Cancer-specific Therapeutic Potential of Resveratrol: Metabolic Approach against Hallmarks of Cancer

Dong Hoon Suh[1], Mi-Kyung Kim[2], Hee Seung Kim[2], Hyun Hoon Chung[2], Yong Sang Song[2, 3, 4, *]

[1]Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam, Korea; [2]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea; [3]Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [4]Major in Biomodulation, World Class University, Seoul National University, Seoul, Korea

Corresponding Author: Yong Sang Song, Department of Obstetrics and Gynecology, Seoul National University College of Medicine, 101 Daehak-ro Jongno-gu, Seoul 110-744, Korea

ABSTRACT:

Cancer hallmarks include evading apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis. Cancer cells undergo metabolic reprogramming and inevitably take advantage of glycolysis to meet the increased metabolic demand: rapid energy generation and macromolecular synthesis. Resveratrol, a polyphenolic phytoalexin, is known to exhibit pleiotropic anti-cancer effects most of which are linked to metabolic reprogramming in cancer cells. This review summarizes various anti-cancer effects of resveratrol in the context of cancer hallmarks in relation to metabolic reprogramming.

INTRODUCTION:

Tumor cells rely on glycolysis rather than oxidative phosphorylation for ATP production even in the presence of oxygen, this is called the Warburg effect. Since the proposal of metabolic shift from aerobic respiration to aerobic glycolysis in neoplastic cells [1], supporting evidence has been accumulated in many types of cancers [2]. The Warburg effect in the context of concerted changes in energy metabolism including mitochondrial function for carcinogenesis is often referred to as metabolic reprogramming [3]. Although most of the exact molecular mechanisms underlying metabolic reprogramming are needed to be elucidated, many anti-cancer agents targeting the metabolic reprogramming are under investigation in the preclinical and clinical setting [4].

Among the agents is a naturally occurring compound, phytochemicals, which comprise different classes such as terpenoids, glucosinolates, anthraquinones, and polyphenolics [5]. Resveratrol (3, 5, 4'-trihydroxy-trans-stilbene), a biologically potent member of polyphenolics, was known as one of phytoalexins [6]. Tremendous interest in resveratrol of earlier days was mainly due to the epidemiological finding of so-called "French paradox", i.e., despite high fat intake, mortality from coronary heart disease of people who regularly drink wine is low [7]. Parallel to the anti-cardiovascular effect, anti-cancer effect of resveratrol has been extensively studied for the past several years. An enormous amount of evidence has proposed many different mechanisms associated with resveratrol, including anti-oxidant and anti-mutagenic properties [8]. Despite the fact that a lot of anti-cancer mechanisms of resveratrol are still largely obscure, the pleiotropic nature of its anti-cancer effect is noteworthy (figure 1). This review, herein, summarizes various anti-cancer effects of resveratrol in the context of cancer hallmarks in relation to metabolic reprogramming.
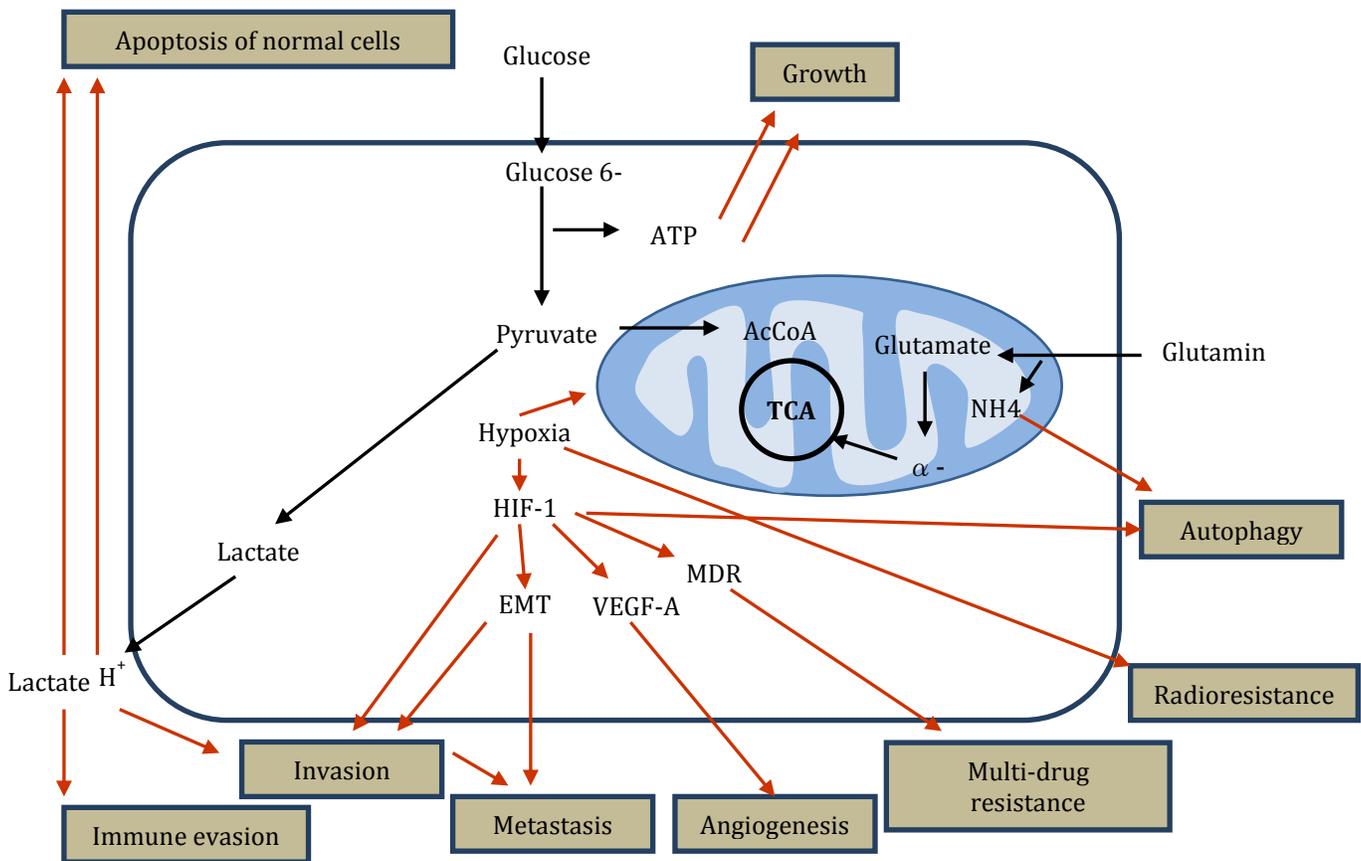

Figure 1. Possible targets of resveratrol and proposed roles of cancer metabolism in the expression of cancer hallmarks. The hallmarks concern the cancer cells themselves except apoptosis, which concerns neighboring normal cells. The glucose uptake rates of cancer cells are much higher than those of neighboring cells, leading to apoptosis of the latter. High glycolytic fluxes allow rapid processing of glucose into lactate, which, together with protons, induces apoptosis in normal cells, blocks immune cell function and guides tissue invasion by tumors. Hypoxia existing in tumors is not only responsible for tumor resistance, but also supports angiogenesis and metastasis through HIF-1 activity. Abbreviations: AcCoA; EMT, epithelial-mesenchymal

transition; HIF-1, hypoxia inducible factor-1; α-KG, α-ketoglutarate; MDR, multi-drug resistance; TCA, tricarboxylic acid cycle;VEGF, vascular endothelial growth factor. Adapted from Ferreira et al. (2012) under permission from nature publishing group.

Anti-cancer mechanisms of resveratrol against hallmarks of Cancer - Inhibiting three key glycolytic enzymes: hexokinase, phosphofructokinase, and pyruvate kinase: Hexokinase (HK) catalyzes the essentially irreversible first step of the glycolytic pathway where glucose is phosphorylated to glucose-6-phosphate. Among four isoforms of HK, HK II is known to be overexpressed in most neoplastic cells where it contributes to the proliferation and survival of tumor cells through enhancing aerobic glycolysis [9]. There is no evidence suggesting that resveratrol directly inhibits the enhanced activity of HK II in tumor cells. However, growing evidence supports indirect HK II inhibition by resveratrol through the inhibitory effect of resveratrol on receptor tyrosine kinase (RTK)/phosphoinositide-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway in many types of cancer cells [10, 11]. Resveratrol-induced HK II inhibition also seems to be mediated through the inhibition of hypoxia-inducible factor-1α (HIF-1α), a transcription factor that reprograms cancer cell metabolism [12]. HIF-1α overexpression is observed in a wide array of human cancers, which is known to be substantially responsible for the higher rate of glycolysis by the induction of glycolytic enzymes including HK II [13, 14]. Zhang et al. indicated that resveratrol treatment down-regulated the expression of HIF-1α proteins in human nasopharyngeal carcinoma cells [15].

The enzyme 6-phosphofructo-1-kinase (PFK1) is another critical glycolytic enzyme which catalyzes the transfer of a phosphate from ATP to fructose-6-phosphate to produce fructose-1,6-bisphosphate and adenosine diphosphate (ADP) [16]. The expression of PFK-L isoform was shown to correlate directly with aggressiveness and glycolytic efficiency, i.e., lactate produced per glucose consumed, in breast cancer cell lines [17]. Moreover, PFK1 inhibition can lead to cell death in human breast cancer cell lines, which suggests that PFK1 might play a critical role in cell fate decision in these cell lines [18]. Gomez et al. demonstrated that resveratrol decreased viability, glucose consumption and ATP content in human breast cancer cell line MCF-7, and these effects were correlated with PFK1 inhibition by resveratrol [16]. They also reported that resveratrol directly inhibited purified PFK1 mainly through the dissociation of the PFK1 from fully active tetramers into less active dimers.

Among the enzymes that undergo changes during tumor formation is pyruvate kinase (PK). PK catalyzes the dephosphorylation of phosphoenolpyruvate to pyruvate and yields one molecule of ATP [12]. In tumor cells, the glycolytic PK isoenzyme M2 (PKM2) determines whether glucose is converted to lactate for regeneration of energy (active tetrameric form, Warburg effect) or used for the synthesis of cell building blocks (nearly inactive dimeric form) [19]. Because of the lower glycolytic activity of PKM2 than the constitutively active isoform, PKM1, cancer cells are likely to accumulate several glycolytic intermediates for macromolecular biosynthesis, for example, ribose-5-phosphate using pentose phosphate pathway (PPP) [20]. mTOR up-regulates PKM2 via HIF-1α, while PKM2 conversely promotes transcriptional activity of HIF-1α, activating glycolysis at several levels and compensating the low glycolytic activity of PKM2 [21]. Resveratrol was shown to down-regulate PKM2 expression by inhibiting

mTOR signaling. Down-regulation of PKM2 expression results in the suppression of cancer metabolism. Decreased glucose uptake and lactate production, and reduced anabolism were demonstrated in various cancer cell lines [20]. An over-expression of PKM2 abolished the effects of resveratrol, emphasizing the role of PKM2 down-regulation as a critical function of resveratrol.

Enhancing apoptotic cell death: Cancer cells are characterized by uncontrolled proliferation and defective apoptosis which contributes to chemotherapy resistance [22]. Changes of components of apoptotic machinery on mitochondrial membrane were suggested to be underlying mechanism of the defective apoptosis in cancer cells [9].

In addition to providing the precursor for glycolysis and biosynthesis of key metabolites, mitochondrial HK II may provide one link between inhibition of apoptosis and metabolic reprogramming in cancer cells through the interaction with the voltage-dependent anion channel (VDAC) on outer mitochondrial membrane (OMM) [22]. Partly due to the increased translocation of HK II to OMM by the constitutively activated Akt in cancer cells, the HK II-VDAC interaction was increased in cancer cells compared with normal cells. Furthermore, HK II was shown to bind more tightly to VDAC on OMM in tumor cells than in normal cells [23]. In addition to HK II-VDAC interaction, another critical regulation of the cellular apoptosis is the balance between pro- and anti-apoptotic proteins [24]. HK II may compete with the anti-apoptotic protein Bcl-X_L for VDAC binding site. Thus, HK II binding to VDAC releases Bcl-X_L from VDAC and facilitates binding of Bcl-X_L to Bax, which prevents Bax-Bax oligomerization or Bax-Bak interaction. However, HK II detachment from VDAC, for example, through phosphorylation of VDAC by glycogen synthase kinase 3β, promotes binding of Bcl-X_L to VDAC, leaving Bax free from Bcl-X_L. Free Bax interacts with Bak/Bax to form pore structures for the release of cytochrome c, the commitment step of mitochondria-mediated apoptosis [25].

Resveratrol activity might reduce the translocation of HK II to OMM, thus preventing HK II-VDAC interaction and facilitating the detachment of HK II from VDAC via the inhibition of RTK/PI3K/AKT/mTOR pathway [10, 11]. The detachment of HK II from the mitochondria might sensitize the mitochondria to the cisplatin-induced cell damage, leading to much enhanced apoptotic cell death [26]. Resveratrol was reported to induce apoptosis dominantly via the activation of Bak- but not Bax-mediated intrinsic pathway in human lung adenocarcinoma cells [27]. However, the growth-inhibitory and pro-apoptotic effects of piceatannol, a hydroxylated analog of resveratrol, were shown to be mediated through up-regulation of Bid, Bax. Bik, Bok, Fas: P21(WAF1), down-regulation of Bcl-xL; Bcl-2, clAP, activation of caspases (-3, -7,- 8, -9), loss of mitochondrial potential, and release of cytochrome c in a wide variety of tumor cells [28]. More recently, dimethylated analog of resveratrol, pterostilbene, was demonstrated to down-regulate the anti-apoptotic proteins Bcl-$_X$L and Mcl-1, leading to the up-regulation of mitochondrial apoptosis pathway-related proteins including Bax, Bak, cytochrome c, and cleaved caspase 3 in osteosarcoma cells [29].

There is another mechanism of resveratrol enhancing apoptosis of cancer cells. Low pH, caused by the accumulation of lactate due to up-regulated glycolysis in cancer cells, was shown to induce base rotation in DNA especially copper bound N7 guanine that can lead to exposure of the metal ion. Resveratrol seems to easily attack exposed copper, reducing it and thereby

generating reactive oxygen species (ROS), leading to oxidative DNA damage [30]. These results suggest that resveratrol could be an effective treatment for tumors that are hypoxic and have low pH microenvironment.

Death receptor pathway, also known as the extrinsic pathway, is another apoptotic pathway through which the pro-apoptotic effect of resveratrol might be exhibited. Briefly, resveratrol can up-regulate the expression of death receptor ligands such as FasL and CD95L directly or indirectly through activating p53, leading to increase and relocalization of death receptors in lipid microdomains and forming the death-inducing signaling complex (DISC) [31]. The DISC complex recruits pro-caspase 8 through the adaptor protein Fas-associated death domain (FADD), activating downstream procaspases like caspase 3 to induce apoptosis [32].

Inhibiting proliferation of tumor cell: The anti-proliferative effect of resveratrol in tumor cells has been extensively described [33, 34]. In a wide variety of tumor cells, the growth-inhibitory effects of resveratrol were shown to be mediated through cell-cycle arrest. Most of the cell cycle is controlled by a family of protein kinase complexes which constitutes a cyclin dependent kinase (cdk) and the corresponding cyclin [31]. Wolter et al. showed the down-regulation of the cyclin D1/cdk 4 complex by resveratrol in colon cancer cells [35]. Resveratrol can also induce G1 phase arrest by decreasing the protein expression of cyclin D2, E, and cdk 2, 6 through inhibiting binding of transcription factors such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1). Resveratrol was shown to induce the translocation and expression of cdk inhibitors, p21 and p27, by up-regulation of transcription factors. Cdk inhibitors inhibit active cyclin/cdk complexes and block the G1/S phase transition [31]. Resveratrol can also decrease the expression of c-Myc, a cyclin E/cdk 2 activator, preventing the cell from going through G1/S phase transition [36].   There are several mechanism reported with regard to S phase arrest by resveratrol. Resveratrol can disrupt the dephosphorylation of cdk 1, a key regulator of the cell cycle and the progression through the S phase [31]. Larrosa et al. reported that resveratrol induced S-phase arrest and up-regulation of cyclins A, E and B1 in human melanoma cells [37]. S phase arrest by resveratrol was also induced by direct inhibition of DNA synthesis through, for example, inhibiting ribonucleotide synthase and DNA polymerases [38]. Liang et al. demonstrated that resveratrol induced G2 phase arrest through the inhibition of Cdk 7 and Cdc 2 kinases in colon carcinoma cells [39]. Thus, it seems to be clear that the resveratrol effects on the cell-cycle are highly variable [33].

Another mechanism of anti-proliferative effect of resveratrol was mediated through its role as a calorie restriction (CR) mimetic. CR is widely believed to extend the lifespan and protect against aging-related diseases including cancer [40]. Accumulating evidence showed that CR effect of resveratrol might be associated with increasing silent information regulator 2/sirtuin 1 (SIRT) activity [6]. SIRTs belong to the class III histone/protein deacetylases, which are implicated in CR, aging, and inflammation [41]. One key enzyme thought to be activated during CR is AMP-activated kinase (AMPK), a sensor of cellular energy levels [42]. Once activated, AMPK inhibited 4E-BP1 signaling and mRNA translation via mTOR, leading to inhibition of cellular proliferation. In addition, resveratrol-mediated AMPK activation was shown to be caused by inducing the expression of SIRT1 via elevation in the cellular NAD (+)/NADH in

estrogen receptor-positive breast cancer cells. These findings suggest that targeting SIRT1/AMPK signaling by resveratrol may have potential therapeutic implications for cancer.

P53 is a key tumor suppressor protein that has multiple functions which help to prevent cancer development including regulation of cell growth as well as promoting apoptosis and dampening glycolysis [43]. Tumor cells often mutate or lose p53 to ensure replicative potential. Warburg effect is known to be directly caused by the inactivation of p53. P53 can inhibit the expression of glucose transporters (GLUT) 1 and 4, and phosphoglycerate mutase (PGM), the enzyme that converts 3-phosphoglycerate to 2-phosphoglycerate in glycolysis, while increasing the expression of TP53-induced glycolysis and apoptosis regulator (TIGAR) [22]. TIGAR is an isoform of PFK2 that inhibits overall PFK activity through lowering the levels of fructose-2, 6-bisphosphate, an allosteric activator of PFK1, and hence inhibits glycolysis while channeling glucose to the PPP [44]. Again, PPP is one of the critical pathways for macromolecular biosynthesis which is needed to supply building blocks for cell replication. There are several lines of evidence demonstrating that resveratrol can up-regulate the expression of p53 in various cancer cell lines including breast, prostate, and ovarian cancers [45-47]. The underlying mechanism of p53 up-regulation by resveratrol is not clearly understood. Nevertheless, Zhang et al. proposed that resveratrol could activate p53 with the help of mitogen-activated protein kinase (MAPK), which phosphorylates and acetylates p53 [48].

Angioprevention: anti- metastatic effect through inhibiting inflammation and angiogenesis:
It is now well established that metabolic syndrome is a risk factor for at least some types of cancers including breast, colon, and prostate cancers [5]. Among the involved pathological manifestations are inflammation and endothelial cell dysfunction. Obesity may shift the balance toward a pro-angiogenic and pro-inflammatory function, and become a reservoir for dysregulated inflammatory cells such as macrophages and T lymphocytes. These inflammatory cells are able to release cytokines for tumor promotion and angiogenesis [5]. The inflammatory mediators include cytokines such as interleukin (IL)-1, 6, 8, and tissue necrosis factor-α (TNF-α), prostaglandins, and nitric oxide [49]. Cyclooxygenase (COX), which catalyzes the conversion of arachidonic acid to prostaglandins, was shown to be able to activate procarcinogens, thus, making transgenic mice with an increased expression of COX-2 highly susceptible to spontaneous skin tumor formation [50]. Surh et al. reported that COX-2 was implicated in increased invasiveness as well as metastatic potential of tumor cells [51]. Transcription of COX-2 is regulated by several transcription factors including NF-κB [31]. NF-κB, one of the most important transcription factors regulating inflammatory responses, cellular proliferation and growth as well as oncogenesis, is known to exist as a heterodimer and sterically blocked by IκB [52]. The balance between NF-κB and IκB was considered important to the tumor development [53].

Resveratrol was demonstrated to directly block NF-κB activation in cell type non-specific manner [54]. In addition, accumulating evidence proposed several mechanisms underlying the NF-κB inhibition by resveratrol. Kundu et al. reported that resveratrol could prevent the activity of NF-κB by inhibiting degradation of IκBα in oxidative stress-stimulated mouse skin model [55]. MAPK phosphatase 5 (MAPK5) is known as a potent inhibitor of cellular inflammatory responses because MAPK5 can block the enzymatic activation of MAPK, which is one of the

upstream kinases that regulate the activation of NF-κB, with a high selectivity for p38. It was shown that resveratrol could up-regulate MAPK5 and inhibit p38 pathway in prostate cancer cell lines [56]. Moreover, resveratrol can inhibit NF-κB both by blocking the upstream activator PKCδ and by activating the inhibitor SIRT1 [57].

Angiogenesis is essential for tumor to survive and metastasize. It is usually required for tumor growth beyond a diameter 1-2 mm and stimulated by, most importantly, vascular endothelial growth factor (VEGF) [58]. Resveratrol was shown to inhibit tumor-induced neovascularization through inhibiting VEGF expression in various cancer cell lines [59, 60]. The anti-angiogenic effect of resveratrol is also through inhibiting other mediators including basic fibroblast growth factor (bFGF) and matrix metalloproteinase-2, 9 (MMP-2, 9). MMPs are endopeptidases that cleave protein components of extracellular matix contributing to cell migration for angiogenesis as well as metastasis [61]. Resveratrol was shown to markedly inhibit MMP-9 activity and expression at both protein and mRNA levels in breast cancer cells [62]. In this study, resveratrol attenuated PI3K and phosphorylation of AKT and mTOR. In addition, resveratrol inhibited NF-κB transcriptional activity and DNA binding of NF-κB on MMP-9 promoter. These results suggest that resveratrol may suppress breast cancer cell invasion through the inhibition of MMP-9 involved in PI3K/AKT and NF-κB pathways. Mousa et al. showed that resveratrol could inhibit bFGF-induced angiogenesis in the chick chorioallantoic membrane model [63].

Tosetti et al. have shown the capacity of dietary phytochemicals including resveratrol to inhibit inflammation and angiogenesis, termed angioprevention [5]. Along with down-regulation of NF-κB by resveratrol, a variety of inflammatory cytokines such as IL-1, 6, 8, and TNF-α were main targets of resveratrol [33]. Given that MAPK is a crucial component in both signaling pathways for inflammatory responses and endothelial cell proliferation, the inhibitory effect of resveratrol on MAPK suggests that resveratrol might play an important role in angioprevention to prevent tumor metastasis.

CONCLUSIONS:

Resveratrol is widely considered to exhibit beneficial health effects. Anti-cancer effects of resveratrol seem to be of particular interest at present, because resveratrol shares most of its targets with metabolic reprogramming of tumor cells. Metabolic reprogramming is a reemerging issue in recent cancer biology. Briefly, resveratrol down-regulates the increased glycolytic activity of tumor cells at multiple levels, facilitating apoptosis of tumor cells and inhibiting tumor cell proliferation. Moreover, resveratrol might prevent metastasis and tumor invasion through inhibiting inflammation and angiogenesis.

Of note, the anti-cancer effects of resveratrol are thought to have cancer selectivity with minimal toxicity to normal cells. Low pH condition around tumor cells due to increased lactate production from enhanced glycolysis may promote the pro-oxidant anti-cancer activity of resveratrol [30]. It should be pointed out that the IC50 of resveratrol for proliferation inhibition was significantly lower for cancer cells as compared to normal cells [64]. The cancer selectivity of resveratrol might help to circumvent its limit of low bioavailability. There are several clinical trials of resveratrol for testing its efficacy in prevention and treatment of cancer. We should wait for their results to find out whether the promising experimental and preclinical data will be

proven in clinical setting.

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