules have the potential to act as prototypes for future drug development. Ultimately, the therapeutic value of targeting the ONRs may go well beyond prostate and breast cancers.

Introduction

The nuclear receptor (NR) superfamily is composed of transcriptional factors that enable multicellular organisms to regulate gene expression in response to a wide variety of stimuli from developmental, physiological and environmental sources. NR actions are modulated by several endogenous mechanisms that include: (1) ligand binding, (2) posttranslational modification of amino acid residues, (3) protein dimerization, (4) nuclear transfer, (5) protein–protein interactions with activators and repressors, and (6) cooperative DNA binding with other transcription factors [1]. Of the 48 members of the superfamily, 36 receptors were originally described as orphan NRs (ONRs) because their exact function and native ligands were undefined [2]. As a result of recent research efforts, 21 of these ONRs became annotated as "adopted" due to the discovery of natural or synthetic ligands (Fig. 1A).

NRs are commonly classified into 7 subfamilies based on their sequence similarity [3] and have been studied for their associations with cancers in a wide range of human organs (Table 1). However, there is a disparity of research efforts dedicated to ONRs, as illustrated by the number of published articles in PubMed (Fig. 1B). For example, during the year 2013 alone, 543 and 1312 articles were published on the androgen receptor (AR) and estrogen receptor (ER) in the context of their corresponding cancers. By comparison, less than 30 articles were published in the same year on the role of each ONR in cancer, as highlighted by Fig. 1C. This imbalance in research activity is also mirrored in the number of drugs and chemicals targeting the ONRs (Fig. 1A).

Conventionally, targeting transcriptional factors has been a challenging task in drug discovery due to the lack of well-defined active sites [4]. Thus, the unique presence of the ligand binding domain in NRs has made them very attractive drug targets, and NRs are among the top four families of drug targets and account for approximately 13% of all Food and Drug Administration (FDA)-approved drugs [5]. To gain insight into the number of existing small molecules targeting the NR family, each NR was queried based on its gene symbol, protein name and protein sequence

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http://dx.doi.org/10.1016/j.ctrv.2014.10.005
0305-7372/

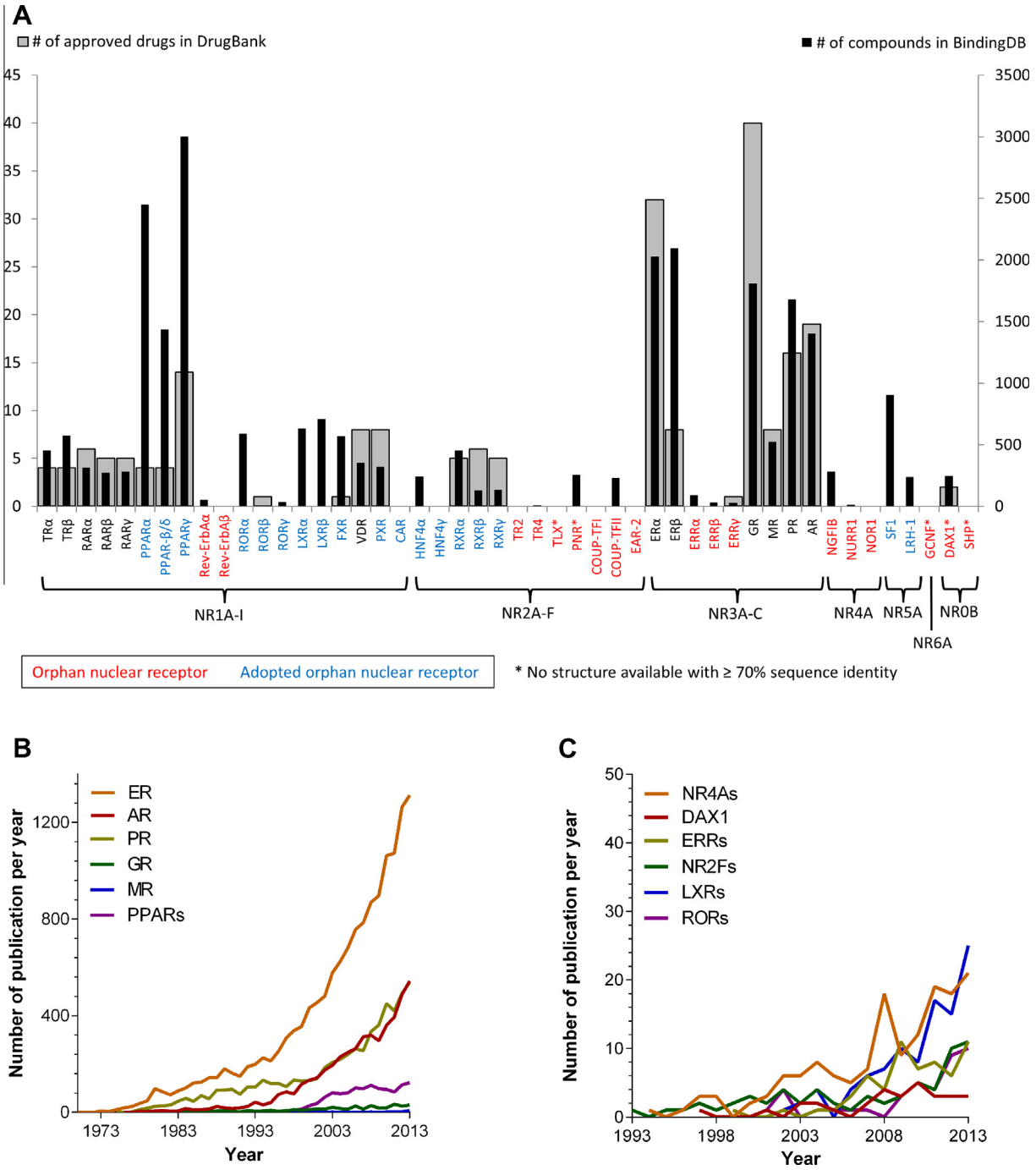

Fig. 1. Comparison of existing approved drugs, experimental compounds and publications for NR and ONRs. (A) Each NR was queried for the number of approved drugs (the left *y*-axis shown in gray bar) in DrugBank [6], and for the number of published compounds (the right *y*-axis shown in black bar) with experimentally-determined binding affinities in BindingDB [7] in October 2013. The NRs are arranged according to the subfamily as appeared in Table 1, and further classified as orphan or adopted ONR according to Shi et al. [2] Their protein sequences were compared with those with existing experimental structures in PDB [25] by using standard protein BLAST [40]. NRs that have no structural template with sequence identity higher than 70% are marked by '*'. The number of articles published on (B) the five hormone receptors (ER, AR, PR, GR and MR) and PPARs and (C) the ONRs discussed in this review paper, were extracted from PubMed in December 2013 using a search query consisted of: (Cancer [Title/Abstract]) AND ("Name of the nuclear receptor"[Title/Abstract]). Gene names and synonyms were used wherever applicable.

through the DrugBank [6] and BindingDB [7] databases. The DrugBank contains information on existing drugs and their direct targets, including 1541 FDA-approved small molecule therapeutics and 5082 experimental drugs that interact with 4323 proteins. BindingDB currently contains over one million binding affinity records corresponding to 427,325 small molecules and 6589 protein targets, extracted from the literature. As illustrated in Fig. 1, five hormone NRs (AR, ER, glucocorticoid receptor (GR), mineralocorticoid receptor (MR), and progesterone receptor (PR)) are associated with a large number of synthetic inhibitors developed for the treatment of prostate- and breast cancers among other diseases [8,9]. Similarly, some adopted ONR such as peroxisome proliferator-activated receptors (PPARs) have received considerable attention and have clinically approved drugs for the treatment of diabetes and obesity [2]. In contrast, most other members of the ONR family have fewer associated inhibitors identified due to