Regulation of Apoptosis and Cell Survival by Resveratrol

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Abstract: Tissue homeostasis is maintained by tight control of signaling events that regulate cell death and cell survival. Apoptosis or programmed cell death plays a key role in maintaining tissue homeostasis under various conditions during normal development and in the adult organism. Thus, defective apoptosis programs contribute to the pathogenesis of various human diseases, for example to cancer formation. In addition, the antitumor activity of most cancer therapies, including chemotherapy, radiotherapy or immunotherapy, is mediated by the activation of apoptosis in cancer cells. Natural compounds including resveratrol have attracted much attention over the last decade both as cancer chemopreventive agents and as cancer therapeutics. To this end, resveratrol inhibits signal transduction pathways that block apoptosis and/or promote cell survival. Insights into the molecular mechanisms of how resveratrol regulates cell survival and cell death signaling is expected to open new avenues for the exploitation of resveratrol in the prevention and treatment of cancer.

Keywords: Apoptosis, resveratrol, cancer.

1. INTRODUCTION

Tissue homeostasis is controlled by a balance between cell growth and proliferation on one end and cell death on the other end [1]. If this balance is shifted towards one or the other side, unlimited proliferation or alternatively excessive cell loss can occur, which provides the molecular basis of a large variety of human diseases. For example, too much proliferation or too little apoptosis contribute to the development of autoimmune diseases and also promote tumor formation and progression [1]. Vice versa, too much cell death causes tissue damage and loss in ischemic and neurodegenerative disorders [1]. In addition, the antitumor activity of various cytotoxic approaches such as anticancer drugs, γ-irradiation, suicide genes or immunotherapy is largely mediated by the induction of cell death in tumor cells [2,3]. The failure to initiate cell death programs, for example secondary to intrinsic defects in the cell death machinery or because of the dominance of survival stimuli can cause resistance of cancer cells towards current treatment protocols [4]. This primary or secondary resistance of cancers to cytotoxic therapies presents nowadays one of the key problems in oncology that remains to be solved [4]. Thus, attempts to improve the prognosis of cancer patients will have to incorporate strategies that specifically tackle tumor cell resistance to cell death. To this end, the identification of naturally occurring compounds such as resveratrol that can stimulate cell death while restraining proliferative signals may open new perspectives for the development of novel approaches to overcome cancer resistance.

2. CELL DEATH PATHWAYS

Apoptosis (programmed cell death) is the cell's intrinsic death program that plays a pivotal role in various physiological processes during normal development and in the adult organism as well as in many pathophysiological conditions [1,5,6]. There are two major apoptosis signaling pathways, i.e. the death receptor (extrinsic) and the mitochondrial (intrinsic) pathway [7]. Stimulation of apoptosis pathways typically results in the activation of caspases, which function as effector molecules of cell death in many forms of cell death [8]. Caspases cleave numerous substrates in the cytoplasm and in the nuclear compartment once they are activated, which results in the manifestation of many of the morphological hallmarks of apoptosis, including polynucleosomal DNA fragmentation, nuclear shrinkage, loss of cell shape and proteolytic degradation of cytoskeletal proteins [8].

In the death receptor pathway, stimulation of death receptors of the tumor necrosis factor (TNF) receptor superfamily such as CD95 (APO-1/Fas) or TRAIL receptors at the surface leads to receptor oligomerization and the recruitment of signaling molecules to form a multimeric complex, the death inducing signaling complex (DISC) [9]. Within this complex, the initiator caspase-8 becomes activated, which then propagates the apoptosis signal either by direct proteolytic processing of downstream effector caspases such as caspase-3 or alternatively, by cleavage of Bid [9]. Bid is a proapoptotic member of the Bcl-2 family of proteins that is cleaved by e.g. caspase-8 into its processed form tBid, which translocates from the cytosol to the mitochondria to initiate the release of apoptogenic factors from the mitochondrial interspace into the cytosol [10]. In the mitochondrial pathway, the release of mitochondrial intermembrane space proteins such as cytochrome c or Smac/DIABLO into the cytosol catalyzes the activation of caspase-3 in a multimeric complex called the apoptosome that comprises besides cytochrome c also Apaf-1 and caspase-9 [11]. Smac/DIABLO enhances activation of caspase-3, -7 and -9 by binding to and neutralizing "Inhibitor of Apoptosis" (IAP) proteins [11]. IAP proteins are a family of endogenous caspase inhibitors with eight human members, among them XIAP, cIAP1, cIAP2, survivin and livin (ML-IAP) [12].

Activation of apoptosis pathways is tightly controlled by a variety of positive and negative regulators under normal conditions, since accidental stimulation of the apoptotic machinery potentially has detrimental effects on cell survival [4]. These anti-apoptotic mechanisms are often abnormally upregulated in human cancers, which enables cancer cells to evade apoptotic cell death [4].

Besides caspase-dependent and caspase-independent apoptosis, additional non-apoptotic modes of cell death have also to be taken into consideration, e.g. necrosis, autophagy, mitotic catastrophe and lysosomal cell death [13-16]. Activation of these non-apoptotic cell death modes presents an alternative approach to induce cell death in apoptosis resistant types of human cancers [17]. However, the relative contribution of these diverse cell death mechanisms under various stress conditions both *in vitro* and *in vivo* remains an open question to be resolved in future studies.

3. RESVERATROL

Resveratrol (3,4',5-trihydroxystilbene) is a polyphenolic natural product, synthesized by a wide variety of plant species including grapes, and is present in red wine [18]. Its stilbene structure is re-

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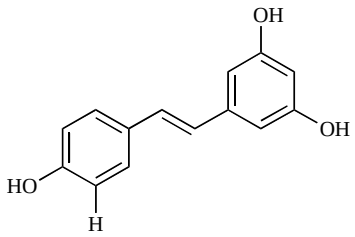

Fig. (1). Structure of resveratrol.

lated to the synthetic estrogen diethylstilbestrol (Fig. **1**) [18]. Resveratrol has gained considerable attention because of its potential cancer chemopreventive or anticancer properties [18]. In addition, resveratrol may be beneficial in the control of atherosclerosis, heart disease, arthritis, or autoimmune disorders. Numerous biological activities have been ascribed to resveratrol, which may explain its antiinflammatory, anticarcinogenic or anticancer properties [19,20]. Among its various actions, resveratrol has been demonstrated to inhibit cellular survival signaling. For example, resveratrol may interfere with apoptosis pathways both by directly triggering apoptosis-promoting signaling cascades, by blocking antiapoptotic mechanisms and by restraining proliferation. Structure-activity studies indicated that the 4-hydroxy group in the transconformation on 4- and 4'- positions of the stilbenic backbone of resveratrol is critical for mediating its antiproliferative effect [21]. Direct targets of resveratrol include, for example, COX-2, resulting in inhibition of enzyme activity, an effect that has been implicated to contribute to resveratrol's antinflammatory, proapoptotic and chemopreventive properties [22]. By counteracting survival and antiapoptotic pathways, resveratrol can sensitize cancer cells, which may result in synergistic antitumor activities when resveratrol is combined with conventional chemotherapeutic agents or cytotoxic compounds [23].

4. RESVERATROL AS INHIBITOR OF ANTIAPOPTOTIC PATHWAYS

Apoptosis is tightly regulated at various levels to prevent inappropriate initiation of apoptosis upon accidental stimulation of the cell death machinery [4]. Mechanisms that block apoptotic cell death have also been implicated in tumorigenesis and cancer resistance, since they allow tumor cells to escape apoptosis [4]. Resveratrol has been shown to interfere with many of these antiapoptotic programs that are operative in cancer cells (Fig. **2**). For example, resveratrol has been reported to induce p53-independent upregulation of p21, p21-triggered cell cycle arrest and subsequently cell cycle-dependent depletion of the antiapoptotic protein surviving, a member of the Inhibitor of Apoptosis proteins (IAPs) [24]. This suppression of survivin by resveratrol was the result of both transcriptional and posttranscriptional mechanisms, including inhibition of promoter activity, reduced stability of the survivin protein as well as increased degradation of survivin protein *via* the proteasome [24]. It is interesting to note that cell cycle arrest, survivin depletion and sensitization for TRAIL-induced apoptosis upon treatment with resveratrol was present in p53 wild type and p53-deficient cells, thus pointing to p53-independent events [24]. These results indicate that the dietary component resveratrol can be used to target aberrant survivin expression in cancers and to prime cancer cells for cell death induction.

Moreover, the chemopreventive activity of resveratrol has been linked to its ability to downregulate the expression of survivin. For example, in a mouse model of skin tumorigenesis induced by the carcinogene dimethyl benz(a)anthracene (DMBA), administration of resveratrol significantly delayed the onset of tumor formation, reduced the total number of tumors as well as their volume [25]. In a model of SKH-1 hairless mice, resveratrol was reported to protect against ultraviolet B radiation-mediated damage of the skin by downregulating survivin levels in a mouse model of ultraviolet B radiation-induced skin tumorigenesis [26]. Accordingly, topical pre-treatment with resveratrol prevented upregulation of both protein and mRNA levels of survivin following ultraviolet B radiation and also blocked phosphorylation of survivin in the skin of the SKH-1 hairless mouse [26].

In medulloblastoma cells, resveratrol induced neuronal differentiation and suppressed tumor growth in a STAT3-dependent fashion [27]. Downregulation of survivin expression by resveratrol has been observed in variety of hematological malignancies as well as in solid tumors including adult T cell leukemia, breast carcinoma and multiple myeloma [28-30].

Resveratrol has also been reported to downregulate the expression of additional antiapoptotic proteins besides survivin. In non-Hodgkin's lymphoma and multiple myeloma cell lines, resveratrol caused decreased levels of the antiapoptotic proteins Bcl-x_L and Mcl-1 *via* mechanisms involving the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway and activator protein-1 [31]. In models of drug-refractory non-Hodgkin's lymphoma and multiple myeloma, low concentrations of resveratrol were able to potentiate paclitaxel-induced apoptosis [31] indicating that resveratrol may overcome some forms of drug resistance. Resveratrol was described to suppress Bcl-x_L and Mcl-1 levels in a STAT3-dependent manner in breast, pancreatic and prostate carcinoma cells [32].

Structural biology work has recently revealed that resveratrol interferes with F_1-ATPase activity *via* binding to a hydrophobic pocket in the γ-subunit, thereby blocking mitochondrial ATP synthesis and triggering cell death [33]. Also, resveratrol has been shown to improve mitochondrial functions by stimulating the SIRT1-dependent deacetylation of the transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) [34]. Deacetylated PGC-1α was shown to function as a coactivator for the nuclear respiratory factor-1 (NRF-1), which transactivates genes that are involved in oxidative phosphorylation and mitochondrial biogenesis [34]. Whether or not this resveratrol-induced stimulation of mitochondrial functions is linked to its chemopreventive and antitumor activities remains to be investigated in future studies.

The targeting of resveratrol to mitochondria has been accomplished by coupling it to the membrane-permeant lipophilic TPP cation [35]. These resveratrol derivatives comprise 4-tri-phenylphosphoniumbutyl-4'-O-resveratrol iodide and its bis-acetylated variant, which were reported to accumulate in mitochondria [35]. Recently, a novel resveratrol derivative, 4-(6-hydroxy-2-naphthyl)-1,3-benzenediol (HS-1793), was shown to overcome the Bcl-2-imposed resistance to apoptosis in U937 leukemic cells, possibly by downregulating 14-3-3 at a post-transcriptional level [36]. The 14-3-3 protein family comprises cytosolic multifunctional binding proteins, which can interact with and inhibit various client proteins, e.g. the proapoptotic proteins BAX and BAD [37]. Additionally, resveratrol has been shown to induce apoptosis in a CD95-dependent manner [38].

5. INHIBITION OF THE NF-κB PATHWAY BY RESVERATROL

The antiproliferative and anticarcinogenic properties of resveratrol have also been attributed to its negative effect on NF-κB activation. NF-κB is a nuclear transcription factor that plays an important role in various aspects of tumor formation and progression [39]. NF-κB consists of hetero- or homodimers of NF-κB/Rel family of proteins that function as dimers to mediate specific DNA binding [40]. Under basal conditions, NF-κB is sequestered in the cytosol *via* binding to IκB proteins [40]. Upon stimulation, activation of the IKK complex results in phosphorylation of IκB proteins followed by their proteasomal degradation [40]. This frees NF-κB

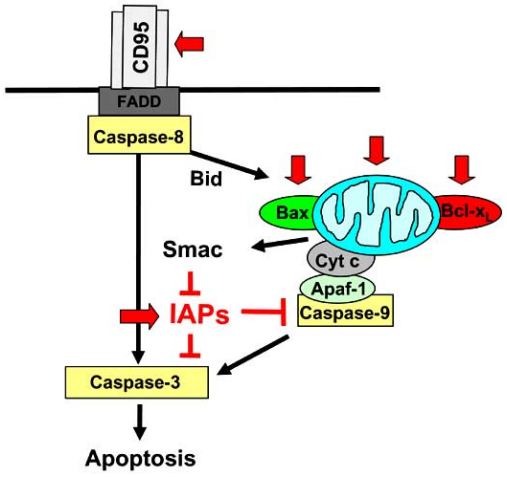

Fig. (2). Modulation of apoptosis signaling by resveratrol.
Resveratrol has been shown to interfere with apoptosis signaling pathways by inhibiting antiapoptotic proteins such as the IAP protein survivin, Bcl-2 family proteins such as Bcl-x_L, Bcl-2 and Mcl-1 and by stimulating proapoptotic elements such as CD95. To directly target mitochondria resveratrol has been linked to the membrane-permeant lipophilic TPP cation. See text for more details.

subunits to translocate into the nuclear compartment to stimulate transcription of NF-κB target genes [40]. Those comprise a panel of genes that have been implicated in tumor initiation and progression, e.g. by promoting cell survival, angiogenesis, metastasis and inhibition of apoptosis [39].

Resveratrol was found to block activation of NF-κB in response to the pro-inflammatory cytokine TNFα *via* inhibition of TNFα-induced IκB kinase activity, nuclear translocation of the NFκ-B subunit RelA/p65 and subsequently NF-κB-dependent reporter gene transcription [41, 42], which likely contributes to its antitumor properties. It has also been suggested that resveratrol plays a role in controlling NF-κB activation *via* modulation of chromatin remodeling through altered histone deacetylase activity [43]. This activity of resveratrol has been attributed, at least in part, to its Sirtuin activity [44]. SIRT1 is the mammalian ortholog of the yeast SIR2 (Silencing Information Regulator) that belongs to the Sirtuin family of histone deacetylases and has been implicated in mammalian longevity [45]. Resveratrol as natural Sirtuin agonist has been reported to inhibit NF-κB-dependant gene expression, thereby enhancing TNFα-induced apoptosis [43].

Moreover, resveratrol exerts antileukemic activity at least in part *via* downregulation of NF-κB activation and NF-κB-stimulated gene expression. To this end, resveratrol was shown to inhibit the generation of interleukin-1β and its stimulatory effect on the proliferation of acute myeloid leukemic (AML) cells [46,47]. In multiple myeloma resveratrol blocked proliferation and triggered apoptosis even in chemoresistant cells at least in part through inhibition of STAT3 and nuclear factor-κB [30]. In epidermoid carcinoma cells, resveratrol acted in concert with ultraviolet B to trigger cell death *via* inhibition of NF-κB activation secondary to decreased phosphorylation of IκBα [48]. In prostate cancer cells, the inhibition of NF-κB activation and subsequently the suppression of cell survival by resveratrol have been linked to their negative effect on PI3K signaling [49].

The chemopreventive activities of resveratrol have also been attributed to its negative impact on NF-κB activation. For example, suppression of 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in rats by resveratrol have been linked to resveratrol-triggered inhibition of NF-κB and cyclooxygenase 2 [50]. Recently, a large library of resveratrol analogues with variations in the two aryl rings and alkene was synthesized that possess NF-κB inhibitory effects [51].

6. INHIBITION OF THE PI3K/AKT OR MAPK PATHWAY BY RESVERATROL

The cancer preventive and antitumor activities of resveratrol have been linked to its ability to interfere with two key survival cascades, i.e. phosphatidylinositol-3 kinase (PI3K)/AKT and MAPK pathways. The PI3K/AKT cascade presents a key mediator of survival signals that originate from growth factor or integrin receptors [52]. Following the binding of growth factors to their respective transmembrane receptors or upon ligation of integrins, receptor tyrosine kinases are auto- and transphosphorylated, which results in the recruitment of PI3K to the surface where PI3K recruits AKT through the generation of phospholipids [52]. This leads to activation of AKT which now controls various signaling pathways that are implicated in the control of apoptosis, growth, glucose metabolism or angiogenesis [52].

In a mouse model of carcinogene-triggered skin cancer, inhibiton of PI3K/AKT-mediated signaling by resveratrol significantly reduced the incidence of tumors and also suppressed tumor growth [25]. Similarly, in a cellular culture model of epidermal carcinogenesis using murine JB6 epidermal cells, derivatives of resveratrol were reported to suppress cellular transformation by interfering with EGF-mediated activation of PI3K and AKT [53].

Not only the chemopreventive properties of resveratrol, but also its anticancer activities have been linked to suppression of PI3K/AKT-mediated signal transduction. To this end, resveratrol has been suggested to interfere with the growth factor receptor tyrosine kinase pathway. In endometrial cancer cells, downregulation of EGF and suppression of cell growth was observed following treatment with resveratrol [54]. Recently, the eukaryotic elongation factor 1A2 (eEF1A2), which has been implied in oncogenesis, has been identified as a molecular target that mediates the antiproliferative activities of resveratrol in ovarian cancer cells downstream of Akt upon growth factor stimulation [55]. Also, resveratrol was shown to interfere with PI3K activation and cell proliferation in estrogen-responsive human breast cancer cells *via* suppression of estrogen receptor alpha-mediated PI3K signaling independently of the nuclear functions of the estrogen receptor alpha [56]. Reduction of Akt levels and downregulation of ribosomal protein S6 phosphorylation upon exposure to resveratrol may contribute to its antiproliferative effect [57]. Combined administration of resveratrol together with quercetin, a structurally related, polyphenolic natural compound, has documented cooperative activity against glioma cell lines, but not rat astrocytes, possibly *via* inhibition of Akt phosphorylation and stimulation of a senescence-like growth arrest [57,58].

Additionally, inhibition of MAPK signaling has been implicated in resveratrol-mediated suppression of tumor growth. For example, inhibition of MAPK signaling and suppression of tumor growth was observed in UV-irradiated cervical carcinoma cells in the presence of resveratrol [59]. Furthermore, MAPK-induced p53 activation has been implicated to contribute to the induction of apoptosis and resveratrol's antitumor activity [53,60,61]. However, there is also evidence that resveratrol may differentially modulate MAPK signaling in a concentration-dependent manner. Accordingly, while relatively high resveratrol concentrations (50-100 microM) inhibited phosphorylation of MAP kinases, low concentrations of resveratrol (from 1 pM to 10 microM) stimulated ERK1 and ERK2 phosphorylation [62] highlighting the context-dependent activities of this natural phytoalexin.

Resveratrol exerted its apoptosis-inducing and anti-proliferative effects in human epidermoid carcinoma cells by blocking the phosphorylation of JAK, which in turn resulted in inhibition of STAT1 phosphorylation [63]. The resveratrol derivative 2,3',4,4',5'-

Pentamethoxy-trans-stilbene was shown to promote the polymerization of microtubules, thereby causing G(2)/M cell arrest, inhibition of PI3K/Akt signaling and caspase-dependent apoptosis in colon carcinoma cells [64]. 3,5,4'-trimethoxy-trans-stilbene, another resveratrol analog, was reported to suppress the invasion of human lung adenocarcinoma cells by interfering with MAPK pathway signaling and reduced matrix metalloproteinase-2 expression [65].

7. CLINICAL DEVELOPMENT OF RESVERATROL

As far as the clinical development is concerned, resveratrol is currently being tested for cancer chemoprevention as well as for the treatment of cancer. In a phase I dose escalation pharmacokinetic study in healthy volunteers, the oral administration of resveratrol was found to be safe and to yield measurable plasma levels of resveratrol and its metabolites [66]. Resveratrol is also under early clinical evaluation for the treatment of colon cancer and multiple myeloma, both as monotherapy or in combination with the proteasome inhibitor bortezomib (http://clinicaltrials.gov).

CONCLUSIONS

Resveratrol exerts beneficial effects in chemoprevention as well as cancer treatment that are mediated by interference with cell survival programs. This involves resveratrol-mediated inhibition of antiapoptotic proteins or survival signaling such as the PI3K/AKT, MAPK or NF-κB pathway. However, resveratrol at low concentrations has also been reported to inhibit cell death signaling by producing an intracellular milieu that lowers the threshold for apoptosis induction [67]. Moreover, the question which of the many biological activities of resveratrol mediates its effect in individual types of cancer remains to be answered in the future. Conceptually, phytochemicals with more than one mechanism of action such as resveratrol may be advantageous to concomitantly target several distinct mechanisms of resistance. Such agents may be effective even in otherwise resistant cancers. A better understanding of the molecular mechanisms of how resveratrol modulates signal transduction pathways that control cell death and survival in cancer cells is anticipated to open new perspectives for the use of resveratrol and its derivatives in the prevention and treatment of cancer.

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