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Effectiveness of Resveratrol on Metastasis: A Review

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Abstract: *Resveratrol's effects on different cancers have been studied extensively over the past 15 years. Researchers have noted the compound's potential ability to mitigate cell proliferation and metastasis and promote apoptosis. This review primarily focuses on the former, while noting that both processes are intrinsically related. This thorough analysis of resveratrol finds that it can inhibit cancer progression through a multitude of pathways, making it a potential candidate for future drug therapies. This review also highlights the need to study combinatorial effects of resveratrol with other compounds in an attempt to develop more effective and efficient drugs.*

Keywords – *angiogenesis, cancer, metastasis, resveratrol, review*

I. INTRODUCTION

Cancer is a cellular disease that affects millions of people worldwide. The Centers for Disease Control and Prevention (CDC) reports that 14.1 million new cases were diagnosed and 8.2 million deaths due to cancer occurred in 2012. The American Cancer Society reported in 2008 that cancer cost the globe $895 billion, a number that will only increase alongside cancer rates. As such, researchers are constantly studying new methods of treatment for various types of cancers. Resveratrol serves no exception, as it has gained considerable attention in the past 15 years. Resveratrol exists as a plant-derived polyphenol phytoestrogen found in the skin of red grapes, raspberries, blueberries, red wine, peanuts, and certain types of pines. Certain plants may also produce resveratrol to fend off pathogenic attacks, thereby having it serve as an antimicrobial agent. Studies have highlighted its positive effects in multiple cancers, including pancreatic cancer, breast cancer, and more. A number of experiments have examined resveratrol's ability to target multiple pathways, which could ideally combat metastasis and migration – the primal cause of cancer lethality.

This review examines the multitude of effects resveratrol has on cancer pathways, with a focus on metastasis. It considers the studies done investigating the role of resveratrol on MMP inhibition, cell microcolonization, angiogenesis, cell migration and motility. This review concludes by summarizing the findings discussed and highlighting how the various pathways affected by resveratrol can help inhibit or prevent metastasis, and the potential for combinatory effects of resveratrol with other compounds.

II. LITERATURE REVIEW

2.1 MMP Inhibition

Studies have documented the role of resveratrol decreasing the invasive potential of cancer cells through the down-regulation of gelatinases, MMP-2, and MMP-9. Individuals with ER+ breast cancer may overproduce HER-2. This can lead to greater MMP-9 expression when up-regulated, thus increasing invasive potential. HER-2, along with HER-3 and -4, becomes active through the expression of heregulin-β1 (HRG-ß1).

Lee et al. examined into the effects resveratrol has on MMP-9. They found that SIRT1 inhibited MMP9 expression in HT1080 cells, suggesting that "resveratrol can be a potential candidate for chemoprevention of cancer." (Lee, 2011, p. 465). Supplementing these findings, Kim et al. (2012) found that resveratrol reduces MMP-9 transcription by inhibiting transactivation of NF-kB and AP-1 in human lung and cervical cancer cells. In addition, their results show a positive relationship between oxidative stress and cancer development, which demonstrates the significance of antioxidant treatments.

A different team, Pan et al. (2011), used ER positive MCF-7 cell lines to examine the effects of resveratrol on MMP-9 expression through modulation of HER-2 at various concentrations of resveratrol (2, 5, and 10 μM) and at a level slightly higher than physiological concentrations (100 pM to under 2 μM). The treatment decreased HRG-β1 induced MMP-9 expression through the inhibition of ERK1/2 activation within the MAPK cascade, resulting in reduced invasion (Fig. 1). The down regulation of HRG-β1 also led to decreased activation of Akt of the PI3K/Akt pathway, which decreased cell proliferation and cell survival. Subsequent *in vitro* studies conducted by Banerjee et al. (2002) and Lin et al. (2014) have illustrated a dose-dependent decrease in MMP-9 expression. They also conducted an *in vivo* animal study using female Sprague Dawley rats and found that resveratrol inhibits MMP-9 activation by down regulating NF-kB, a transcription factor (TF).

Tang et al. (2008) also investigated the effects of IGF-1's role on MMP-2 expression. Previous studies have shown that IGF can enhance protease expression and increase invasiveness of cancer cells. In this study, human breast cancer cell lines, MDA-MB 435, showed a dose-dependent decrease in IGF-1 induced MMP-2 expression. Maximal inhibition occurred at 20 μM via down-regulation of PI3K/Akt pathway. Similarly, *in vivo* studies using nude mice transfected with heptoma cancer cells found that resveratrol caused a dose-dependent decrease of MMP-2 expression, possibly by means of modulating NF-kB expression, and ultimately, down-regulation of MMP-2. Gagliano et al. (2005) also studied resveratrol's effect on MMP-2 expression on glioblastoma cells. They found a dose-dependent effect on MMP-2 mRNA levels after 72 hours of administering resveratrol (1-50 μM). The team attributed the down-regulation to the inhibition of NF-kB activation.

2.2 Cell Proliferation

Previous research illustrates that resveratrol can alter signaling pathways vital for microcolonization. One method involves resveratrol binding to ER receptors (due to its structural similarity to estrogen) and inhibiting cellular transcription. In the presence of estradiol, resveratrol had an elevated affinity for binding to the ER in prostate cancer cell lines, displaying the compound as an ER agonist at lower concentrations (10 and 50 μM) and an antagonist at concentrations higher than 50 μM. While serving as an antagonist, resveratrol can inhibit proliferation. This trend occurred in breast cancer cell lines as well; however, the concentrations that caused ant/agonistic effects varied among different cell lines: 10-25 μM for agonistic effects; >25 μM for antagonistic effects. ER negative cell lines treated with resveratrol also exhibited dose-dependent anti-proliferative effects.

Resveratrol can also regulate NF-kB, a transcription factor (TF) activated by various signals and involved in multiple cellular processes. This TF normally remains inactive, existing as a complex with the inhibitor of IkBα. Activation of IKK from certain extracellular signals results in the phosphorylation of IkBα, and subsequently, its degradation. This allows NF-kB to serve as a TF and ultimately increase cell proliferation. Resveratrol was found to reverse this effect through various means either by the inhibition of TNF-activated NF-kB expression by the phosphorylation and binding of the p65 NF-kB subunit or by inhibiting the TF AP-1 through TNF at concentrations ranging from 1-25 μM. Exposure to 5 μM of resveratrol led to a 90% inhibition of TNF-mediated events.

The PI3K/Akt pathways also serves a significant role in cell proliferation. In these pathways, PIP2 converts to PIP3, and the concentration of both remain balanced through the protein PTEN. Faulty PTEN leads to higher PIP3 concentrations and increased cell proliferation. In addition, IFG-1 can activate this pathway in ER negative breast cancer cells. Tang et al. therefore analyzed the effects of resveratrol on IGF-1 and found that the compound reduced the activation of Akt by 70% at 20 μM. In other words, resveratrol can effectively down-regulate the PI-3K/Akt pathway in ER negative breast cancer cells and decrease proliferation (similar effects were found in ER positive cells). Regarding MCF-7 cells, resveratrol diminished PI3K activity at increasing concentrations. It also inhibited ERα regulated genes, illustrating that resveratrol prevented cell proliferation of MCF-7 cells through the PI3K pathway. Lastly, Jiang et al. (2009) found that 100 μM of resveratrol over 24 hours inhibited PI3K/Akt/mTOR activation in U251 glioma cells as well as other cancers that over expressed Akt1 and/or Akt2.

Researchers have also studied resveratrol's effect on other pathways. For example, IGF-1 can activate the Wnt/β-catenin pathway in colon cancer cells, leading to increased production of cells. Resveratrol successfully inhibited this effect by inhibiting IGF-1R at 100-150 μM, resulting in decreased transcription from the Wnt pathway. Supplementing these findings, Ji et al. (2013) found that resveratrol inhibited the pathway through MALAT1 regulation.

2.3 Cell Cycle Proteins

Cell cycle regulators ensure proper cell growth rates. Because over activation of certain regulators, such as cyclin D1, can lead to uncontrolled proliferation, they have become a target for research. For instance, researchers found that 100 μM of resveratrol can inhibit the effects of cyclin D1 in U251 glioma cells. The compound also repressed the cell cycle by regulating cdk-cyclin activity in the MCF-7 breast cancer cell line. In prostate cancer cells, resveratrol blocked proliferation by acting on the G1/S and G2/M checkpoints and by apparently regulating the activation of p53.

Zhou et al. (2011) investigated the effects resveratrol has on p53 expression in multiple pancreatic cancer cell lines. Treatment of the compound led to the up regulation of p53 by ATM phosphorylation. It also demonstrated MAPK activation (maximally at 200 μM), which led to the downstream up-regulation of p21 through p53, and ultimately, cell cycle arrest. This effect occurred in both p53 dependent and independent pathways.

Resveratrol can also target and inhibit the expression of Cdk1. This down regulates survivin, making it harder for c-MYC tissues to grow. Both *in vivo* and *in vitro* studies identified the inhibitory effects resveratrol has on c-MYC cells. S phase arrest occurred in over 50% of the cells with treated with 100 μM of resveratrol for 24 hours, while no cells exhibited movement through the G2/M phase.

2.4 Apoptosis

Resveratrol promotes apoptosis by activating caspases 2 and 8. The former alters the permeability of the mitochondrial membrane leading to the formation of apoptosomes initiating a caspase cascade resulting in apoptosis. Another caspase from this mechanism deactivates IAPs, resulting in cytochrome c-dependent apoptosis. Caspase 8, in contrast, utilizes membrane-bound death receptors (i.e. mitochondria-independent pathway). Y79 retinoblastoma cells and MCF-7 breast cancer cells also showed similar effects when exposed to resveratrol. However, MCF-7 cells induced cell death by increasing the expression of cell cycle regulators (instead of caspases) when exposed to less than 50 μM of resveratrol. This suggests that estrogen or androgen and lack thereof could influence the type of apoptotic mechanism involved when exposed to resveratrol. Administering 200 μM of resveratrol failed to enhance cell cycle regulators. This supports the notion that apoptosis could occur through different mechanisms. Baribeau et al. (2014) observed this effect in resveratrol induced apoptotic-independent cell death in A2780 and A2780CP cell lines.

Both *in vivo* and *in vitro* studies supported the premise that resveratrol functions through the extrinsic and intrinsic routes. Mohan et al., for example, treated MEF Bak and Bax deficient cells with 50 μM resveratrol and found that the compound worked through an extrinsic pathway, activating caspase 2 and/or 8. They also found that, in HCT 116 cell lines, administering 50 μM or more of resveratrol induced apoptosis through caspase activation upstream of the mitochondria. Studies suggest that ceramide production in MDA-MB-231 cells could trigger caspase 2 activation, though the mechanism in colon cancer remains unclear. However, studies have shown colon cancer cells releasing cytochrome c, AIF, and endonuclease G upon resveratrol administration, triggering apoptosis. Resveratrol also affects p53 production. COX-2 increases Ser15-phosphorylated p53 in the cells, inducing p300 activation. This p53 protein also increases ERK1/2 activity. The elevated apoptosis rate from these two mechanisms suggests that p53 acts through MAPK pathways as well as p300. Zhou et al. (2011) further studied p53; they found that resveratrol mediated p53 effects on colon cancer cell lines, inducing apoptosis in a time and dose-dependent manner. They also found that nonfunctional p53 pathways cannot utilize resveratrol to induce apoptosis.[43] However, cancers still used the actual p53 protein, which indicate that apoptosis still occurred.

The PI3K/Akt/mTor pathway also involved resveratrol-mediated apoptosis. Vanamala et al. (2010) investigated these apoptotic effects in the presence of IGF-1. They found that apoptotic effects in colon cancer cells maximally occurred at 100-150 μM by suppressing IGF-1R, leading to decreased Akt activation and increased p53 expression. Studies have also shown an increase in caspase 3 activation, illustrating that a time and dose-dependent increase in apoptosis exists in cell lines regulated by this pathway. Resveratrol also suppresses transcription factors such as NF-kB and STAT3, leading to increased apoptosis. Bhardwaj et al. (2007) found this effect in multiple myeloma cell lines after exposure to 50 μM of resveratrol Mediation of NF-kB can occur by inhibiting IkBα kinase and p65 sub-units. This down-regulation increases Bax, ultimately activating caspase-3. In addition, several other anti-apoptotic proteins became inactive, further increasing the rate of apoptosis. Harikumar et al. (2010) found similar results. In PaCa cell lines, resveratrol inhibited the activation of NF-kB (as well as VEGF, MMP-9, COX-2, and other proteins) (Fig. 1). Finally, Mohan's (2006) research research has indicated that intrinsic pathways display increased activation of pro-apoptotic proteins, possibly due to upstream signals of caspase 2. This leads to increased levels of cytochrome c, and subsequently, caspases 3 and 9. Cathepsin D, a protein over-expressed in epithelial breast cancers, can offset this. It effectively inhibits caspase 3 and 9 production, which lowers the rate of apoptosis. Resveratrol can reverse this effect in ER-positive cells by inhibiting Cathepsin D's lysosomal pathway. This occurred under high concentrations of resveratrol (10^{-4} M). Observations using lower concentrations (10^{-6} M) showed an increase in cathepsin D production.

2.5 Inhibition of Angiogenesis

Studies suggest that resveratrol can serve as an angiogenic inhibitor by reducing VEGF-dependent angiogenesis. Up-regulation of growth factors leads to an increase in VEGF. It then binds to VEGFR, effectively initiating multiple signaling pathways (e.g. MAPK, ERK1/2) that promote angiogenesis. *In vitro* studies using myeloma cells have shown that 50 μM or more of resveratrol over 48 hours suppressed HIF-1α expression (Fig. 1). Doing so caused VEGF levels to decrease, thus reducing angiogenesis. Studies have also shown that 25 μM of resveratrol can inhibit the secretion of VEGF in multiple myeloma cell lines. Additionally, MDA-MB-231 cells displayed lower VEGF activity, though with 100 μM instead. Researchers believe that the decrease in activity stems from a decreased phosphorylation of ERK1/2 in the MAPK pathway.

Experiments using BCE cell lines have illustrated this point: 10 and 20 µM of resveratrol inhibited FGF-2 induced phosphorylation of ERK1/2. A different study led by Yu et al. (2010) found similar results using HepG2 cells: resveratrol inhibited VEGF, tumor growth, and angiogenesis.

On the other hand, gliomas behaved slightly different. While they did exhibit a dose-dependent response to resveratrol, VEGF suppression did not correlate with a decrease in MAPK activity. Instead, the effect probably occurred from a lower micro vessel density and lower proliferation. VEGF had a decreased binding affinity with HUVECs - crucial for producing micro-sized tubes for angiogenesis. Following this, Tseng et al. demonstrated that other pathways besides MAPK can inhibit angiogenesis, including PI3K/Akt. In other words, resveratrol can inhibit angiogenesis through multiple pathways.

In vivo studies have also illustrated resveratrol's adverse effect on angiogenesis. Studies concerning the mouse cornea have highlighted resveratrol's ability to inhibit both VEGF and bFGF secretion (Fig 1.). Nude mice models injected with MDA-MB-231 and treated with 25 mg/kg of resveratrol per day for three weeks. The decrease in VEGF expression probably resulted from lower MAPK pathway activity. Brakenhielm et al., (2001) found similar results on male and female C57B16/J mice implanted with murine fibrosarcomas. These mice were exposed to 25 µM of resveratrol orally, emulating oral intake by humans through food consumption. Similarly, mice implanted with FGF-2 and VEGF corneas that consumed 48µg/kg resveratrol showed lower neovascularization in the cornea due to the suppression of those proteins. Another study involved RT-2 glioma cells in a rat model exposed to 40 mg/kg/day of resveratrol for four weeks and experienced increased survival time and decreased the tumor growth rate. This probably resulted from resveratrol decreasing micro vessel density in the gliomas.

2.6 Inhibition of Cell Migration and Motility

Focal adhesions, activated by the recruitment of FAKs and Srcs by integrin and growth factor receptors, can spur cell migration and proliferation (Fig. 1). While this occurs, certain GTPases help remodel the actin skeleton. Cdc424, for example, helps produce filopodia, while Rac helps create lamellipodia. Studies suggest that resveratrol can combat this process by possibly having an impact on the development of focal adhesions by restructuring filopodia. Indeed, estrogen and EGF treated MDA-MB-231 cell lines showed lower cell migration when treated with resveratrol. To supplement this, the increased presence of filopodia in the resveratrol-treated cells appeared to have little or no polarity, which also effectively suppressed cell migration.

In addition, the same cell line exhibited lower lamellipodia production in the presence of resveratrol through Cdc42; however, the production of unpolarized filopodia (as well as effects by other GTPases) may have also lowered production, albeit independently of Cdc42. Kumerz et al. (2010) study support this observation by showing that resveratrol inhibite lamellipodia production. This, along with impaired Rac1 activation, led to anti-migratory effects in EGF-activated vascular smooth muscle cells. Finally, 150 µM of resveratrol in HT-29 can suppress talin and phosphorylated FAK in IGF-1 (Fig. 1). This prevents the mediation of cell survival pathways and cytoskeleton changes that enhance motility. Subsequently, the inhibition of the cytoskeleton talin-FAK pathway leads to enhanced cell detachment as well as decreased protein interactions.

III. FIGURE

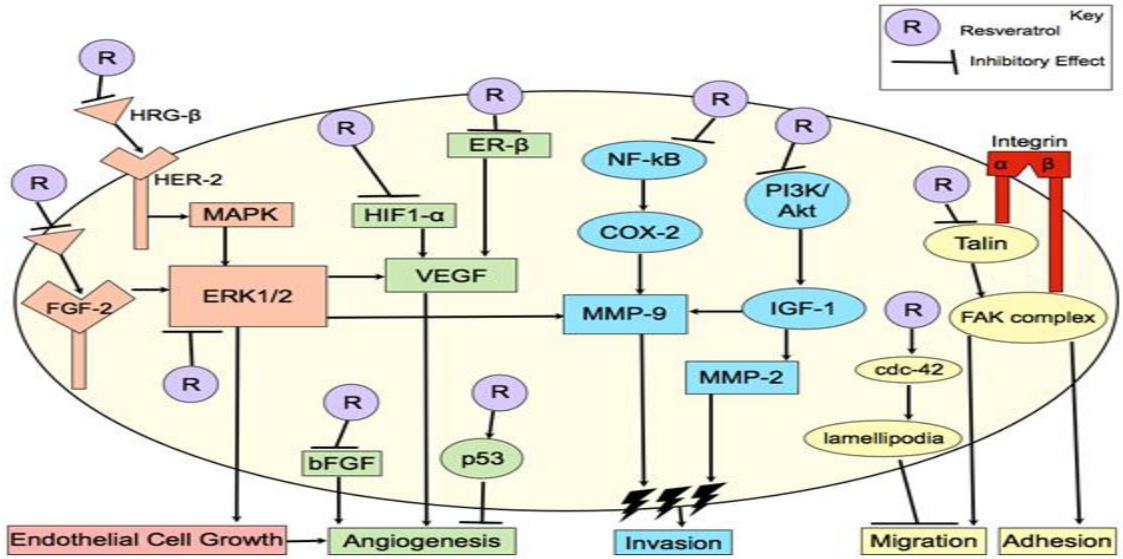

Figure 1: Compilation of resveratrol's effect on major pathways

IV. CONCLUSION

This review highlights the effects resveratrol has on inhibiting cancer growth and metastasis. It examines resveratrol's ability to down regulate MMP-2 and MMP-9 expression. Tang et al. have found multiple avenues of decreasing MMP-2 expression: one through down-regulation of the PI3K/Akt pathway and the other by modulating NF-kB expression. As shown in Fig.1, both avenues serve as viable methods for ultimately hindering metastasis. In addition, by regulating the PI3K/Akt pathway and NF-kB expression, resveratrol can help mitigate cell proliferation. Resveratrol can also be used to target cell cycle proteins. Doing so can affect the MAPK activation in such a way as to prevent endothelial cell growth. Targeting cell cycle proteins such as p53 can also spur apoptosis. Targeting the MAPK, ERK1/2, and/or PI3K/Akt pathways can also inhibit angiogenesis. Lastly, Mario et al. found that resveratrol can affect cdc-42, which reduced lamellipodia production, leading to anti-migratory effects as shown in Fig. 1.

The evidence suggests that resveratrol has the potential to inhibit metastasis. Some evidence has shown it can destroy certain cancer cells as well; though considering that the lethality of cancer greatly amplifies after metastasis occurs, focus on novel methods that hinder metastasis is an imperative need. Such methods might include combinatory effects of resveratrol mixed with another compound(s), such as genistein. Finally, because many patients undergo a variety of treatments, there is the need for some studies to focus on the combinatorial effects of treatments such as radiation therapy, chemotherapy and diet as well. Cancer is at its deadliest once it metastasizes and because resveratrol can potentially combat this, it warrants future studies and attention.

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