Available online at www.sciencedirect.com
SCIENCE DIRECT®
Cancer Letters 229 (2005) 127–134
CANCER Letters
www.elsevier.com/locate/canlet

Inhibition of carcinogenesis in transgenic mouse models over-expressing 15-lipoxygenase in the vascular wall under the control of murine preproendothelin-1 promoter

Dror Harats[a,d,*,1], Dikla Ben-Shushan[a,1], Hofit Cohen[a], Ayelet Gonen[a], Iris Barshack[b], Iris Goldberg[b], Shoshana Greenberger[a,d], Israel Hodish[a], Ayelet Harari[a], Nira Varda-Bloom[a], Keren Levanon[a], Ehud Grossman[c], Pavlos Chaitidis[e], Hartmut Kühn[e], Aviv Shaish[a,d]

[a]*Institute of Lipid and Atherosclerosis Research, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, 52621 Hashomer Tel, Israel*
[b]*Institute of Pathology, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, 52621 Hashomer Tel, Israel*
[c]*Division of Internal Medicine, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, 52621 Hashomer Tel, Israel*
[d]*Vascular Biogenics Ltd, Or-Yehuda, Israel*
[e]*Institute of Biochemistry, University Medicine Berlin-Charité, Monbijoustr. 2, 10117 Berlin, Germany*

Received 16 June 2004; received in revised form 8 February 2005; accepted 11 February 2005

Abstract

Oxygenases are a family of enzymes that dioxygenate unsaturated fatty acids, thus initiating membrane oxidation and signaling molecule synthesis. The lipoxygenases (LOs), a family of lipid-peroxidizing enzymes that induce structural and metabolic changes in the cell in a number of pathophysiological conditions, belong to the oxygenases family. This class of enzymes has several subgroups, named 5-, 8-, 12- and 15-LOs, and these LO-isoforms are capable of oxygenating arachidonic and linoleic acid. 15-LOs were reported to play an inhibitory role in tumor angiogenesis and, consequently, they slow down carcinogenesis. It has been suggested that its anti-carcinogenic effect is conferred by promoting cell differentiation and apoptosis. Using transgenic mice that over-express 15-LO-1 in endothelial cells under the regulation of the murine preproendothelin-1 promoter, we studied its effect on tumor and metastasis growth. We found that 15-LO-1 inhibited tumor and metastasis growth in the transgenic mice in two different models of cancer (mammary gland and Lewis lung carcinoma). This inhibition was concomitant with a higher number of apoptotic cells in the metastases of the transgenic mice and with a complicated network of multiple small blood vessels.

This finding targets 15-LO as a new candidate in the treatment of carcinogenesis.
© 2005 Elsevier Ireland Ltd. All rights reserved.

Keywords: 15-lipoxygenase; Angiogenesis; Carcinogenesis; Transgenic Mice; Endothelial cells

* Corresponding author. Tel.: +972 3 5302940; fax: +972 3 5343521.
E-mail address: dharats@post.tau.ac.il (D. Harats).
[1] Both are first authors.

0304-3835/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.canlet.2005.02.017

1. Introduction

Oxygenases are a family of enzymes that dioxygenate unsaturated fatty acids, thus initiating membrane oxidation and signaling molecule synthesis [1]. Cyclooxygenase (COX), a member of the oxygenase family, is an enzyme that produces prostanoids, a large family of arachidonic acid (AA)-derived lipid mediators with diverse biological roles and activities [2]. Other members of the oxygenases family include the lipoxygenases (LOs), a family of lipid-peroxidizing enzymes that induce structural and metabolic alterations in cells in a number of pathophysiological conditions. When AA is used as a substrate, various LO isoenzymes introduce a hydroperoxy group at carbons 5-, 8-, 12- or 15 of the fatty acid backbone, and thus, they may be designated 5-, 8-, 12- or 15-LO. Linoleic acid (LA) is also a substrate for the LOs family [1]. Hydroperoxidation of fatty acids by these enzymes is potentially relevant to inflammation, atherosclerosis, membrane re-modeling and angiogenesis [3]. Distinct LO isoforms exist in platelets (pl. 12-LO), leukocytes (le. 12/15-LO) and epithelial cells (ep. 8/15-LO). 5-, 8-, 12- and 15-HETE are the major AA metabolites formed by mammalian LOs and 9- and 13-HODE are the principle reaction products of linoleic acid oxygenation [2]. 15-lipoxygenases (15-LOs) can further be subdivided in two isoforms, named 15-LO-1 and 15-LO-2 [4,5] and the intracellular activity of these enzymes is regulated at transcriptional, translational and post-translational levels [3]. 15-LO-1 is mainly expressed in reticulocytes, eosinophils and airway epithelial cells [6–9], as well as in macrophages and in atherosclerotic lesions [10]. Its expression in peripheral blood monocytes is up-regulated specifically by interleukins (IL) four and 13 [3]. The enzyme plays a role in cell differentiation and maturation, inflammation, asthma, carcinogenesis and atherogenesis [3]. Several lines of experimental evidence suggested that 5- and 12-LO metabolites promote angiogenesis and carcinogenesis [11]. In contrast, 15-LOs may play an inhibitory role in tumor angiogenesis and thus, may slow down carcinogenesis [1,11,12]. Interestingly, Shureiqi and colleagues demonstrated that NSAIDs induce 15-LO-1 expression in colorectal cancer cells and that this up-regulation is critical to NSAID-induced apoptosis [13]. The mechanism by which 15-LO inhibits carcinogenesis has not yet been elucidated in detail. However, the major 15-LO-1 product of linoleic acid oxygenation, 13-HODE, has been reported to impact carcinogenesis via activation of the nuclear receptors PPAR-γ [14] and PPAR-δ [15]. The major 15-LO-1 product of arachidonic acid oxygenation, 15S-HETE, appears to bind to PPAR-γ and induces apoptosis via activation of the death receptor and caspase-3 pathway [16]. Moreover, it was shown that upregulation of PPARγ expression suppresses tumor growth via 15-LO metabolite [17]. In a recent tumor implantation experiment, in which prostate cancer (PC3) cells stably expressing 15-LO-2 were injected into mouse prostate, the tumors expressing 15-LO-2 were significantly smaller, suggesting that 15-LO-2 suppresses prostate tumor growth in vivo [18]. Although all the studies mentioned above support the role of 15-LO as an anti-carcinogenic enzyme, more detailed experiments are needed to establish its effect in vivo.

In the current study we provide in vivo evidence that over-expression of 15-LO-1, regulated by the murine preproendothelin-1 promoter in transgenic mice, affects angiogenesis and inhibits tumor development.

2. Materials and methods

2.1. Mice

We used transgenic mice over-expressing 15-LO-1 under the control of the murine preproendothelin-1 promoter. These mice were prepared using cDNA of the human enzyme and crossbred for eight generations with either C57BL/6 (15-LO/C57BL/6) or BALB/c (15-LO/BALB/c) [19]. The transgenic mice over-expressing 15-LO-1 in endothelial cells were housed in the animal care facility. Control C57BL/6 and BALB/c mice were purchased from Harlan, Israel (Harlan Laboratories, Jerusalem, Israel). All animal procedures were in accordance with the guidelines of the Animal Care and Use Committee at the Sheba Medical Center.

2.1.1. Lewis lung carcinoma model

Lewis lung carcinoma cells (LLC, D122-96) were kindly provided by Prof Lea Eizenbach of the Weizmann Institute of Science, Rehovot, Israel.

Download English Version:

https://daneshyari.com/en/article/10902466

Download Persian Version:

https://daneshyari.com/article/10902466

Daneshyari.com