Multiple molecular targets of resveratrol: Anti-carcinogenic mechanisms.
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Abstract
Plant-derived polyphenolic compounds, such as the stilbene resveratrol (trans-3,4',5-trihydroxystilbene), have been identified as potent anti-cancer agents. Extensive in vitro studies revealed multiple intracellular targets of resveratrol, which affect cell growth, inflammation, apoptosis, angiogenesis, and invasion and metastasis. These include tumor suppressors p53 and Rb; cell cycle regulators, cyclins, CDKs, p21WAF1, p27KIP and INK and the checkpoint kinases ATM/ATR; transcription factors NF-kappaB, AP-1, c-Jun, and c-Fos; angiogenic and metastatic factors, VEGF and matrix metalloprotease 2/9; cyclooxygenases for inflammation; and apoptotic and survival regulators, Bax, Bak, PUMA, Noxa, TRAIL, APAF, survivin, Akt, Bcl2 and Bcl-X(L). In addition to its well-documented anti-oxidant properties, there is increasing evidence that resveratrol exhibits pro-oxidant activity under certain experimental conditions, causing oxidative DNA damage that may lead to cell cycle arrest or apoptosis. This review summarizes in vitro mechanistic data available for resveratrol and discusses new potential anti-cancer targets and the antiproliferative mechanisms of resveratrol.

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Resveratrol as an anticancer nutrient: molecular basis, open questions and promises.
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Abstract
The polyphenol resveratrol is an anticancer nutrient that was shown to inhibit cancer initiation and promotion [Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 1997;275:218-20]. The absorption, transport and metabolism of resveratrol will be reviewed as well as its actions in multiple pathways involved in the regulation of the cell cycle and the induction of apoptosis. Resveratrol acts as a selective estrogen receptor modulator (SERM) and regulates proteins involved in DNA synthesis and cell cycle, such as p(53) and Rb/E2F, cyclins, cyclin-dependent kinases (CDKs) and their inhibitors. Resveratrol affects the activity of transcriptional factors involved in proliferation and stress responses, such as NF-kB, AP1 and Egr1. Part of these events is mediated by mitogen-activated protein kinase (MAPK) and tyrosine kinases (e.g., Src) and leads to the modulation of survival and apoptotic factors [e.g., Bcl2 family members, inhibitors of apoptosis (IAPs), ceramide] as well as enzymes involved in carcinogenesis [cyclooxygenases (COXs), nitric oxide synthase (NOS)], phase I and II enzymes]. Moreover, resveratrol affects the expression and the activity of cotranscriptional factors such as p(300) and sir21. Thus, resveratrol potential as an anticancer chemopreventive and chemotherapeutic agent and its implication in the prosurvival versus prodeath pathway induction will be discussed.
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Fighting cancer with red wine? Molecular mechanisms of resveratrol.
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Abstract
Resveratrol, a red wine constituent, has been known for its cardioprotective effects. Recent data give ample evidence that resveratrol can act as a chemopreventive agent as well. Tumor initiation, promotion, and progression are affected by resveratrol via multiple pathways, which are discussed in this review. Resveratrol has anti-inflammatory effects by countering NF-kappa B and AP-1 transcription and can prevent bioactivation of procarcinogens by interacting with drug metabolizing enzymes. Furthermore, resveratrol exerts antioxidant activities, hence contributing to the prevention of tumor initiation. Growing or metastasizing carcinomas are inhibited by resveratrol through prevention of angiogenesis by inhibiting VEGF and matrix metalloproteases. Induction of apoptosis and cell cycle arrest, important mechanisms for cancer therapy, are stimulated by resveratrol through different mechanisms, e.g., activation of p53 and modulation of cell cycle proteins. Although there has been remarkable evidence for resveratrol as a potent chemopreventive agent in vitro, it seems that the low bioavailability of resveratrol in humans could interfere with a successful in vivo treatment. Nevertheless, resveratrol offers two major advantages over conventional chemotherapy. The cytotoxic effects of resveratrol on healthy cells can be neglected, and, as several pathways leading to chemotherapeutic effects are activated by resveratrol, chemoresistance-inducing mutations in cancer cells can be overcome.
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