Cancer Treatment Reviews 40 (2014) 739–749

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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

Laboratory-Clinic Interface

Retinoids and breast cancer: From basic studies to the clinic and back again

Enrico Garattini [a,*], Marco Bolis [a], Silvio Ken Garattini [a], Maddalena Fratelli [a], Floriana Centritto [a], Gabriela Paroni [a], Maurizio Gianni' [a], Adriana Zanetti [a], Anna Pagani [b], James Neil Fisher [a], Alberto Zambelli [b], Mineko Terao [a]

[a] Laboratory of Molecular Biology, IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", via La Masa 19, 20156 Milano, Italy
[b] Laboratory of Experimental Oncology and Pharmacogenomics, IRCCS-Fondazione S. Maugeri, Università degli Studi di Pavia, via Maugeri 10, 27100 Pavia, Italy

ARTICLE INFO

Article history:
Received 9 December 2013
Received in revised form 9 January 2014
Accepted 10 January 2014

Keywords:
Retinoic acid
Breast cancer
RAR/RXR
Gene pathways
Chemo-prevention
Treatment

ABSTRACT

All-*trans* retinoic acid (ATRA) is the most important active metabolite of vitamin A controlling segmentation in the developing organism and the homeostasis of various tissues in the adult. ATRA as well as natural and synthetic derivatives, collectively known as retinoids, are also promising agents in the treatment and chemoprevention of different types of neoplasia including breast cancer. The major aim of the present article is to review the basic knowledge acquired on the anti-tumor activity of classic retinoids, like ATRA, in mammary tumors, focusing on the underlying cellular and molecular mechanisms and the determinants of retinoid sensitivity/resistance. In the first part, an analysis of the large number of preclinical studies available is provided, stressing the point that this has resulted in a limited number of clinical trials. This is followed by an overview of the knowledge acquired on the role played by the retinoid nuclear receptors in the anti-tumor responses triggered by retinoids. The body of the article emphasizes the potential of ATRA and derivatives in modulating and in being influenced by some of the most relevant cellular pathways involved in the growth and progression of breast cancer. We review the studies centering on the cross-talk between retinoids and some of the growth-factor pathways which control the homeostasis of the mammary tumor cell. In addition, we consider the cross-talk with relevant intracellular second messenger pathways. The information provided lays the foundation for the development of rational and retinoid-based therapeutic strategies to be used for the management of breast cancer.

Introduction

ATRA (All-*trans*-retinoic-acid) and 13-*cis*RA (13-*cis*-retinoic-acid) are the active metabolites of vitamin A, while the physiological significance of the other retinoic acid isomer, 9-*cis*RA (9-*cis*-retinoic-acid), is debated [1]. ATRA is the first clinically useful cyto-differentiating agent, being employed in the treatment of acute promyelocytic leukemia (APL) [2]. There is interest in expanding the therapeutic use of ATRA and derivatives to breast cancer. The biological activity of classic retinoids (ATRA, 13-*cis*RA) is primarily mediated by nuclear retinoid-receptors, which are ligand-activated transcription factors. Retinoid receptors are divided into RARs (RARα, RARβ and RARγ) and RXRs (RXRα, RXRβ and RXRγ) [3], which are encoded by distinct loci producing alternative-splicing variants (Fig. 1). Active retinoid-receptors consist of RAR/RXR heterodimers, which bind to Retinoic-Acid-Responsive-Elements (RAREs) in retinoid-responsive genes [3]. ATRA and 13-*cis*RA are pan-RAR agonists activating all RAR-isoforms with similar efficiency. 9-*cis*RA binds both RARs and RXRs, although the mechanisms underlying the pharmacological/anti-tumor activity of the retinoid may stem from the activation of RAR/RXR, VDR/RXR and the elusive RXR/RXR homodimers [4–6].

RARs and RXRs are not the only nuclear receptors binding ATRA, as PPARβ/δ (Fig. 1) is also bound and activated by the retinoid [7,8]. Partitioning of ATRA between RARs and PPARβ/δ is controlled by the cytosolic retinoid-binding proteins, CRABP2 and FABP5, delivering ATRA to RARs and PPARβ/δ, respectively [8]. We intend to provide an overview of the anti-tumor activity of retinoids in breast cancer, concentrating on the cellular/molecular determinants and the underlying mechanisms of action. The main focus of our analysis is ATRA, the prototype of classic retinoids.

* Corresponding author. Tel.: +39 02 39014533.
E-mail addresses: enrico.garattini@marionegri.it (E. Garattini), marco.bolis@marionegri.it (M. Bolis), silvioken@hotmail.it (S.K. Garattini), maddalena.fratelli@marionegri.it (M. Fratelli), floriana.centritto@marionegri.it (F. Centritto), gabriela.paroni@marionegri.it (G. Paroni), maurizio.gianni@marionegri.it (M. Gianni'), adriana.zanetti@marionegri.it (A. Zanetti), anna.pagani@fsm.it (A. Pagani), jamesneil.fisher@marionegri.it (J.N. Fisher), alberto.zambelli@fsm.it (A. Zambelli), mineko.terao@marionegri.it (M. Terao).

0305-7372/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ctrv.2014.01.001

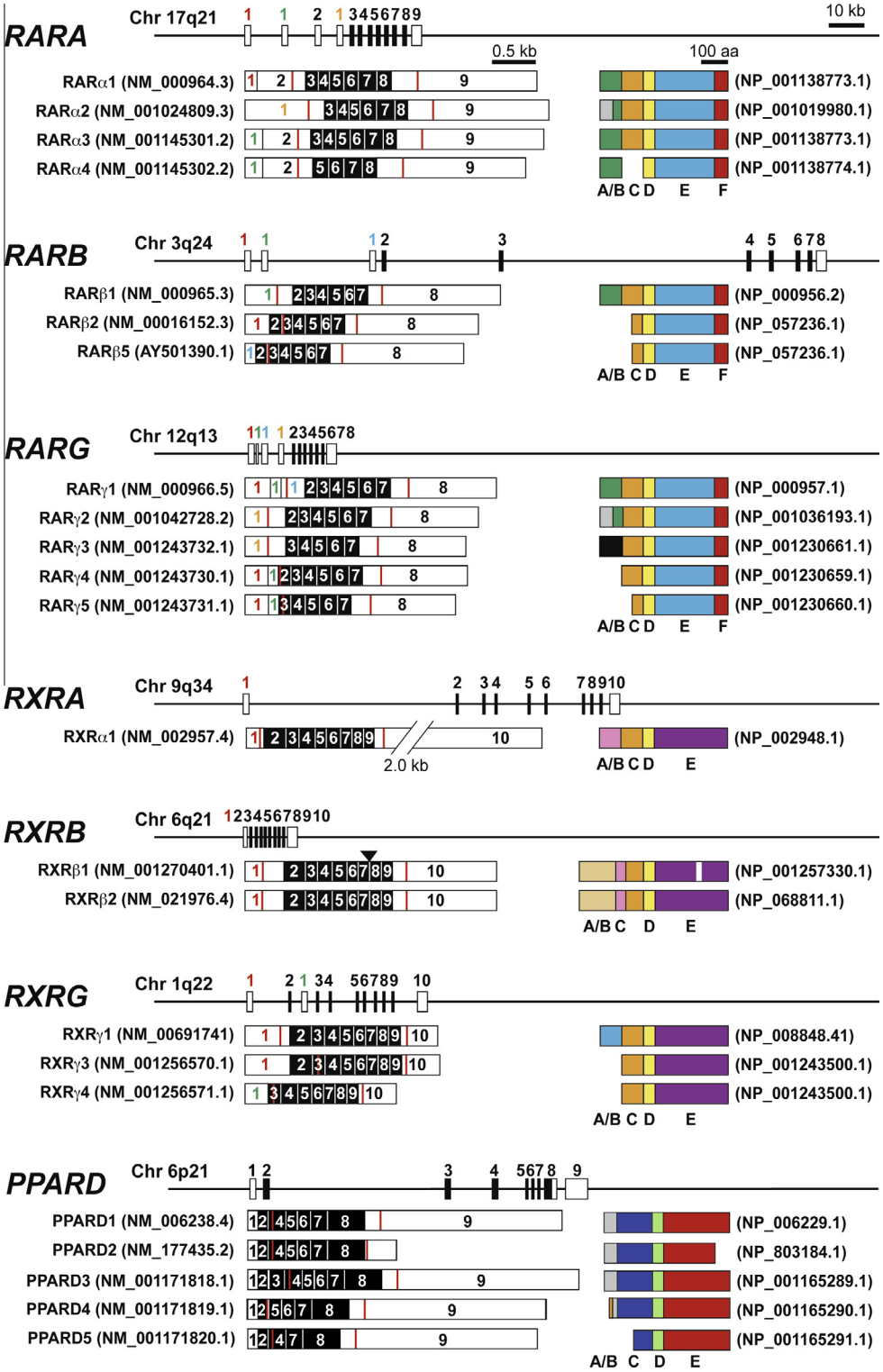

Fig. 1. Structure of the genes, mRNAs and proteins of the various retinoid-binding nuclear receptors. The figure illustrates the exonic structure of the human genes encoding RARα (*RARA*), RARβ (*RARB*), RARγ (*RARG*), RXRα (*RXRA*), RXRβ (*RXRB*), RXRγ (*RXRG*) and PPARβ/δ (*PPPARD*) along with the chromosomal location of each gene. Underneath each gene the structures of the known RAR, RXR and PPARβ/δ mRNAs resulting from differential splicing events are shown on the left side. The NCBI accession number of each splicing variant is indicated in parenthesis. It must be noticed that the transcript variant indicated as RARβ1 is often referred to as RARβ2 in the old literature. In addition, the accession No. of RARβ5 is provisional, as the evidence for its existence is still incomplete. The vertical red lines indicate the position of the first ATG and the STOP codons. On the right, the structure of the encoded proteins is shown. The various domains constituting each protein are indicated with different colors. The NCBI accession number of each protein is indicated in parenthesis. A/B = N-terminal ligand-independent transactivating domains; C = DNA binding domain; D = hinge domain; E = ligand-binding domain; F = C-terminal domain of unknown function.