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Advanced progress on the relationship between RA and its receptors and malignant tumors

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Contents

Abstract

Retinoic acid (RA) is an active derivative of vitamin A, and it has different isomers, including ATRA (all-trans-retinoic acid), 13-cRA (13-cis-retinoic acid) and 9-cRA (9-cis-retinoic acid), etc. Combining with RARs and RXRs, RA plays important roles not only in embryonic development but also in cellular growth and differentiation through transcriptional regulation of its target genes. Following the successful

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application in the differentiation therapy of acute promyelocytic leukemia (APL) in clinical, recent studies have found that the disturbance of RA signal transduction was also related to differentiation, proliferation or apoptosis of tumor cells. To develop novel mechanisms-based differentiation therapy for other tumors, the relationship between RA or its receptors and tumors will be summarized in this review.
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Keywords: Retinoic acid; Receptors; Target genes; Regulation; Tumors

1. Introduction

Retinoic acid (RA), an active derivative of vitamin A, is comprised of three units: a bulky hydrophobic region, a linker unit, and a polar terminus, which is a carboxylic acid. Modification of each unit has generated many more compounds. Based on the difference in the polarity of the molecule groups and side chain, RA has many isomers, such as all-trans-retinoic acid (ATRA), 13-cis-retinoic acid (13-cRA) and 9-cis-retinoic acid (9-cRA). The chemical structure of ATRA, 13-cRA and 9-cRA is shown in Fig. 1. Combining with retinoic acid receptor (RAR, also known as nuclear receptor subfamily 1 group B, NR1B) and retinoid X receptor (RXR, also known as nuclear receptor subfamily 2 group B, NR2B), they play an important role not only in embryo development but also in cellular growth, differentiation and apoptosis by regulating the expression of target genes. Inspired by the exciting discovery that ATRA was a strong differentiation-inducing agent for APL cells in 1980s, ATRA and its signal transduction was demonstrated to be closely related with proliferation, differentiation, and apoptosis of tumor cells [1]. In the following the relationship between RA or its receptors and tumors will be summarized.

2. RA-mediated signal transduction

2.1. RA metabolism

Vitamin A is a group of compounds, which includes retinol, retinal, retinoic acid, and retinyl esters etc. Since it cannot be synthesized by the body, it must be taken from the diet, either as preformed vitamin A (retinol and its esterified form, retinyl ester) from animal sources or as provitamin carotenoids such as β-carotene (BCAR) from plants, and the major metabolic pathway of retinol in mammalian cells is shown in Fig. 2.

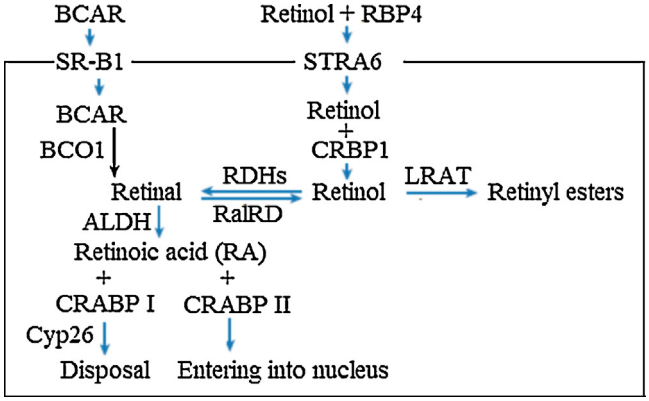

Fig. 2. The major metabolic pathway of retinol in mammalian cells.

2.1.1. RA from dietary vitamin A

BCAR is taken up by the cells through scavenger receptor class B, type 1 (SR-B1) and converted to retinal by β-C 15, 15′ oxygenase 1 (BCO1). And then the retinal may be oxidized to RA or converted to retinol. Vitamin A in animal-derived foods is found as long chain acyl esters of retinol, which are digested to free fatty acids and retinol before uptake by the intestinal mucosal cells. The retinol is then reesterified primarily by lecithin retinol acyltransferase (LRAT) to retinyl esters for incorporation into the lipid core of the chlylomicrons for secretion into lymph. Most of the newly absorbed chylomicron retinyl esters are cleared from plasma and are taken up by hepatocytes. After hydrolysis and reesterification, retinyl esters are stored in lipid droplets in both hepatocytes and stellate cells [2].

2.1.2. RA biosynthesis

As needed, retinol is released from storage and delivered to peripheral tissues in the form bound to plasma retinol-binding protein (RBP4), and the form of all-trans-retinol (holoRBP4) is the main source of vitamin A for most extrahepatic tissues. Further it binds to RBP4 receptor STRA6 and is taken up by

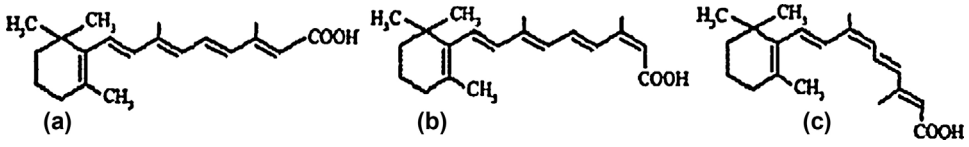

Fig. 1. The chemical structure of ATRA (a), 13-cRA (b), and 9-cRA (c).

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