Cancer Letters 287 (2010) 123–135

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Molecular mechanisms involved in farnesol-induced apoptosis

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ARTICLE INFO

Article history:
Received 10 March 2009
Received in revised form 14 May 2009
Accepted 15 May 2009

Keywords:
Farnesol
Apoptosis
Isoprenoid
Chemoprevention
Endoplasmic reticulum stress
Unfolded protein response
CTP:phosphocholine cytidylyltransferase
Nuclear receptor
Cancer
NF-κB
Apoptosome
MAP kinase

ABSTRACT

The isoprenoid alcohol farnesol is an effective inducer of cell cycle arrest and apoptosis in a variety of carcinoma cell types. In addition, farnesol has been reported to inhibit tumorigenesis in several animal models suggesting that it functions as a chemopreventative and anti-tumor agent *in vivo*. A number of different biochemical and cellular processes have been implicated in the growth-inhibitory and apoptosis-inducing effects of farnesol. These include regulation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase and CTP:phosphocholine cytidylyltransferase α (CCTα), rate-limiting enzymes in the mevalonate pathway and phosphatidylcholine biosynthesis, respectively, and the generation of reactive oxygen species. In some cell types the action of farnesol is mediated through nuclear receptors, including activation of farnesoid X receptor (FXR) and peroxisome proliferator-activated receptors (PPARs). Recent studies have revealed that induction of endoplasmic reticulum (ER) stress and the subsequent activation of the unfolded protein response (UPR) play a critical role in the induction of apoptosis by farnesol in lung carcinoma cells. This induction was found to be dependent on the activation of the MEK1/2-ERK1/2 pathway. In addition, farnesol induces activation of the NF-κB signaling pathway and a number of NF-κB target genes. Optimal activation of NF-κB was reported to depend on the phosphorylation of p65/RelA by the MEK1/2-MSK1 signaling pathway. In a number of cells farnesol-induced apoptosis was found to be linked to activation of the apoptosome. This review provides an overview of the biochemical and cellular processes regulated by farnesol in relationship to its growth-inhibitory, apoptosis-promoting, and anti-tumor effects.

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1. Introduction

Isoprenoids are essential in the regulation of cell proliferation, apoptosis, differentiation, and lipid biosynthesis [1–9]. The isoprenoid pathway leads to the synthesis of farnesyl pyrophosphate (farnesyl-PP) and to geranylgeranyl pyrophosphate (geranylgeranyl-PP) which are involved in the prenylation of many proteins, and subsequently the biosynthesis of cholesterol, sterols, and other cholesterol derivatives [6,8–10]. The non-sterol isoprenoid farnesol is produced by dephosphorylation of farnesyl-PP, a metabolite of the cholesterol biosynthetic pathway. In addition to being produced endogenously, farnesol and the related isoprenoids (Fig. 1A), perillyl alcohol and geraniol, are natural compounds found in many fruits and aromatic plants, including citrus (perillyl alcohol, geraniol), sage, spearmint, nutmeg (perillyl alcohol), basil (geraniol), lemon grass (farnesol and geraniol), and chamomile (farnesol) [11–13]. This article reviews the current status of our knowledge of the effects of farnesol on mammalian cell proliferation, differentiation, apoptosis, and tumor suppression.

2. Inhibition of cell proliferation and induction of apoptosis

2.1. In vitro cell systems

A number of studies have demonstrated that farnesol and related isoprenoids, including geraniol and perillyl

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0304-3835/$ - see front matter Published by Elsevier Ireland Ltd.
doi:10.1016/j.canlet.2009.05.015

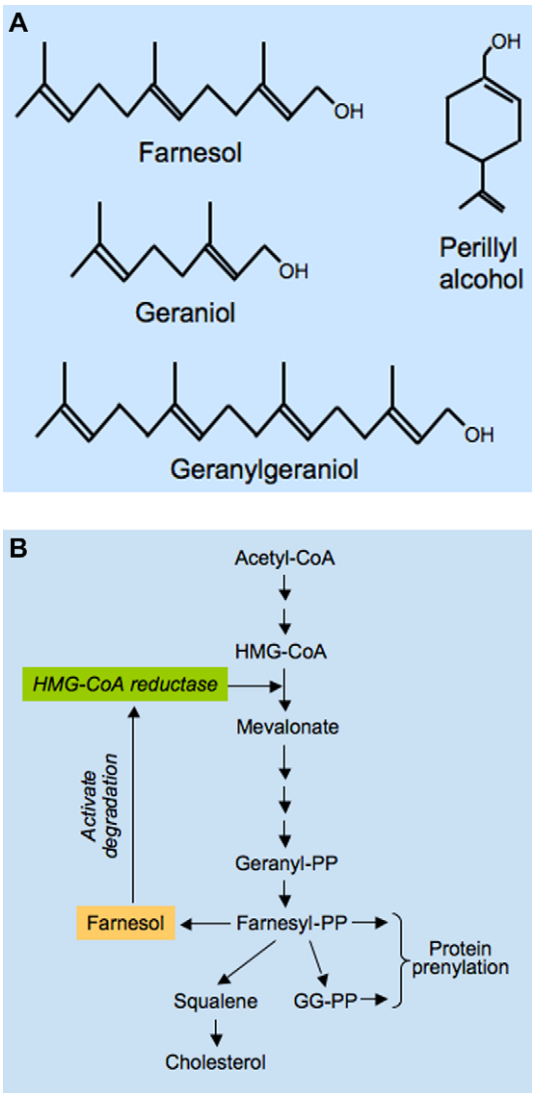

Fig. 1. (A) Molecular structure of farnesol and farnesol-related isoprenoids, geraniol, geranylgeraniol, and perillyl alcohol. (B) Farnesol is found in many fruits and herbs and a catabolite of the mevalonate pathway. The mevalonate pathway starts with the formation of HMG-CoA that subsequently is converted into mevalonate by HMG-CoA reductase, the rate-limiting enzyme in this pathway. Mevalonate leads to the synthesis of farnesyl-PP, which is at the branch-point of several pathways. In addition to serving as precursor of cholesterol biosynthesis, it can be converted to geranylgeranyl-PP. Both farnesyl-PP and geranylgeranyl-PP are involved in the prenylation of a variety of proteins and can be metabolized to their alcohol derivatives. HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; farnesyl-PP, farnesyl pyrophosphate; geranyl-PP, geranyl pyrophosphate; GGPP, geranylgeranyl-pyrophosphate.

alcohol, inhibit cell proliferation and induce apoptosis in a broad range of malignant cell types. Tumor cells were generally found to be considerably more sensitive to farnesol-induced growth inhibition than normal cells [2,14,15]. For example, in contrast to leukemic cells, human primary T lymphocytes or monocytes are rather resistant to farnesol-induced apoptosis. The mechanism underlying this differential sensitivity is not yet understood. Farnesol inhibits cell proliferation with IC_{50}s that range from 25 to 250 μM. Leukemic cells appear among the most sensitive to the growth-inhibitory effects of farnesol [2,16,17]. Farnesol is usually more effective in inhibiting the proliferation of tumor cells than the related isoprenoids, nerolidol, geraniol, geranylgeraniol, and perillyl alcohol [11,16,18,19].

In most cell types, including lung adenocarcinoma, hepatoma, melanoma, lymphoblastic leukemia, colorectal carcinoma, oral squamous carcinoma, and pancreatic adenocarcinoma, farnesol, geraniol, and perillyl alcohol induce a G_0/G_1 cell cycle arrest [2,18–30]. In some cell types a transient accumulation in G_2 has been observed. The G_0/G_1 cell cycle arrest in farnesol-treated human pancreatic adenocarcinoma cells was shown to be accompanied by a significant increase in the expression of the cyclin-dependent kinase (Cdk) inhibitors $p21^{Cip1}$ and $p27^{Kip1}$, and a reduction in the level of cyclin A, cyclin B1, and Cdk2 protein levels, while the expression of Cdk4 and Cdk6 was unaffected [18]. Cdk inhibitors play an important role in regulating the activity of Cdks and cell cycle progression [31]. An increased association of $p21^{Cip1}$ and $p27^{Kip1}$ with cyclin E/Cdk2 complexes was detected in farnesol-treated cells consistent with the observed reduction in Cdk2 activity and G_0/G_1 cell cycle arrest. As reported for farnesol, treatment with perillyl alcohol and geraniol also increased $p21^{Cip1}$ in pancreatic carcinoma and non-small cell lung carcinoma [18,32]. In general, farnesol was more effective in enhancing $p21^{Cip1}$ levels and inhibiting Cdk2 than geraniol and perillyl alcohol. The relative efficacies of these isoprenoids to enhance $p21^{Cip1}$ levels correlated with their growth-inhibitory effects. Down-regulation of both $p21^{Cip1}$ and $p27^{Kip1}$ by corresponding siRNAs resulted in a considerable protection from the growth-inhibitory effect of these isoprenoids suggesting that inhibition of proliferation of pancreatic carcinoma cells is $p21^{Cip1}$- and $p27^{Kip1}$-dependent. Regulation of $p21^{Cip1}$ and $p27^{Kip1}$ protein expression and activity has been shown to be complex and controlled at the transcriptional and posttranscriptional level, including phosphorylation and protein stability. BCL2 and BCL-X_L, which promote $p27^{Kip1}$ protein stability [33,34], are down-regulated in farnesol-treated cells [19,28] and, therefore, do not appear to be involved in the increase in $p27^{Kip1}$. The molecular mechanism by which these isoprenoids induce $p21^{Cip1}$ and $p27^{Kip1}$ has yet to be elucidated.

The presence of a sub-G_0/G_1 population suggested that in most cell types inhibition of cell growth by farnesol, geraniol, geranylgeraniol, or perillyl alcohol is accompanied by apoptosis. This was supported by the appearance of apoptotic bodies, increased annexin V binding, activation of various caspases, cleavage of poly-ADP-ribose polymerase (PARP), and DNA fragmentation [4,7,12,18–20,23–25,28,30,32,35–48]. In human lung adenocarcinoma H460 cells, the induction of apoptosis by farnesol was associated with activation of caspase-3, -4, and -9, while farnesol had little effect on caspase-8 [19]. Activation of caspases occurred within 4 h of farnesol treatment, a time course that correlated with that of PARP cleavage.

2.2. In vivo studies

Farnesol and other dietary isoprenoids have been shown to exhibit anti-tumor and -carcinogenesis effects