EXPERIMENTAL CELL RESEARCH 324 (2014) 1–12

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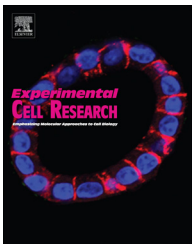

Review Article

Retinoid receptor signaling and autophagy in acute promyelocytic leukemia

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ARTICLE INFORMATION

Article Chronology:
Received 17 February 2014
Received in revised form
20 March 2014
Accepted 22 March 2014
Available online 30 March 2014

Keywords:
AML
APL
Arsenic trioxide
ATRA
Autophagy
Differentiation
Hematopoiesis
PML–RARα
Retinoid

ABSTRACT

Retinoids are a family of signaling molecules derived from vitamin A with well established roles in cellular differentiation. Physiologically active retinoids mediate transcriptional effects on cells through interactions with retinoic acid (RARs) and retinoid-X (RXR) receptors. Chromosomal translocations involving the *RARα* gene, which lead to impaired retinoid signaling, are implicated in acute promyelocytic leukemia (APL). All-*trans*-retinoic acid (ATRA), alone and in combination with arsenic trioxide (ATO), restores differentiation in APL cells and promotes degradation of the abnormal oncogenic fusion protein through several proteolytic mechanisms. RARα fusion-protein elimination is emerging as critical to obtaining sustained remission and long-term cure in APL. Autophagy is a degradative cellular pathway involved in protein turnover. Both ATRA and ATO also induce autophagy in APL cells. Enhancing autophagy may therefore be of therapeutic benefit in resistant APL and could broaden the application of differentiation therapy to other cancers. Here we discuss retinoid signaling in hematopoiesis, leukemogenesis, and APL treatment. We highlight autophagy as a potential important regulator in anti-leukemic strategies.

Contents

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http://dx.doi.org/10.1016/j.yexcr.2014.03.018
0014-4827/

Introduction

Retinoids are an important class of signaling molecules related to vitamin A (retinol). Mammals lack the biosynthetic machinery to synthesize retinoids, therefore the primary sources of vitamin A are plant-derived carotenoids and animal food sources in the form of retinyl esters. Over the last two decades the molecular basis of the diverse roles of retinoids in the regulation of cellular differentiation and metabolism has emerged [1]. Furthermore, retinoids remain the backbone of therapy for acute promyelocytic leumekia (APL) and hold promise for the prevention and treatment of some solid malignancies [2–4] (Fig. 1). In this review we will summarize recent advances in understanding retinoid signaling pathways and how defects in retinoid signaling are implicated in leukemogenesis. We will highlight mechanistic links between retinoid signaling and the cellular process of autophagy and explore how these links may be exploited in future therapies for APL.

Retinoid uptake, metabolism and transcriptional roles

The intestinal absorption and metabolism of food-derived retinoids has been reviewed in detail recently [5]. Briefly, dietary retinoids in the form of unesterified retinol derived from β-carotene or retinyl esters from animal sources are transported

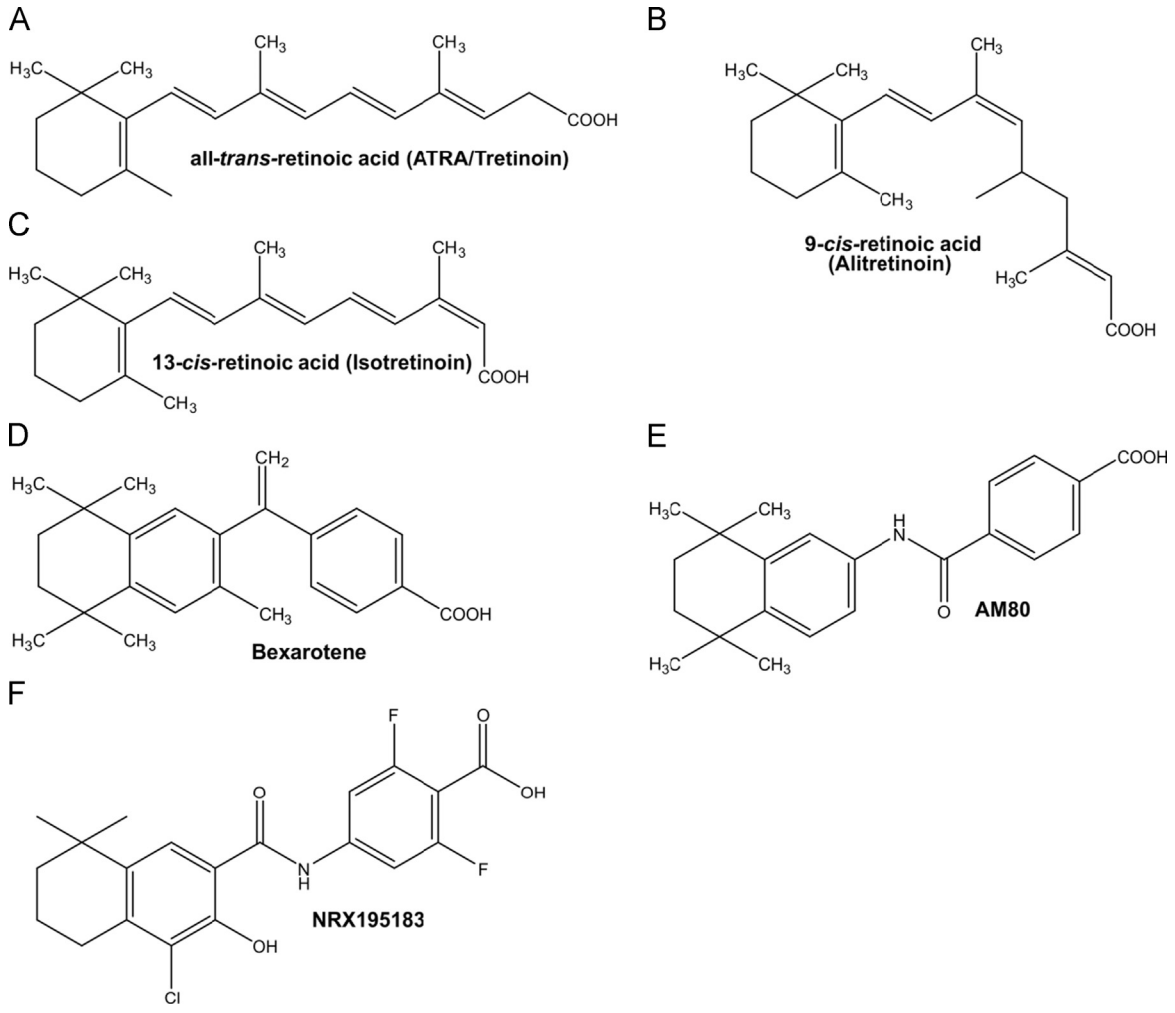

Fig. 1 – Physiological and clinically relevant retinoids. Chemical structures for retinoids are provided for comparison. (A) all-*trans*-retinoic acid (ATRA/Tretinoin), (B) 9-*cis*-retinoic acid (Alitretinoin), (C) 13-*cis*-retinoic acid (Isotretinoin), (D) bexarotene (Targretin™), (E) AM80 (Tamibarotene) and (F) NRX195183.