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Review

Anti-metastatic potential of resveratrol and its metabolites by the inhibition of epithelial-mesenchymal transition, migration, and invasion of malignant cancer cells

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ABSTRACT

Background: Increased epithelial-mesenchymal transition (EMT) and cell migration and invasion abilities of cancer cells play important roles in the metastatic process of cancer. Resveratrol is a stilbenoid, a type of natural polyphenol found in the skin of grapes, berries, and peanuts. A number of experiments have examined resveratrol's ability to target diverse pathways associated with carcinogenesis and cancer progression.

Purpose: This article aims to present updated overview of the knowledge that resveratrol and its metabolites or analogs have the potential to inhibit metastasis of cancer via affecting many signaling pathways related with EMT, cancer migration, and invasion in diverse organs of the body.

Chapters: This article starts with a short introduction describing diverse beneficial effects of resveratrol including cancer prevention and the aim of the present study. To address the effects of resveratrol on cancer metastasis, mechanisms of EMT, migration, invasion, and their relevance with cancer metastasis, anti-metastatic effects of resveratrol through EMT-related signaling pathways and inhibitory effects of resveratrol on migration and invasion are highlighted. In addition, anti-metastatic potential of resveratrol metabolites and analogs is addressed.

Conclusion: Resveratrol was demonstrated to turn back the EMT process induced by diverse signaling pathways in several cellular and animal cancer models. In addition, resveratrol can exert chemopreventive efficacies on migration and invasion of cancer cells by inhibiting the related pathways and target molecules. Although these findings display the anti-metastatic potential of resveratrol, more patient-oriented clinical studies demonstrating the marked efficacies of resveratrol in humans are still needed.

Introduction

Cancer prevention or treatment by natural dietary agents has drawn attention worldwide due to their ingenious chemopreventive ability (Bishayee, 2009). Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a natural polyphenololic compound belonging to stilbene phytoalexin, which is the stilbene' sub-group of non-flavonoid phenolic compounds (Bastin and Djouadi, 2016; Lee et al., 2016; Waterhouse, 2002). Resveratrol exists in various vegetables such as berries, grapes, peanuts, and red wine (Athar et al., 2007; Carter et al., 2014). Particularly, red wine has been believed to be the main source of resveratrol found in the human, but recent study discovered that peanut sprout contains abundant bioactive resveratrol by accumulating it through germination (Yu et al., 2016). Certain plants may also produce resveratrol to fend off pathogenic attacks, thereby having it serve as an antimicrobial agent (Brittany Wolfe, 2015).

Abbreviations: EMT, epithelial-mesenchymal transition (EMT); TGF, transforming growth factor; ECM, extracellular matrix; MET, mesenchymal-epithelial transition; EGF, epidermal growth factor; MMP, matrix metalloproteinases; CRC, colorectal cancer; RPE, retinal pigment epithelial; TCF/LEF, T-cell factor/lymphoid enhancer factor; LPS, lipopolysaccharide; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; ERK 1/2, extracellular signal-regulated kinase 1/2; Gli1, glioma-associated oncogene homolog 1; ROS, reactive oxygen species; HGF, hepatocyte growth factor; LLC, Lewis lung carcinoma; HUVECs, human umbilical vein endothelial cells; VCAM-1, vascular adhesion molecule 1; HSE, hepatic sinusoidal endothelium; SPARC, secreted protein acidic and rich in cysteine; TPA, 12-O-tetradecanoylphorbol-13-acetate; JNK, c-Jun N-terminal kinase; HRG-β1, heregulin-β1; HER-2, human epidermal growth factor receptor 2; MTA1, metastasis associated 1; DHS, 4,4′-dihydroxy-trans-stilbene; HPIMBD, 4-(E)-[(4-hydroxyphenylimino)-methylbenzene,1,2-diol]; miR, microRNA; Ago2, argonaute2.

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The extensive studies over the past decades have shown that resveratrol has potential to chemopreventive and chemotherapeutic effects. Moreover, recent studies discovered that resveratrol has been shown to have many biological activities related to cancer prevention and treatment by regulating cell division and growth of cancer cells, apoptosis, angiogenesis, and metastasis (Athar et al., 2007; Ndiaye et al., 2011; Saiko et al., 2008). These studies have demonstrated a strong chemopreventive effect of resveratrol in diverse organs undergoing cancer progression such as skin, breast, prostate, lung, pancreas, and ovary (Fremont, 2000; Kang et al., 2012; Kopp, 1998; Roldan et al., 2003; Shankar et al., 2011; Yi et al., 2011).

In addition, these chemopreventive actions of resveratrol have been extensively studied at the molecular and cellular levels, such as cellular signalings, enzymatic pathways, p53-mediated apoptosis (Kroon et al., 2010; Lin et al., 2002; Shih et al., 2004). Nevertheless, the biological activity of resveratrol may be limited by poor absorption and first-pass metabolism, and these limitations lead to low bioavailability (Cottart et al., 2010; Kapetanovic et al., 2011; Walle et al., 2004). Whereas resveratrol is metabolized into sulfated and glucuronidated forms within 15 min of entering the bloodstream, its metabolites, which may be the active principle, circulate in serum for up to 9 h (Saiko et al., 2008). For this reason, some researchers have studied inhibitory effects of resveratrol metabolites or its analogs on cancer progression and metastasis (Savio et al., 2016). For instance, a study has revealed anti-cancer effects of resveratrol metabolite on highly metastatic colon cancer cells (Aires et al., 2013). Dias et al. also showed that two resveratrol analogs (trimethoxy-resveratrol and piceatannol) displayed the higher bioavailability and chemopreventive effects, which reduced tumor volume and decreased tumor growth in the LNCaP-Luc-xenograft model (Dias et al., 2013).

Up to date, anti-tumor mechanisms and pathways of resveratrol have been extensively reviewed in different cancers (Athar et al., 2007; Carter et al., 2014; Smoliga et al., 2011). In the present review, we will highlight the current understanding of the inhibitory role of resveratrol in cancer metastasis developed through fundamental steps such as epithelial- mesenchymal transition (EMT), migration, and invasion processes (Kim et al., 2015). Furthermore, we will also focus on the anti-metastatic effect of metabolites and analogs of resveratrol.

Effects of resveratrol on cancer metastasis via regulation of EMT

EMT and its relevance with cancer metastasis

Epithelial cells normally interact each other via cell-cell adhesion and are bound by a basal lamina at their basal surface. EMT is an critical process through epithelial cells lose their cell-cell interaction and gain mesenchymal phenotype, leading to enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, greatly increased production of extracellular matrix (ECM) components, and rearrangement of cytoskeletons (Jeon et al., 2016; Kalluri and Weinberg, 2009; Son and Moon, 2010). EMT constitutes recognized mechanisms for regulating developmental processes in embryos (Kong et al., 2011), forming mesenchymal cells in injured tissues, and initiating the invasive and metastatic behavior of epithelial cancer (Kalluri and Weinberg, 2009).

The principal difference between normal development and pathological processes such as cancer metastasis is that normal cellular and molecular events follow highly regulated spatial and temporal plans during development, whereas during pathological transformation the order of events may be stochastic and time-independent, or particular events may be bypassed (Larue and Bellacosa, 2005). During tumorigenesis, malignant transformation may be associated with signaling pathways promoting EMT, and EMT may increase the motility and invasiveness of cancer cells and initiate cancer metastasis (Chaffer and Weinberg, 2011; Thiery et al., 2009).

Mesenchymal-epithelial transition (MET), the reverse process of EMT, is also critical for normal development of many tissues and organs, numerous embryonic events, and metastasis of carcinomas (Thiery et al., 2009). Cancer cells in primary tumor lose epithelial properties by E-cadherin repression and penetrate through the basement membrane with increased invasive properties. As an epithelial marker, E-cadherin is expressed in epithelial tissues and mediates cell-cell interactions, and therefore, loss of E-cadherin function has been implicated in cancer progression and metastasis (Beavon, 2000). These cells enter into the bloodstream through intravasation, and then when the cells circulating bloodstream exit the blood vessel, they undergo MET for anchoring at the metastasis site (Chaffer and Weinberg, 2011). This type of cancer is well known as secondary tumor, which means spreading of the primary tumor to other sites and is responsible for 90% of mortalities linked to cancer (Xue and Hemmings, 2013). Therefore, EMT and MET are thought to play a fundamental role during the early steps of invasion and metastasis of carcinoma cells (Boyer et al., 2000).

E-cadherin expression in epithelial tumors can be negatively regulated by a number of zinc finger-family transcription factors, including Snail, Slug, Twist, E12, SIP1 (ZEB2) and δEF1 (ZEB1), each of which has been reported to bind to the E-cadherin promoter to repress its transcription (Bolos et al., 2003, Alves et al., 2007; Conacci-Sorrell et al., 2003; Grooteclaes and Frisch, 2000; Hajra et al., 2002; Huber et al., 2005; Rosivatz et al., 2002; van Grunsven et al., 2003). Snail and ZEB proteins directly bind to E-cadherin promoter to repress its transcription, whereas Twist represses E-cadherin indirectly (Peinado et al., 2007; Yang and Weinberg, 2008). And also the downregulation of E-cadherin is balanced by the increased expression of mesenchymal neural cadherin (N-cadherin), which results in a 'cadherin switch' that alters cell adhesion (Wheelock et al., 2008; Yilmaz and Christofori, 2009). The switch usually refers to EMT and is closely associated carcinoma and metastasis (Rai, 2014; Pyo et al., 2007). The cells undergoing EMT also express high levels of fibronectin and vimentin. Fibronectin is a glycoprotein of ECM that binds to membrane-spanning receptor protein called integrins (Pankov and Yamada, 2002). It plays important roles in cell adhesion and induces EMT (Pankov and Yamada, 2002; Park and Schwarzbauer, 2014). During EMT, epithelial cell adhesion switches from cell-cell contacts to mainly cell-ECM interactions to raise the possibility that fibronectin may have a role in promoting this transition (Park and Schwarzbauer, 2014). Lately, a study suggested that vimentin, a type III intermediate filament protein that is expressed in mesenchymal cells, mediated the reorganization of cytoskeletons to maintain the mechanical integrity in cancer cells undergoing EMT (Liu et al., 2015; McDonald, 1989). The intermediate filament composition changes with the repression of cytokeratin and the activation of vimentin expression (Huang et al., 2012), and the changes in intermediate filament composition may enable cell motility, possibly owing to the interaction of vimentin with motor proteins (Mendez et al., 2010).

In addition, several signaling pathways have been known to be associated with the EMT process. TGF-β, Wnt, and Notch signaling pathways are the key signaling pathways which induce EMT pathways, and they regulate the activation of EMT-inducing transcription factors mentioned above. In recent studies within 5 years, Hedgehog and epidermal growth factor (EGF) signaling pathways also have appeared as the new mechanisms mediating the EMT process on early cancer metastasis (Gao et al., 2015; Li et al., 2016; Vergara et al., 2011). Recently, microRNAs (miRs) that are 22-nucleotide non-coding RNAs and suppress their targets