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Involvement of 5-lipoxygenase in survival of Epstein–Barr virus (EBV)-converted B lymphoma cells

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Abstract

Epstein–Barr Virus (EBV) is involved in the progression of lymphomas through still unknown mechanism involving increased resistance to induced apoptosis. We show here that in a set of apoptosis-resistant EBV-converted Burkitt's lymphoma clones, 5- and 12-lipoxygenases (LOXs) are over-expressed. Further investigations on 5-LOX showed that resistance to apoptosis increases parallely with the expression of 5-lipoxygenase (5-LOX). Inhibitors of 5-LOX: (a) decrease peroxides level, indicating that this enzyme promotes the generation of oxidative stress in EBV+ cells, and (b) potently induce apoptosis in the EBV resistant cell line E2R. 5- and 15-HETE, the products of the 5 and 15-LOXs, respectively, counteract 5-LOX inhibitor induced apoptosis, indicating that products of arachidonate metabolism, rather than peroxides, trigger a signal transduction that is required for survival of the EBV-converted cells. These findings suggest that 5- and, to a lesser extent, other LOXs, that are involved in tumor progression of several cell types, may also participate in lymphomagenesis, especially that EBV-mediated.

Keywords: Apoptosis; Peroxides; LOXs; Epstein–Barr virus; Lymphoma cells; Quantitative RT-PCR

1. Introduction

Many factors are involved in putative EBV tumorigenesis, among them important are de-regulation of cell cycle, increase in survival signals and augmented apoptosis resistance [1–3]. Multiple routes seem to be involved in EBV-mediated resistance to apoptosis, such as the expression of latent membrane proteins LMP-1 and LMP-2A which activate the PI3K/Akt [4,5] or NF-κB [6] survival/

Abbreviations: LOX, lipoxygenase; FLAP, 5-lipoxygenase activating protein; EBV, Epstein–Barr virus ; LMP1, latent membrane protein 1; COX, cyclo-oxygenase; NF-κB, nuclear factor kB; HETE, hydroxyeicosatetraenoic acid; 13-*S*-HODE, 13-*S*-hydroxyoctadecadienoic acid; BL, Burkitt's lymphoma; IAP, inhibitor of apoptosis protein; ROS, reactive oxygen species; NDGA, nordihydroguaiaretic acid; CAPE, Caffeic acid phenyl ether; DCFH-DA, 2',7'-dichlorofluorescein diacetate; NOS, nitric oxide synthase.

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