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REVIEW

Resveratrol and Cancer

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ABBREVIATIONS
AMPK = adenosine monophosphate-activated protein kinase
COX = cyclooxygenase
CREB = cyclic AMP response element-binding (protein)
ERK = extracellularly-regulated kinase(s)
MAPK = mitogen-activated protein kinases
mTOR = mammalian target of rapamycin
nF-kB = nuclear factor kappa-light-chain-enhancer of activated B cells
SIR = silent information regulator
STAT3 = signal transducer and activator of transcription 3 (factor)
VEGF = vascular endothelial growth factor

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ABSTRACT

Resveratrol is a stilbene substance that belongs to the superfamily of phytoalexins, which are compounds synthesized by plants when stress occurs, such as during plant infection. It is abundant in red wine, red grapes, blueberries, peanuts and pistachios. Resveratrol induces p53-dependent apoptosis. A novel resveratrol analogue, HS-1793, has recently been demonstrated to inhibit vascular endothelial growth factor in human prostate cancer cells. Pterostilbene, an analog of resveratrol, has been demonstrated to exert both autophagy and apoptosis in human bladder and breast cancer cell lines. It has also been found to cause accumulation of autophagic vacuoles, as well as promote cell death via a mechanism involving lysosomal membrane permeabilization in human melanoma, colon, lung and breast cancer cell lines. Identification of a receptor site for resveratrol in cancer cells supports the potential of this compound as a therapeutic agent. The receptor could also serve as a vehicle for studies of future resveratrol analogues. Resveratrol has also been documented to overcome chemo-resistance by inhibiting NF-ϰB and STAT3 pathway. Resveratrol has shown much promise in preclinical trials and because of its good safety profile it may be an ideal chemo-preventive and chemotherapeutic agent.

INTRODUCTION

Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) (Fig. 1) is a stilbene substance belonging to the superfamily of phytoalexins, which are compounds synthesized by plants in response to injury or stress, such as when the plant is infected by bacteria or fungi. It is abundant in red wine, in red grapes, blueberries, peanuts, and pistachios (Table 1).[1-3]

Resveratrol exerts beneficial effects in humans and may be helpful in preventing and treating metabolic diseases, such as obesity, cardiovascular disease and diabetes mellitus.[4-6] Resveratrol also possesses anti-oxidant and anti-cancerous properties, which will be discussed in this review.[7,8] The anti-cancerous mechanisms of action of resveratrol are not well-understood, but it has been suggested from several studies that they are the result of resveratrol's action in inducing apoptosis.[9-15]

RESVERATROL AND p53

Resveratrol induces p53-dependent apoptosis.[9-16] The p53 gene is a suppressive

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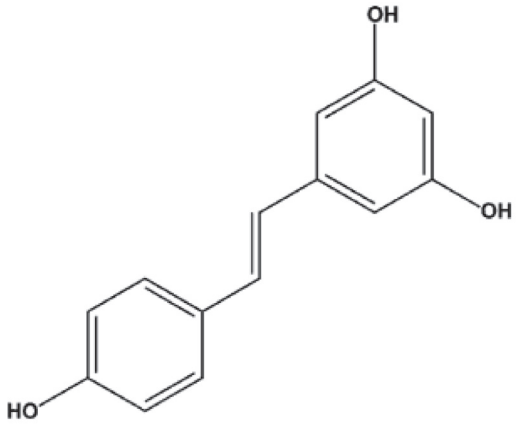

FIGURE 1. The chemical structure of resveratrol (3,5,4'-trihydroxy-trans-stilbene).

TABLE 1. Foods rich in resveratrol.

Red grapes
Red wine
Blueberries
Peanuts
Pistachios
Itadori tea
Sherries
Cranberry juice
Grape juice
Hops

oncogene, which exists at low concentrations in normal cells, whilst if there is DNA damage, levels of p53 activity rise, because of a post-translational mechanism that stabilizes the p53 encoded protein.[17-19] p53 is involved in apoptosis and DNA repair.[17,18] Phosphorylation of p53 occurs at some serine and threonine residues.[19,20] Activated p53 binds to DNA by a mechanism, which depends on phosphorylation and acetylation of this protein. Phosphorylation of p53 at N-terminal site may promote stabilization of p53, and may be a factor that facilitates or is required for the acetylation of p53 at a C-terminal site. Acetylation has been reported to increase sequence-specific DNA binding of p53 *in vitro* and has been found to be essential for recruitment of the protein to coactivators--such as cyclic AMP response element-binding (CREB) protein/p300.[21] These co-activators contain intrinsic histone acetyl-transferase properties. Acetylation of the p53 protein appears to be a related with p300/CREB-binding protein-associated factor (PCAF) (a histone acetyltransferase) and several other p53 co-activators.[22] It has also been suggested that resveratrol induces acetylation of p53. Phosphorylation of specific p53 residues is considered necessary for the activation of certain promoter regions.[23]

Resveratrol-induced apoptosis factor (PCAF), another p53 co-activator, and CREB-binding protein/p300 are also co-activators for various transcription factors besides p53. Resveratrol is capable of phosphorylating p53 at N-terminal and C-terminal serine residues in many human cancer cell lines and also of promoting acetylation of p53. Activation of extracellularly-regulated kinases (ERK)-1 and -2 has been implicated in resveratrol-induced serine phosphorylation of p53 in cancer cells.[9-15] It has been documented that resveratrol induces serine residue phosphorylation of a mutant p53 in prostate cancer cells, a phenomenon which induces apoptosis.[9,10]

RESVERATROL AND CYCLOOXYGENASE (COX)-2

Cyclooxygenase (COX), the enzyme involved in prostaglandin synthesis, is secreted by increased production of various inflammatory mediators. Two COX iso-enzymes have been described until now.[24,25] COX-1 is a constitutively expressed form of the enzyme and is present everywhere, whereas COX-2 is inducible and is present in inflammatory lesions, and is known to be constitutively expressed in tumors. Constitutive expression of COX-2 in cells and animal models is associated with tumor cell growth and metastasis, enhanced cellular adhesion and inhibition of apoptosis.[26]

COX-2 has been found in the endoplasmic reticulum, Golgi complex, and nuclear envelope.[27,28] COX-1 and COX-2 are localized in the nuclear envelope and endoplasmic reticulum of prostaglandin-2 releasing cells. Recent data have documented that prostaglandin-2 biosynthesis, COX iso-enzymes, and prostaglandin-2 are located in the perinuclear region. Resveratrol induces nuclear accumulation of COX-2 in various cancer cells, such as human breast tumor cells, glioma, head and neck squamous cells, ovarian and prostate tumor cells.[28] These results suggest that inducible COX-2 may play a major role in p53-dependent apoptosis in tumor cells. Other researchers have also documented that COX-2 can be pro-apoptotic, while Hinz *et al* have demonstrated that COX-2 inhibitors could be deleterious for certain tumors because of the pro-apoptotic action of this protein.[29-31] Nevertheless, pharmacologic inhibition of COX-2 has resulted in conflicting results.[32,33] Other data have suggested that over-expression of COX-2 could induce an anti-proliferative effect, which is attributed to p53 and p21 expression.[34,35] Other studies support the notion that constitutive COX-2 expression induces tumor growth and is anti-apoptotic, whereas inducible COX-2, induced, e.g. by resveratrol and localized largely to the cell nucleus, is pro-

apoptotic by means of phosphorylation of the serine residue of p53. Such a mechanism may be unique for the treatment of many cancers. Clinical anti-cancer regimens could possibly be designed to target the constitutively expressed and inducible pools of COX-2, particularly for the management of tumors in which pharmacologic COX-2 inhibition produces cell cycle arrest, rather than apoptosis, and when resveratrol or other agents capable of inducing COX-2 result in apoptosis.[36,37]

RESVERATROL AND SIRTUINS

The silent information regulator (SIR) genes (sirtuins) comprise a highly conserved family of proteins, with one or more sirtuins present in virtually all species, from prokaryotic organisms to eukaryotic ones. In mammals, 7 sirtuin genes -SIRT1 to SIRT7- have been identified.[38] There is emerging evidence that sirtuins constitute a very perplexed biological response system, which has a major impact on many other molecular pathways, such as aging, apoptosis and inflammation in complex manners. Resveratrol has been the first compound discovered, able to mimic calorie restriction by stimulating sirtuins.[39,40] Calorie restriction is a process that alters the concentrations of many genes implicated in a variety of biological processes, such as growth, metabolism, immune system, as well as oxidative stress and DNA damage repair.[41] The molecular effects induced by calorie restriction overlap with two major pathways linked with lifespan modulation *in vitro*, insulin/insulin-like growth factor signaling and target of rapamycin signaling.[41] Calorie restriction is suggested to induce gene expression patterns in multiple tissues. Indeed, treatment with resveratrol has reduced tumorigenesis in SIRT1+/-;p53+/- mice, and this protective effect has been attributed to SIRT1 activation.[42]

RESVERATROL AND EXTRACELLULAR SIGNAL-REGULATED KINASES (ERK) 1/2

Identification of a receptor site for resveratrol in cancer cells, by the implication of extracellular signal-regulated kinases 1 and 2 (ERK1/2) of the resveratrol signal downstream into p53-dependent apoptosis, supports the potential of this compound as a therapeutic agent.[41] The receptor could also serve as a vehicle for studies of future resveratrol analogues.

Regarding tumor cells, the role of integrins is more complex than simply the transduction of outside in signals originating from integrin-matrix protein interactions. It is noteworthy that dysregulation of the β-3 integrins has been involved in the pathogenesis of cancer. Tumor growth and angiogenesis, such as those associated with vascular endothelial growth factor pathway, are enhanced in β-3-null mice.[43] On the contrary, integrin β-3 overexpression may suppress tumor growth of a human glioma model in rats.[44] The above-mentioned paradigms suggest that promotion of integrin β-3 expression in tumor cells could act as a therapeutic goal combating the process of carcinogenesis.

ERK1/2 are **mitogen-activated protein kinases** (MAPK) iso-enzymes, which serve as inducible components of the normal cellular signal transduction process. ERK1/2 activation pathway may be triggered in the setting of growth factor stimulated cells or by inflammation. MAPK-kinase activates ERK1/2 straight-forward.[45] Resveratrol activates MAPK at low concentrations, but higher concentrations of resveratrol can inhibit this signal transducing kinase in tumor cells.[46] It has been demonstrated that resveratrol induces ERK1/2 activation in prostate, breast, glial, head and neck, and ovarian cancer cells.[47] The activation of ERK1/2 by resveratrol may be blocked by a MAPK kinase or mitogen/extracellular signal-regulated kinase (MEK) inhibitor, PD98059.[48]

RESVERATROL AND ADENOSINE MONOPHOSPHATE-ACTIVATED PROTEIN KINASE (AMPK)/MAMMALIAN TARGET OF RAPAMYCIN (MTOR) PATHWAY

Adenosine mono phosphate-activated protein kinase (AMPK) is linked with the phosphatidyl-inositol-3 kinase/AKT/mTOR signaling pathway, a cellular signaling cascade, which is of vital importance for cell growth, in response to mitogenic stimuli.[49,50] AMP-activated protein kinase (AMPK) activation inhibits phosphorylation and activation of the mTORC1 complex and is partly controlled by the upstream kinase AKT (protein kinase B), whose activation decreases the AMP:ATP ratio".[51] Resveratrol has also been shown to modulate AMPK in breakpoint cluster region protein (BCR)- Abelson murine leukemia viral oncogene homolog 1 (ABL 1) (BCR/ABL) gene transformed cells and to exhibit antileukemic effects.[53-55] Treatment of either imatinib mesylate-sensitive or imatinib mesylate-resistant chronic myelogenous leukemia cells with resveratrol has resulted in apoptosis.[56]

RESVERATROL, NUCLEAR FACTOR KAPPA-LIGHT-CHAIN-ENHANCER OF ACTIVATED B CELLS (NF-ϰB) AND SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3) FACTOR

The transcription factor, nuclear factor (NF)-ϰB, regulates many genes implicated in growth regulation and inflammation.[57,58] *In vitro* and *in vivo* studies have documented that constitutive activation of NF-ϰB results in inhibition of chemotherapy-induced apoptosis in a number of cancer cells.[59-64] Signal transducer and activator of transcription 3 (STAT3)

factor is also a ubiquitously expressed –like NF-κB- member of the STAT family of transcription factors, which is activated by tyrosine phosphorylation by means of upstream receptors such as epidermal growth factor, platelet-derived growth factor and cytokines, for example interleukin-6.[65] Recent studies have demonstrated that STAT3 may confer cancer resistance to chemotherapeutic agents.[66-69]

STAT3 is one of the major compounds implicated in carcinogenesis.[70,71] The oncogenic significance of activated STAT3 molecules is due to their effects on apoptosis, cell proliferation, angiogenesis, and immune system evasion.[72,73] Constitutively active STAT3 has been involved in the promotion of resistance to apoptosis, probably through the expression of B-cell lymphoma-extra large (Bcl-xL) and cyclin D1 proteins.[74,75] Its role in carcinogenesis is mediated through the induction of genes that suppress apoptosis and mediate proliferation and angiogenesis. Constitutive activation of STAT3 has been implicated in a variety of cancers, including breast, brain, colon, gastric, esophageal, ovarian, nasopharyngeal, pancreatic, prostate cancer, head and neck squamous cell carcinoma, multiple myeloma, lymphomas and leukemia.[76-78] Nevertheless, it is not completely understood why STAT3 is constitutively active in cancer cells.

Resveratrol exerts its sensitization effect by modulating one or more mechanisms of chemo-resistance. Recent data have shown that resveratrol may overcome chemo-resistance in cancer cells by modulating apoptotic pathways, down-regulating drug transporters and down-modulating proteins involved in tumor cell proliferation. In addition, resveratrol has also been documented to overcome chemo-resistance by inhibiting NF-κB and STAT3 pathway.[79,80] Resveratrol has been suggested to enhance the apoptotic and anti-proliferative potential of bortezomib and thalidomide in multiple myeloma cells. Such an enhancement has been related to the inhibition of NF-κB and STAT-3 activation pathways. Resveratrol administration has also been associated with accumulation of sub-G(1) population, increase in Bax release, and activation of caspase-3. This has been further related with down-regulation of various proliferative and anti-apoptotic gene products, including cyclin D1, cellular inhibitor of apoptosis 2 (cIAP-2), X-linked inhibitor of apoptosis protein (XIAP), survivin, B-cell lymphoma 2 (Bcl-2), Bcl-xL, Bfl-1/A1, and tumor necrosis factor receptor-associated factor 2 (TRAF2).[81] Investigation of the mechanism has revealed that resveratrol inhibited NF-κB activation through inhibition of IκBα phosphorylation and (IκB kinase) IKK activation. These observations have been further supported by an inhibition of NF-κB and STAT-3 in patients with multiple myeloma.[82]

RESVERATROL AND AUTOPHAGY

Autophagy is an evolutionarily conserved intracellular process, characterized by lysosomal degradation of proteins, which is essential for survival of eukaryotic cells under metabolic stress. It has also been suggesting to act as a form of programmed cell death.[83-86] Pterostilbene, an analog of resveratrol, has been demonstrated to exert both autophagy and apoptosis in human bladder and breast cancer cell lines.[87, 88] It has also been found to cause accumulation of autophagic vacuoles as well as promote cell death *via* a mechanism involving lysosomal membrane permeabilization in human melanoma, colon, lung and breast cancer cell lines.[89, 90] Pterostilbene has been documented to produce autophagy in human leukemia cells.[91]

RESVERATROL, VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) AND PI3K/Akt

A novel resveratrol analogue, HS-1793, has recently been demonstrated to inhibit vascular endothelial growth factor (VEGF) in human prostate cancer cells. HS-1793 has been suggested to inhibit phosphorylation of PI3K and Akt in human prostate cancer cells.[92] Resveratrol itself has been suggested to inhibit the PI3K and Akt pathway in acute lymphoblastic leukemia cells.[93] Also, it has substantially induced HIF-1a protein degradation by means of the proteasome pathway. Moreover, HS-1793 has shown more potent effects than resveratrol on the cytotoxic effects on PC-3 cells.[94] Resveratrol has been found to possess anti-angiogenic properties, through the inhibition of VEGF, useful for the prevention of breast cancer, too.[95] Also, this resveratrol analogue, HS-1793, has been shown to induce cell cycle arrest and apoptotic cell death, in human breast cancer cells. In particular, it has been found to induce G2/M cell arrest in human breast cancer cells.[96]

RESVERATROL AND ATF3 TRANSCRIPTION FACTOR

Recently, ATF3 has been identified as a novel target of resveratrol in colorectal cancer cells.[97] ATF3, a member of the ATF/CREB family of transcription factors, is characterized as an adaptive response gene.[98] Latest data suggest that ATF3 may function as a tumor suppressor gene in colorectal tumorigenesis. First, ATF3 expression is substantially reduced in cancer tissues, compared to normal tissue.[99] Second, ATF3 over-expression is reported to produce inhibition of proliferation, promotion of apoptosis, inhibition of invasion and decrease of tumor formation in vivo.[100-103] Finally, ATF3 is demonstrated to enhance induction of apoptosis by substances known to possess anti-cancerous properties.[104-106] Thus, it is suggested that ATF3 plays an anti-carcinogenic role in colorectal cancer (Fig. 2).[107]

BIOAVAILABILITY OF RESVERATROL

Resveratrol's bioavailability is compromised by its physicochemical properties, such as low stability, increased oxidation on heat and light exposure, low water solubility as well as its high hepatic uptake. Data obtained from human pharmacokinetic studies have shown a low amount of intact resveratrol in the systemic circulation, which does not justify its therapeutic activities, raising doubts about resveratrol's potential in vivo.[108] Recently, a soluble form of trans-resveratrol has been developed, which has been demonstrated to be better absorbed and to have efficient serum levels compared to the dry powder. A single dose of 40 mg of this soluble galenic form resulted in blood levels of 0.1-6μM for several hours and without any observed intolerance or toxicity.[109]

CONCLUSION

Resveratrol has shown much promise in preclinical trials and because of its good safety profile it may be an ideal chemopreventive and chemotherapeutic agent. However, the rapid metabolism of resveratrol has been a continuing challenge. Researchers now are focusing on approaches to overcome this problem, which appears to be a major obstacle in the clinical use of resveratrol. However, resveratrol seems to have a long way ahead until it could find its place as an effective chemotherapeutic agent.

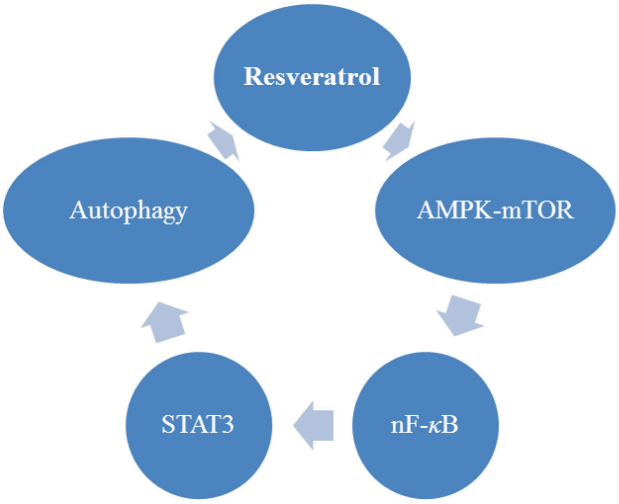

FIGURE 2. The main different molecular pathways through which resveratrol exerts its anti-cancerous effects. AMPK = 5' adenosine monophosphate-activated protein kinase; mTOR = mammalian target of rapamycin; nF-kB = nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3 = signal transducer and activator of transcription 3 (factor).

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