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Modulatory potential of resveratrol during lung inflammatory disease

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ABSTRACT

Neutrophils are the first cells to achieve the sites of infection or inflammation in the lungs. The massive accumulation of these cells is associated with acute and chronic lung injury. Therefore, they have been implicated in the pathogenesis of many lung diseases through the release of reactive oxygen intermediates, proteolytic enzymes and Neutrophil Extracellular Traps (NETs). The excessive and continuous release of NETs, fibers composed by decondensed chromatin coated with neutrophil proteins, are associated to the impairment of lung function in different pathological settings.

Flavonoids inhibit the respiratory burst of neutrophils in mammals. However, one of these flavonoids, resveratrol has a particular chemical property. It reduce Cu(II) to Cu(I) form with concomitant formation of reactive oxygen species, which can produce DNA breakage as reported in several in vitro models.

We hypothesize that direct resveratrol administration in lungs can cleave DNA in NETs, improving lung function during acute airway infections or chronic inflammatory lung diseases.

If the hypothesis is correct, the control of NET formation can be used to reduce the inflammatory environment in lung after neutrophil stimuli. Additionally, the production of proinflammatory cytokines by neutrophils could be also diminished by resveratrol administration. In this sense, this flavonoid provides a multifaceted opportunity for treatment of lung diseases with strong or chronic neutrophil activation.

Introduction

Neutrophils constitute the first line of defense against infections by eliminating phagocytosed pathogenic bacteria, fungi and viruses [1–5]. Generally, neutrophils are present in pulmonary capillaries in higher numbers compared to systemic blood even in the absence of inflammatory stimuli [6]. This phenomenon allows neutrophils to migrate into the lungs as a response to an inflammatory insult. During inflammation, neutrophils are activated upon stimulation and migrate into the lungs [7].

Neutrophils recruited to the lungs engulf microbes into a phagocytic vacuole that fuse with intracellular granules [8]. These granules contain an overlapping set of antimicrobial proteins, such as gelatinase, lipocalin, and lysozyme among other proteins [9]. More recently, neutrophils have been shown to possess an alternative mechanism of pathogen killing, designated as Neutrophil Extracellular Traps (NETs). NETs are extracellular structures composed by decondensed chromatin complexed with granule and cytoplasmic proteins [10–12]. These traps bind and kill pathogens by juxtaposing microbes with neutrophil antimicrobial proteins and histones [10,11]. NET formation is accompanied by neutrophil death (NETosis), a non-conventional form of cell death [11–13]. Besides being expressed on NETs, neutrophil elastase and myeloperoxidase also regulate NET formation [14]. Furthermore, histone deimination by peptidylarginine deiminase 4 (PAD4) is a central step to NET formation [15]. Additionally, reactive oxygen species produced by the assembly and activation of NADPH oxidase are also required for NET release [13,16].

Although NETs are released to kill microorganisms and prevent microbial spreading, the excessive NET formation leads to tissue injury. Massive NET production has been demonstrated to be involved in the pathogenesis of several diseases, such as acute respiratory distress syndrome (ARDS), viral infections, cystic fibrosis, asthma and chronic obstructive pulmonary disease (COPD) [6,17–19]. In an inflamed tissue, prolonged or excessive release of cytotoxic molecules anchored on NETs, accompanied by delayed apoptosis of neutrophils, amplify inflammation, increasing tissue damage [20] and reduction of lung function [21–23], as is the case in severe influenza pneumonia, where NETs contribute to lung tissue injury [24].

Current development of therapies to target NETs in inflammatory lung diseases include treatment with recombinant human

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DNase (dornase alfa/pulmozyme) [25,26], anti-histone antibodies [27,28] and antiproteases [29]. However, these therapies require the use of recombinant DNA technologies with high-quality purification. Therefore, the need for alternative approaches to dismantle NETs structure is clear.

Flavonoids, a group of plant secondary metabolites, affect inflammation and particularly neutrophil activity [30]. This group have been attributed to the capacity of plant phenols to prevent activation of nuclear factor-kappa B (NF-κB) and the subsequent overexpression of pro-inflammatory mediators (cytokines, adhesion molecules, cyclooxygenase-2, 5-lipoxygenase, myeloperoxidase or inducible nitric oxide synthase), and to inhibit neutrophil apoptosis [20]. However, a flavonoid member, resveratrol has an additional property; it is capable of inducing oxidative damage in DNA in the presence of certain transition metal ions [31–33]. This characteristic can be used to develop chemical modulators of NETs.

Hypothesis

We hypothesize that resveratrol (Rsv) could act as a DNA cleavage agent of NETs, produced by inflammatory lung diseases and microbial infections improving lung function. Our hypothesis is represented in Fig. 1.

For an easier analysis of our hypothesis, we support in two interrelated points based on Rsv properties: DNA-damaging activity and bioavailability in the lungs.

DNA-damaging activity of resveratrol

Rsv (3,4′,5-trihydroxy-*trans*-stilbene) is a phytoalexin polyphenolic found in grape skins, peanuts, and red wine, has been reported to have a wide range of biological and pharmacological properties [34–36]. These chemical properties facilitate their permeability across cellular membranes to interact with multiple protein targets [37], binding to DNA and chelating metal ions. These properties combined with their pro-oxidant activity convert this polyphenol in a multifaceted component with great therapeutic potential. Rsv forms a complex with intracellular cooper metal [Cu(II)], leading to its reduction [Cu(I)] with in situ formation of reactive oxygen species (ROS), which induce DNA breakage. Several experiments showed DNA damage mediated by the combined reaction Rsv ± Cu(II) in different DNA substrates (bacteriophage DNA, plasmids, calf thymus DNA and intracellular DNA of human peripheral lymphocytes) [31–33].

Fukuhara and Miyata proposed that Cu(II)-dependent DNA damage by Rsv is caused predominantly by a copper ± peroxide complex with diffusible oxygen species production [38]. These authors have further suggested that the reaction occurs without oxygenated transformation of benzene nuclei. However, Ahmad et al. [31] indicate that "transformed species" of Rsv, possibly in an oxidized form, are produced in the presence of Cu(II). It is possible that more than one mechanism of DNA cleavage is involved, but in consensus Cu ions are essentials to oxidative reaction to account. Other metal ions such as [Co(II), Fe(II), Mn(II), Mg(II) and Ni(II)] do not produce DNA cleavage reaction as they do not interact with Rsv [31]. A summary of putative prooxidant reaction

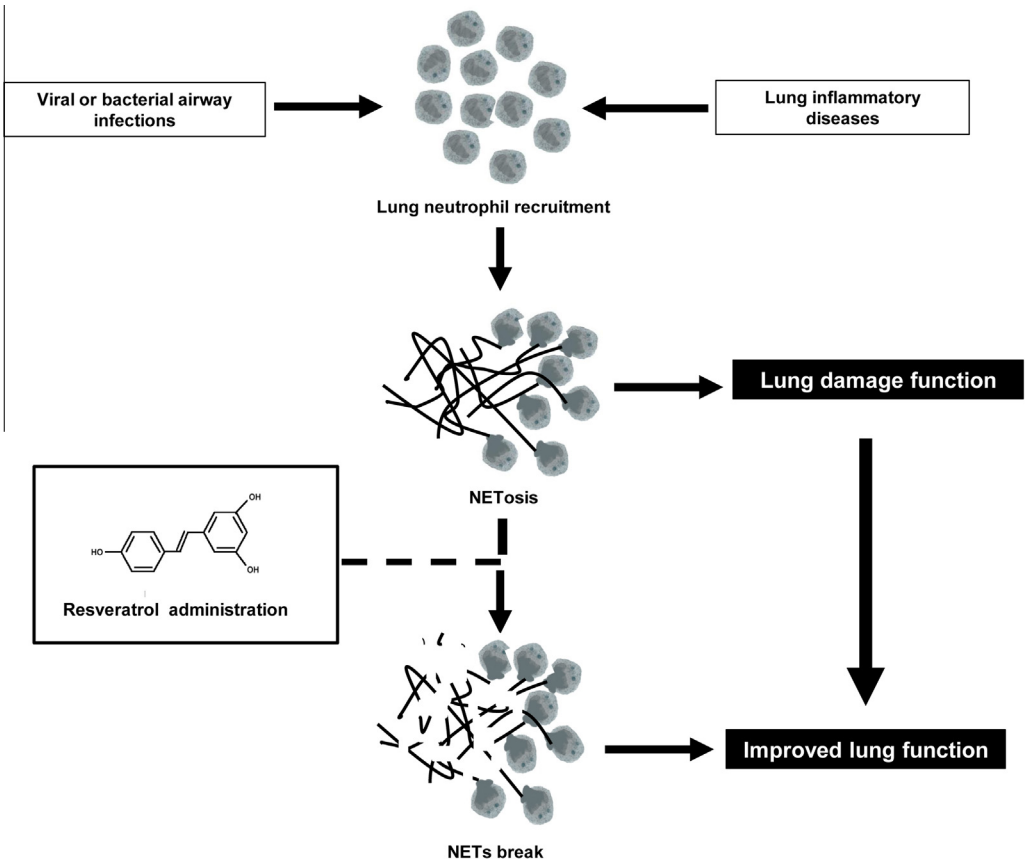

Fig. 1. Schematic representation of hypothesis for resveratrol action on NETs. Viral or bacterial airway infections or inflammatory diseases induce neutrophil recruitment and activation in the lungs. These stimuli can promote NETosis, which leads to lung tissue damage and impair lung function. Resveratrol administration can cleave NETs and induce the improvement of lung function.

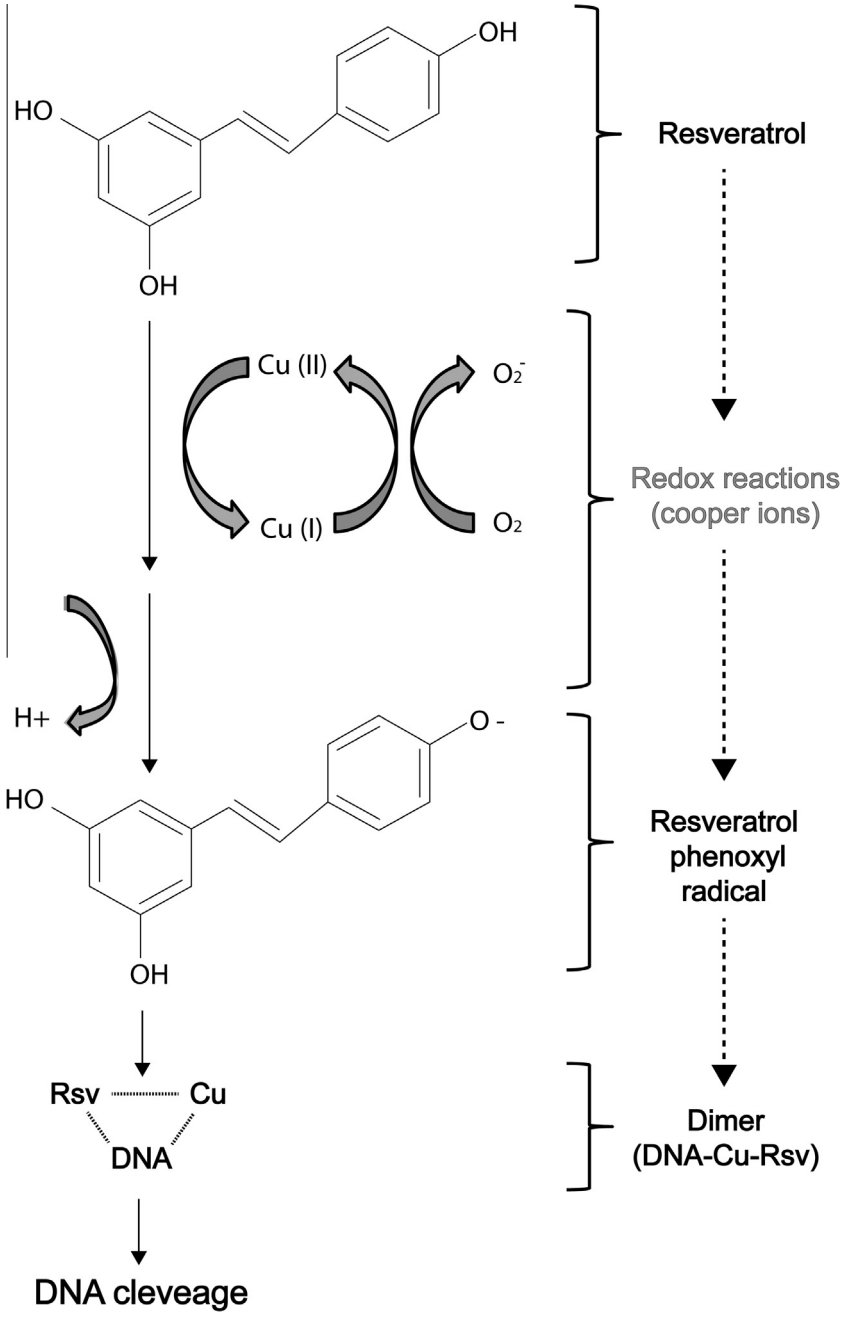

Fig. 2. Putative mechanism showing mobilization of endogenous copper íons mediated by resveratrol. This figure was adapted from Villegas et al. [63].

mediated by Rsv in presence of cooper ions is represented in the Fig. 2.

Cooper metal bioavailability becomes a limiting factor for Rsv ± Cu(II) reaction to induce DNA breakage. The real quantification of cellular copper concentration is imprecise. It is due to the non-existence of free cooper in the nature [39,40]. Extracellular and intracellular cooper is bound to cellular components (i.e., cooper chaperones) [40,41]. Independent of these difficulties, cellular copper concentration could be sufficient to complex to Rsv to catalyze DNA damage reaction, which could support our hypothesis.

Copper ions are closely associated with bases of DNA being a normal component of chromatin. Different levels of copper promote structural and functional modifications of DNA and induce chromatin condensation in a concentration-dependent manner [42]. For this reason, copper is one of the etiological factors most described in neurodegenerative diseases (Alzheimer's disease, Parkinson, Huntington and familial amyotrophic lateral sclerosis), where an abnormal metal accumulation is associated directly to the pathological state [43].

In situ endogenous copper ions are mobilized easily from DNA by chelating agents and the consequent induction of pro-oxidant reactions [31,44]. Gutteridge showed that cooper is loosely bound copper to DNA, which is available for binding to the chelating agent, as 1,10-phenanthroline that cause internucleosomal DNA fragmentation [31,45]. Rsv would react in a similar manner that 1,10-phenanthroline with the intracellular cooper [33]. It is possible that such loosely bound copper of NETs can also be mobilized by Rsv and cleave reaction can account. So far, to our knowledge, any study has shown metal ions associations to NETs. However,

it is possible that NETosis process could maintain cooper ions associated to chromatin after neutrophil death in inflammatory environments.

In the lungs, an alternative mechanism should compensate the possible low ion concentration of cooper in NETs. For example, a redox cycle of this metal ion should result in increased rate of DNA hydrolysis in situ on NETs in the presence of Rsv. Ahmed showed that Cu(I) recycled in the reaction [31,46]. This study suggests that "oxidized species" of Rsv are also able to catalyze the reduction of recycled copper ions [Cu(II)]. It facilitates to obtain cooper concentration necessary to DNA break to takes place.

Other alternative is the administration of Rsv together with Cu (II) ions to the lungs, but it should be performed with precautions, since high levels of cooper can to be toxic to the respiratory tract [47].

Resveratrol bioavailability in the lungs

The bioavailability of a chemical compound is defined by the capacity to become available to the target tissue after its administration [48]. Current knowledge on metabolism and bioavailability of Rsv has been described in humans, dependent on route of administration. The oral bioavailability of Rsv is very low due to its rapid and extensive metabolism, elimination through ABC transporters and incomplete intestinal absorption [49–51]. It is important to note that lungs (along with gut and liver) are third in a series of three putative metabolism sites, which orally ingested Rsv must cross before entering the circulation. First step metabolism by gut, liver and lungs can synergistically promote total body clearance of Rsv [52]. Considering our hypothesis, oral administration of this polyphenol is a problem for therapeutic use. In addition, metabolism of Rsv would produce unexpected difficulties. The metabolism of this polyphenol involves complex pathways that produce alterations on its structure trough glucuronides and sulfates conjugations [53]. In in vitro experiments, Rsv induces DNA damage in a non-metabolized form (above-discussed in previous section). Chemical modifications on Rsv could be important determinants of its pharmacological activity [54]. However, other study suggest that resveratrol's glucuronide or sulfate conjugates may be unconjugated at the target sites of action, thereby releasing to elicit his biological activity [55]. In addition, was described that resveratrol's glucuronide has comparable or same degree of activity that non-metabolized Rsv depending on the test model [56]. In this sense, more studies will be required to understand its effects on the DNA damage.

Aerosol version of Rsv for inhalation probably would be a better option. Ulterior work showed that atomization inhaled Rsv could alleviate rat COPD lung injury inducing an amelioration of pathological changes [57]. Considering our hypotheses, this route of administration offer two major advantages. Firstly, it is a non-invasive manner to deliver drugs or compounds rapidly and directly into the airways. In a second point, aerosol Rsv could increase directly the polyphenol-DNA interactions (without metabolized intermediate, simulating in vitro experiments). In our case, Rsv would interact with extracellular DNA derived from NETosis process. In addition, several approaches to improve inhaled versions of Rsv using vehicles were developed, ie Rsv-loaded gelatin nanoparticles used to treat lung cancer [58] or inhalable microparticles containing budesonide and Rsv to reduce alveolar inflammation [59]. However, the delivery of Rsv directly to the lungs continues to be a challenge.

It is noteworthy that we could not discard the use of other routes of Rsv administration. Rsv administered by an intraperitoneal (IP) route, inhibits airway inflammation, and airway remodeling which are the main contributors to airway hyper reactivity and irreversible lung function loss in rats [60]. However, this route of Rsv delivery has similar availability limitations of oral administration in humans. Additionally, abdominal pain is a common and undesired consequence of the IP route of drug delivery, as described for chemotherapy treatments [61].

We focused our hypothesis to improve lung function using Rsv during Netosis promoted during inflammatory lung diseases. However, other stilbenoid, piceatannol, was described with similar properties (DNA breakage in presence of cooper ions) [62]. Given that the biological properties of Rsv has been more studied, we decided to explore Rsv for this hypothesis, but we do not discard the potential of piceatannol to improve lung function.

Conclusion

Resveratrol could act as a DNA cleavage agent of NETs, produced by inflammatory lung diseases or viral and microbial infections. In this sense, this study could help researchers to develop chemical modulators based on resveratrol to improve lung function.

Conflict of interest statement

The authors declare that no competing interests exist.

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