Biochimica et Biophysica Acta 1852 (2015) 1178–1185

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Resveratrol and cancer: Challenges for clinical translation☆

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ARTICLE INFO

Article history:
Received 14 August 2014
Received in revised form 16 October 2014
Accepted 3 November 2014
Available online 8 November 2014

Keywords:
Resveratrol
Cancer
Clinical trial

ABSTRACT

Significant work has been done towards identifying the health-beneficial effects of the grape antioxidant resveratrol in a variety of bioassay- and disease- models, with much research being focused on its possible application to cancer management. Despite the large number of preclinical studies dealing with different aspects of the biological effects of resveratrol, its translation to clinics is far from reality due to a variety of challenges. In this review, we discuss the issues and questions associated with resveratrol becoming an effective *in vivo* anticancer drug, from basic metabolic issues to the problems faced by incomplete understanding of the mechanism(s) of action in the body. We also explore efforts taken by researchers, both public and private, to contend with some of these issues. By examining the published data and previous clinical trials, we have attempted to identify the problems and issues that hinder the clinical translation of resveratrol for cancer management. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes.

1. Introduction

Worldwide, cancer is one of the most frequently diagnosed diseases and is a major cause of loss of human life. Because of the intense treatment regimens and/or surgeries necessary to treat this malignancy, a diagnosis of cancer puts a major economic burden on the suffering family as well as on communities and society. Alarmingly, approximately 12.7 million cancer diagnoses and 7.6 million cancer deaths were expected to have occurred in 2008 throughout the world [1]. In the United States alone, 1,665,540 new cases of cancer and 585,720 cancer related deaths are estimated for the year 2014 [2]. Interestingly, there are areas throughout the world where certain cancers are less prominent, which could be attributed to prevailing local dietary habits and/or use of natural agents as medicines/remedies [3,4]. In the recent past, increasing research efforts have attempted to make use of these observations and advocate the use of natural agents, alone or in combination with traditional therapeutics for cancer management. The grape antioxidant resveratrol (chemically: 3,5,4′-trihydroxystilbene) is one such agent that has been studied at large for its health-promoting effects, as evidenced from the over 6800 publications available at present on PubMed. Almost one third of these articles have explored the link between resveratrol and cancer, indicating that this natural compound may hold tremendous promise in the field of cancer management.

Resveratrol is a naturally occurring phytoalexin, a substance synthesized *de novo* by plants, to counteract pathogen infections. In preclinical studies, resveratrol has been shown to enhance vascular health by reducing hypertension and counteracting against heart failure and ischemic heart disease in experimental animal models (reviewed in [5]). Further, there is ample evidence that resveratrol protects against high fat diet-induced obesity, improves insulin sensitivity, lowers serum glucose levels in several animal models, and improves diabetic kidney disease in rodents (reviewed in [5]). Similarly, resveratrol has been shown to have neuroprotective effects in experimental models of cerebral stroke [6]. Studies have also suggested that resveratrol can partially mimic the effects of a calorie restricted diet, which is known to slow the aging process and extend lifespan in diverse species ([7] and reviewed in [8,9]). Although the exact mechanisms of the health-promoting effects of resveratrol are still being explored, the promising pharmacologic properties of resveratrol have allowed for its entry into the unregulated nutraceutical sector in the form of over-the-counter nutritional supplement. It is still unclear whether this is a good thing, as the clinical benefits of resveratrol are yet to be realized. Although this interesting compound seems to have potential against a variety of diseases/conditions, one of its most evident health benefits is its ability to elicit chemopreventive as well as therapeutic effects against several cancers [10]. The cancer chemopreventive properties of resveratrol were first discovered in 1997 by Jung and colleagues, when they demonstrated the anti-initiation, anti-promotion, and anti-progression activities of resveratrol in different models [10]. Building on this research, other investigators have shown that resveratrol inhibits tumor growth *in vivo* against several cancer types, which are dose and duration dependent (reviewed in [11]).

Although *in vitro* and animal experimental data are extremely promising for resveratrol's anti-proliferative effects, there is limited

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http://dx.doi.org/10.1016/j.bbadis.2014.11.004
0925-4439/

development regarding its use in clinical settings. One problem with this translation is the limited bioavailability of resveratrol as it is metabolically eliminated from the body extremely fast, so much so that it is difficult to maintain a therapeutically relevant level in the bloodstream [12,13]. Recently, we have advocated the use of other natural agents in combination with resveratrol to improve the overall therapeutic effectiveness, especially for cancer management (reviewed in [14]). One example of this is our recent hypothesis that resveratrol, when given in combination with zinc (Zn), may modulate *in vivo* Zn-homeostasis to enhance the cellular transport of Zn into the prostatic tissue *via* modulating zinc transporter proteins, thereby enhancing the therapeutic efficacy of Zn against prostate malignancy [15]. Similarly, there are considerable ongoing efforts to try to exploit resveratrol's potential against cancer *via* combining it with other compounds/drugs, in order to tackle some of the limitations and to increase the overall therapeutic efficacy.

On the whole, resveratrol has been found to be effective against a number of human cancers in preclinical studies, suggesting that it could be a useful chemotherapeutic agent. A positive property of resveratrol is the fact that it is well tolerated in most patients and appears to have minimal side effects even at very high doses (reviewed in [16]). However, the immense potential that appears to be present in preclinical testing has yet to be realized in human trials. This has been explored in many reviews, including two recent ones that discuss the overall challenges of using resveratrol in humans for multiple conditions [17,18]. In this review, we are focusing on presenting a critical discussion, including relevant clinical studies, to understand the challenges associated with bringing resveratrol into the clinical realm as an anticancer drug. As outlined in Fig. 1, there are specific areas of resveratrol research that need to be extensively explored that may pave the way for efficient translation of resveratrol from *the bench to the bedside*.

2. Bioavailability, absorption and metabolism of resveratrol

The limited bioavailability of resveratrol is perceived as a major hindrance in the potential clinical use of resveratrol for cancer management. *In vivo*, resveratrol is absorbed through the gastrointestinal tract and is rapidly metabolized to its stable glucuronides, sulfates, and hydroxylates. In healthy humans, resveratrol has been demonstrated to be metabolized to its 3- and 4′-O-sulfate, and 3-O-glucuronide conjugates less than 2 h after ingestion [19]. Intestinal bacteria also play a role in the metabolism of resveratrol that contributes to a variation of the fractional ratio of metabolites among individuals. Bode and colleagues have shown that resveratrol can be metabolized by human gut microbiota, resulting in dihydroresveratrol, 3,4′-dihydroxy-trans-stilbene and 3,4′-dihydroxybibenzyl [20]. Pharmacokinetic profiles of resveratrol in healthy volunteers displayed rapid and extensive metabolism to resveratrol-4′-O-glucuronide, resveratrol-3′-O-glucuronide, and resveratrol-3-O-sulfate following single or multiple oral doses of resveratrol between 0.5 and 5.0 g each [19,21]. This does not leave much opportunity for resveratrol to impart its anticancer action, even with a large dose being delivered. Thus, there are ongoing efforts to somehow slow the metabolism of resveratrol to allow for increased tissue exposure in the body. In this direction, we recently proposed some possible scenarios to enhance resveratrol's bioavailability, such as mechanism-based combinations with natural agents that can inhibit the *in vivo* metabolism of resveratrol, nanoparticle-mediated delivery, use of naturally occurring or synthetic analogues of resveratrol, and use of conjugated metabolites of resveratrol (reviewed in [22]).

The most direct way to boost the efficacy of resveratrol is to increase the amount of free resveratrol available at the target organ site. For this purpose, using other moieties, preferably naturally occurring agents, to delay the rapid metabolic elimination of resveratrol, may be useful. In this regard, in a study from our laboratory we have shown that piperine, an alkaloid derived from black pepper (*Piper* spp.) improves *in vivo* bioavailability of resveratrol in mice by inhibiting its glucuronidation [23]. At present, piperine is being considered as a bioavailability enhancer of resveratrol by several private industries. Some other studies further provide reasons to test this combination in greater detail. Huang et al. recently found a synergistic effect of resveratrol and piperine combination on depressive-like behaviors in mice, which may be partly due to the potentiated stimulation of the monoaminergic system in the brain [24]. However, this study did not examine whether or not the addition of piperine affects the bioavailability of resveratrol, as they were focused on determining the mechanism of action. In another recent study, Wightman and colleagues demonstrated that piperine can increase the bioefficacy of resveratrol when co-supplemented in healthy human subjects with regard to cerebral blood flow effects [25]. In this study, co-supplementation of piperine and resveratrol was found to significantly augment cerebral blood flow during task performance without affecting cognitive function, mood or blood pressure. Interestingly, no changes were noticed in resveratrol's bioavailability. This may be due to the metabolic differences in mice *vs.* humans, which may impose a big challenge in the translation of animal data to human studies.

Curcumin, a polyphenolic constituent of the popular South Asian spice turmeric, has also been shown to inhibit glucuronidation in mice by Basu and colleagues [26]. Recently, Malhotra and colleagues demonstrated a synergistic chemopreventive response of curcumin

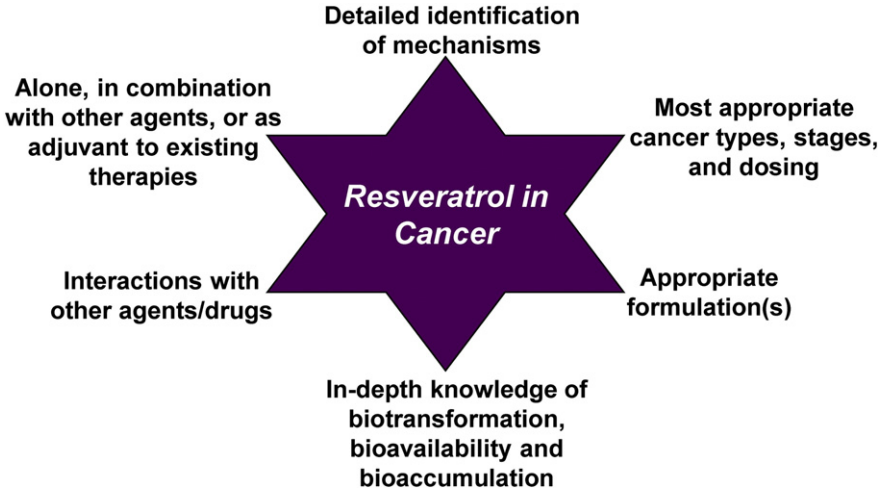

Fig. 1. Specific research areas to be prioritized for resveratrol research. This figure outlines some of the key areas that need to be focused on in order to push resveratrol from being a success in the lab to being an ideal chemopreventive and chemotherapy agent.