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Review

Molecular mechanism of the chemopreventive effect of resveratrol

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Abstract

Chemoprevention is a promising approach to control human cancer. Resveratrol has been shown to have a potent chemopreventive effect in multiple carcinogenesis models. However, the precise mechanism explaining its anti-carcinogenic effect is not clear. This review summarizes recent studies from our laboratory on the mechanisms of resveratrol's effects. In JB6 cells, resveratrol was found to induce apoptosis and inhibit tumor promoter-induced cell transformation. We also found that resveratrol-induced activation of p53 and resveratrol-induced apoptosis occurred through a p53-dependent pathway. The MAP kinases, ERKs, JNKs, or p38 kinases, are involved in resveratrol-induced activation of p53 and apoptosis.

Keywords: Resveratrol; Apoptosis; Chemoprevention; Signal transduction

1. Introduction

Interest in the concept and practice of chemoprevention as an approach to the control of cancer has increased greatly in the past few years. Many agents have been shown to be effective for blocking carcinogenesis in certain human cancer and animal models [1–14]. Resveratrol is thought to be a phytoalexin, one of a group of compounds that are produced in plants during times of environmental stress of pathogenic attack [15]. Resveratrol has been found in at least 72 plant species, a number of which are components of the human diet, such as mulberries, peanuts, and grapes [16]. Relatively high quantities are found in grapes, possibly because of the response of *Vitis vinifera* (Vitaceae) to fungal infection [16]. Fresh grape skin contains about 50–100 μg of resveratrol per gram [17]. In red wine, the concentration of resveratrol is in the range of 1.5–3 mg/l [18,19]. Appreciable amounts are also found in white and rosé wine [19]. Commercial grape juice contains about 4 mg/l of *trans*-resveratrol [20]. The results of several epidemiological studies suggested that decreased coronary heart disease mortality is associated with the moderate consumption of alcohol, especially red wine. This biological activity of red wine has been attributed to one of its constituents, resveratrol [20,21]. Resveratrol has been reported to inhibit platelet aggregation and coagulation, alter eicosanoid synthesis, and modulate lipoprotein mechanisms [22–24].

Data from Jang et al. [10] suggested strong anti-carcinogenesis effects of resveratrol. The inhibition may be due to a blocking effect on the carcinogenesis stages of initiation, promotion, or progression [10]. However, the precise mechanisms of the anti-carcinogenesis effect of resveratrol remain largely unknown.

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Recently, others and we [12,25–29] have reported that the cancer chemopreventive activity of resveratrol is related to the triggering of apoptosis. This review will summarize our work on the mechanisms and activity of resveratrol and its derivatives.

2. Apoptosis, carcinogenesis, and chemoprevention

Carcinogenesis is a complex multistage process in which normal cellular growth processes and genes become altered [30]. Chemical carcinogens may act by modulating or inducing mutations in genes that control normal growth, with subsequent clonal proliferation of the resulting precancerous or cancerous cells [30]. Emphasis has been placed on the significance and utilization of cell proliferation data in the toxicologic evaluation of chemicals [31,32].

Apoptosis of individual cells may represent a protective mechanism against neoplastic development in the organism by eliminating genetically damaged cells or excess cells that have improperly been induced to divide by a mitotic stimulus. This notion is supported by the fact that commonly used chemotherapeutic drugs can induce this form of cell death [33,34]. Apoptosis may therefore function as a common mechanism by which cells containing unrepairable genetic lesions are removed from the host organisms. Suppression of apoptosis plays an important role in nongenotoxic carcinogenesis, because disruption of apoptotic processes results in the survival and outgrowth of damaged or initiated cells. Tumor promoters have been shown to suppress the basal rate of apoptosis and to inhibit apoptosis and the apoptosis-related involution of the hepatocyte hyperplasia response to liver mitogens. The tumor promoting phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate (TPA) inhibited apoptosis induced in cultures of C3H-10T1/2 cells by exposure to ionizing radiation, low energy β-radiation, or acute serum deprivation [35]. Treatment of chronic lymphocytic leukemia cells with TPA also markedly inhibited spontaneous apoptosis of these cells as well as apoptosis induced by diverse stimuli such as colchicine, etoposide, or methylprednisolone [36]. Okadaic acid, a tumor promoter that inhibits protein phosphatases 1 and 2A, has also been reported to inhibit induction of apoptosis in both BM-13674 and CEM-C7 human lymphoid cells [37].

Loss of p53 function during carcinogenesis may also predispose preneoplastic cells to the accumulation of additional mutations by blocking the normal apoptotic response to genotoxic damage. Normal p53 function has been demonstrated to be crucial in the induction of apoptosis in human and murine cells following DNA damage [38–41]. Apoptosis of thymocytes and intestinal crypt cells following irradiation was almost completely blocked in p53-deficient ($p53^{-/-}$) mice [38,40,41]. Hence, p53 deficiency may permit a population of genetically damaged cells to escape the normal process of apoptotic deletion. Spontaneous tumor development in $p53^{-/-}$ mice was very high and occurred rapidly. Taken together, these studies indicate that the tumor promoters enhance carcinogenesis by preserving potentially mutagenized cells from apoptotic cell death and allowing them to proliferate into preneoplastic or neoplastic clones [42,43].

Many chemopreventive agents induce apoptosis. These agents include retinoic acid, perillyl alcohol, aspirin, sulindac, sulindac sefone, glucocorticoid, querattin, D-limonene, phenylethyl-3-methylcaffeate, PETC, EGCG, and other chemicals from tea, curcumin, *N*-(4-hydroxyphenyl)retinamide (HDR), and other retinoids [44–48]. Induction of apoptosis by these agents is reported to be at least partially responsible for their chemopreventive activity [44–48]. These chemoprevention agents also induce p53 protein, p21/WAF, and G1 cell-cycle arrest [44–49].

3. Induction of apoptosis by resveratrol

We and others have reported that resveratrol induced apoptosis in different cells including JB6 epidermal cells, human promyeloctye leukemia HL-60 cells, various colon cancer cell lines, human mammary cancer cell lines, and human prostate cancer cells [3,12,25–29]. In JB6 cells, resveratrol inhibits tumor promoter TPA- or epidermal growth factor (EGF)-induced cell transformation in a dose-dependent manner at a range of 2.3–40 μM [29]. At the same dose, resveratrol induces apoptosis. Resveratrol-induced apoptosis may occur through a ceramide/sphingomyelinase-independent pathway. The ceramide/sphingomyelinase pathway is a very common

pathway required for many factors such as TNFα, interferon, or γ-ionizing-radiation-induced apoptosis. However, resveratrol-induced apoptosis may not require activation of the ceramide/sphingomyelinase pathway, because resveratrol-induced apoptosis in both normal lymphoblast and sphingomyelinase-deficient cell lines [29].

4. The role of p53 in resveratrol-induced apoptosis

The *p53* is one of the most important tumor-suppressor genes and mutation or loss of p53 protein function is related to more than half of human cancers. The p53 protein is critical for apoptosis and lack of p53 expression or function is associated with an increased risk of tumor formation [38–41]. Resveratrol induces p53-dependent transcriptional activation. Resveratrol-induced apoptosis occurs only in cells expressing wild-type p53 ($p53^{+/+}$), but not in p53-deficient ($p53^{-/-}$) cells [29]. These results indicated that p53 is required for resveratrol-induced apoptosis in fibroblasts. Several reports have indicated that p53 is required in resveratrol-induced apoptosis in different cell systems [50]. However, in certain cancer cells lines, resveratrol also induced apoptosis independently of p53 [50,51]. These differences indicate a dependence on cell type.

5. Phosphorylation of p53 and kinases involved in resveratrol-induced apoptosis

Based on the above discussed studies, we offered a possible molecular mechanism by which the anti-tumor activity of resveratrol was shown to occur through extracellular-signal-regulated protein kinases (ERKs)- and p38 kinase-mediated p53 activation and induction of apoptosis [27,29] (Fig. 1). We found that in the mouse JB6 epidermal cell line, a well-developed cell culture model for studying tumor promotion [12,27,29], resveratrol induces apoptosis to inhibit tumor promoter-induced cell transformation through increased transactivation of p53 activity [29]. We further found that resveratrol-induced activation of p53 and apoptosis depends on the activities of ERKs and p38 kinase and their phosphorylation of p53 at serine 15 [27], which plays a critical role in the stabilization, up-regulation and functional activation of p53 [33,39]. On the other hand, we observed that resveratrol could also induce the activation of c-Jun NH_2-terminal kinases (JNKs). Stable expression of a dominant negative mutant of JNK1 or disruption of the *Jnk1* or *Jnk2* gene markedly inhibited resveratrol-induced p53-dependent transcription activation and induction of apoptosis [27]. Furthermore, resveratrol-activated JNKs were shown to phosphorylate p53 in vitro, but this activity was repressed in the cells expressing a dominant negative mutant of JNK1, or in JNK1 or JNK2 knockout ($Jnk1^{-/-}$ or $Jnk2^{-/-}$) cells. These data thus suggested that ERKs, p38 kinase, and JNKs act as mediators of resveratrol-induced activation of p53 and apoptosis, which may occur partially through p53 phosphorylation [27,52] (Fig. 1).

6. Inhibition of cell transformation by resveratrol and its derivatives: structure/activity study

To better understand the mechanistic basis for the chemopreventive properties of resveratrol and develop more effective agents for the prevention of cancer, we synthesized two resveratrol derivatives designated as 3,5,3′,4′-tetrahydroxy-*trans*-stilbene (RSVL-1) and 3,5,3′,4′,5′-phentahydroxy-*trans*-stilbene (RSVL-2). We used the mouse JB6 epidermal cell line to investigate the relationship for structure and anti-tumor activity. Compared with the anti-tumor activity of resveratrol, the structural analogue, RSVL-2, exhibited a more potent inhibitory effect on EGF-induced cell transformation in the same concentration range. Lower concentrations, especially 10 μM RSVL-2, were more effective than resveratrol in inhibiting cell transformation and cell transformation was almost completely blocked with 20 μM RSVL-2. In contrast, another structural analogue, RSVL-1, had no significant effect at 5–10 μM, and showed a lower inhibition of cell transformation at the concentration range of 20–40 μM compared to resveratrol. Our results indicated that one of the resveratrol derivatives exerts a more potent inhibitory effect than resveratrol on EGF-induced cell transformation, but has no cytotoxic effect on normal cells. Compared to resveratrol, this compound acts through a different mechanism by

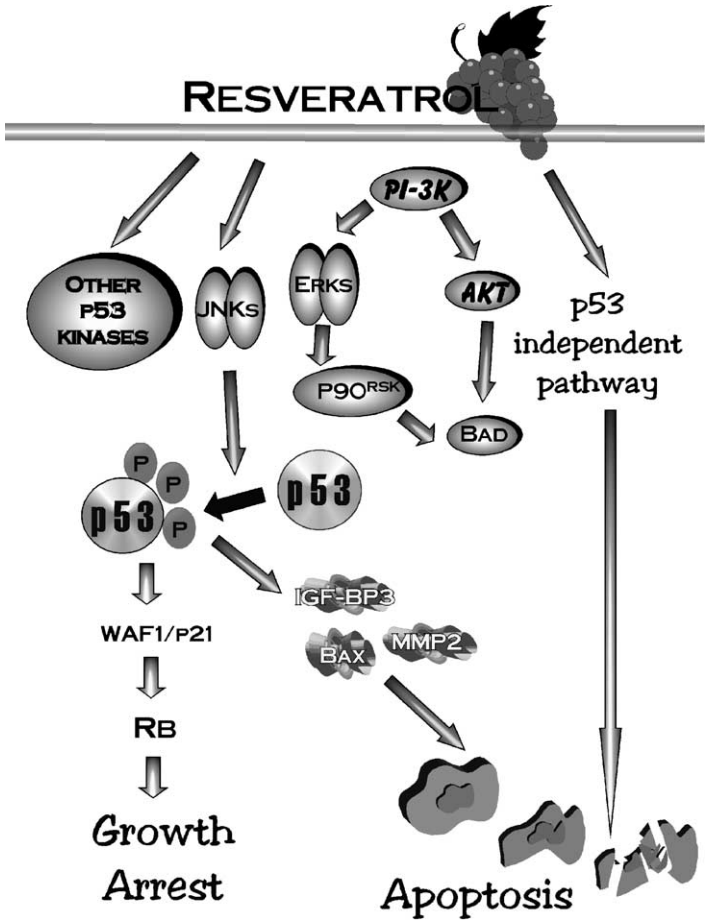

Fig. 1. Resveratrol induces pathways leading to apoptosis.

targeting phosphatidylinositol-3 (PI-3) kinase for its anti-tumor effect.

7. Conclusion

Chemoprevention of carcinogenesis by using non-toxic chemical substances is regarded as a promising alternative strategy to therapy for control of human cancer. In recent years, many naturally occurring substances have been shown to protect against experimental carcinogenesis. In this regard, resveratrol (3,5,4′-trihydroxy-*trans*-stilbene), a phytoalexin found in a multitude of dietary plants including grapes and peanuts, has been shown to provide cancer chemopreventive effects in different systems based on its striking inhibition of diverse cellular events associated with tumor initiation, promotion and progression [10]. This is partly attributable to its anti-oxidant activities and its inhibition of cyclooxygenase 1 and 2 [10,24]. An accumulation of evidence has further shown that the anti-cancer properties of resveratrol are related to its ability to cause cell-cycle arrest in the G1 phase [28] or in the S-G2 phase transition, or to trigger apoptosis in a variety of cancer cell lines [3,25–29]. However, the precise mechanism(s) of its anti-tumorigenic or chemopreventive activities is not well understood. Recently, we offered a possible molecular mechanism by which the anti-tumor activity of resveratrol was shown to occur through ERKs- and p38 kinase-mediated p53 activation and subsequent induction of apoptosis [27,29].

By studying the structure-activity of resveratrol, we have also developed resveratrol derivatives with more potent anti-cancer activity, but with fewer side effects. Understanding the molecular mechanistic basis for the chemopreventive effect of resveratrol and its derivatives will be helpful in designing new generations of chemopreventive agents for control of human cancer.

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