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Dossier: Steroid receptors

Resveratrol and cancer: a review

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Summary – The various properties of the stilbene phytoalexin Resveratrol provide interesting new avenues of research in the field of chemoprevention and chemotherapy. A particular emphasis is given on xenobiotic-related carcinogenesis. © 2002 Éditions scientifiques et médicales Elsevier SAS

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The wealth of literature on polyphenols or flavonoids and cancer is in strong contrast with the absence at this time of an established use of any such molecule, either as chemoprevention or chemotherapy. Such a paradox may however not last much longer if resveratrol, the latest discovery in the field, receives clinical confirmation of its promising experimental properties.

Resveratrol has been known for centuries in Asian medicine as Ko-jo-kon, in the form of the powdered root of *Polygonum cuspidatum*, as an anti-inflammatory drug [1]. However, its interest in the field of cancer therapy is much more recent [2]. Other recent reviews may help the reader in his estimation of the interest of resveratrol [3, 4]. In accordance with the multiple properties of resveratrol against tumorigenesis, we have separated in our description the anti-xenobiotic properties (anti-initiation) from the more general cellular effects of this drug (anti-promotion and anti-progression). Finally, we will stress the advantages of resveratrol over previously described flavonoids.

RESVERATROL

Resveratrol and flavonoids evolve from a common synthesis pathway in plants. Only plants can transform phenylalanin into hydroxy-cinnamoic acid. Then, depending on the number of cinnamoyl radicals combined, chalcone synthase can use three to produce flavonoids while pinosylvin synthase (stilbene synthase) uses two to make resveratrol, also known as 3,5,4'-trihydroxystilbene. Resveratrol is a phytoalexin, used by plants to defend themselves from fungal and other forms of aggression. As it is expressed in grapes skin upon attack by *Bothrytis cinerea*, it is found in red wine in substantial amounts (4–20 mg/L) [5, 6].

RESVERATROL AND XENOBIOTIC CARCINOGENS

Phase I cytochromes

Resveratrol displays numerous properties related to very different mechanisms of action. However, the anti-initiation effects appear to us as essentially related to its anti-xenobiotic abilities.

As a polyphenol, resveratrol is an antioxidant and a free radical scavenger. It has therefore been suspected to be responsible for the cardioprotective effects of red wine dubbed the 'French paradox' [7-9]. On the other hand, tobacco smoke contains high amounts of aryl hydrocarbon and dioxin receptor (AhR) ligands such as Benzo[a]pyrene (BaP) and anthracenes, and smoking is a core problem in cardiovascular diseases but also in at least eight differ

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ent kinds of cancer [10]. Moreover, the carcinogenic effects of dioxins in humans are now considered as established, at least on the basis of epidemiology [11, 12].

The major mechanism in tobacco-related carcinogenesis is mutagenesis caused by peroxidative strand breakage or covalent adduct formation on DNA. Adduct formation is essentially caused by oxidation of tobacco smoke compounds such as BaP by monooxygenases (cytochromes P450 1A1, 1A2 and 1B1, CYPs), which turn these inert molecules into highly mutagenic diol-epoxy derivatives. This process releases free radicals responsible for oxidative DNA damage [13]. BaP itself is an agonistic ligand of the AhR, the principal inducer of CYP 1A transcription.

A number of flavonoids being known as ligands of the AhR, and considering the possible role of resveratrol in cardio-protection, we have hypothesized that the two mechanisms may be linked: resveratrol could be both a cardio-protective and anti-tumour drug through the inhibition of AhR-mediated transactivation of CYP genes and subsequent free radical production leading to cellular and DNA damage. This proved to be the case and we have shown that resveratrol is a competitive antagonist for the AhR and efficiently blocks CYP 1A1 induction ex vivo and in vivo in various organs [14]. At the same time, Ciolino's group also reported the inhibition of CYP 1A1 expression by resveratrol but failed to establish the link with AhR competitive binding [15, 16].

Phase II detoxifying enzymes

The AhR is also able to induce detoxifying enzymes, which take advantage of phase I hydroxylation to conjugate carcinogenic xenobiotics into inactive compounds amenable to metabolic elimination. Such phase II enzymes comprise glutathione-S-transferase, uridyl-diphosphoglucuronosyl-transferase and Menadione Oxido-reductase. Inducers of phase II enzymes may therefore be considered as valuable chemopreventers (review in [17]). The transcription of these enzymes is not induced through the classic 'xenobiotic responsive element' (XRE) but through an 'antioxidant/electrophile responsive element' (ARE/EphRE). This latter DNA binding site interacts with several proteins (including the AhR) in a very complex cross-talk. Fortunately, resveratrol inhibits XRE-mediated transactivation but is inactive on ARE-based mechanisms. Thus, the production of detoxifying enzymes is not hampered by resveratrol treatment.

RESVERATROL AND NON-XENOBIOTICAL CARCINOGENESIS

Anti-promotion effects

The chemopreventive effects of resveratrol have been initially shown by the group of Pezzuto on various cancer models unrelated to the xenobiotic metabolism and AhR activation. These authors reported that resveratrol inhibits the constitutive cyclooxygenase-1 (COX1) but not the inducible COX2 [2]. Contrastingly, other authors report that resveratrol inhibits COX2 activity [18, 19] as well as COX2 gene expression [18]. Cyclooxygenases produce prostaglandins from arachidonic acid. These compounds stimulate tumor growth by acting on cell proliferation, angiogenesis and immunosuppression. Cyclooxygenases inhibitors are thus considered as valuable therapeutic agents against various cancers (review in [20]).

More recently, the chemopreventive activity of resveratrol has been linked to its ability to block the NF-KappaB pathway through IkappaB kinase inhibition [21]. This is not surprising since the correlation between general protein kinase inhibition and anti-tumoral properties of natural polyphenols from various plant species has been observed for a long time [22].

Anti-progression effects

Resveratrol induces the differentiation of human promyelocytic cells (HL-60 line) [23] and also decrease tumor growth in a rat model [24]. This latter effect has been linked to the well-documented effect of resveratrol on cell cycle arrest at the G2/M transition [25]. Arrested cells subsequently undergo apoptosis. Interestingly, resveratrol exerts its pro-apoptotic effects on tumor cells alone, while normal cells remain unharmed [26].

Effects on estrogen-dependent tumorigenesis

One concern remain about the estrogenic properties of resveratrol. A confused controversy, presenting resveratrol as anything from estrogen superagonist [27] to full antagonist [28] has been beautifully

solved by Bowers et al.: resveratrol appears to be an agonist for ER β and an antagonist for ER α in a majority of models and in some cases, a very weak agonist of ER α [29]. From these latter studies, it does not appear that resveratrol should be considered as particularly dangerous from the estrogen agonist point of view. On the contrary, several studies suggest that resveratrol may be interesting for the chemoprevention in reproductive organs: Bhat and Pezzuto suggest that resveratrol may exert beneficial cytostatic effect on endometrial cancers, based on ex vivo experiments using the Ishikawa endometrial cell line [30]. By its ability to inhibit CYP 1A1 and 1B1 induction by AhR ligands, resveratrol may also lower 4-hydroxyestradiol production, which is metabolized locally with an important production of detrimental oxidative free radicals [31].

OTHER POLYPHENOLS AND FLAVONOIDS

As stated in the introduction, a vast amount of publications describe putative chemopreventive effects of polyphenols and flavonoids other than resveratrol. Generally, the literature on polyphenols relates to crude plant extracts such as green tea and is therefore difficult to evaluate. Flavonoids have been the object of more extensive studies. With the notable exception of galangin (review in [32]), most flavonoids present a balance of beneficial and detrimental effects [33] or no effect at all [34]. These studies have very often revealed undesirable estrogenic side effects [35] if not outright toxic effects of these substances, such as AhR agonistic effects [36, 37], synergism with other cancer inducers [38] or an increase in hepatic lipids' peroxidation [39].

CONCLUSION

Resveratrol stands alone in the field of polyphenol-based chemoprevention and/or chemotherapy: it is the most extensively studied molecule and apparently the least toxic. Clinical studies using purified resveratrol in the proper pharmaceutical form are necessary to ascertain the interest of resveratrol in the treatment of cancers, especially tobacco-related cancers. In the future, synthetic derivatives of resveratrol with higher affinity for the AhR and better specificity are definitely worth looking for.

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