● **PERSPECTIVE**

How does resveratrol influence the genesis of some neurodegenerative diseases?

Advancing age and increased lifespan of human populations worldwide in the mid-nineteenth century, have led to a significant increase in the incidence of neurodegenerative diseases, one of the major cause of disability and death for most of those affected. Neurodegeneration is one of the biggest public health problems in modern society also because effective pharmacological interventions for prevention and treatment of the disease, are lacking. Based on the premise that oxidative stress underlies a number of neurodegenerative diseases, the identification of novel antioxidants as potential therapeutics is a prolific area of neuroscience research. There is also a close relationship between specific therapies and the induction of oxidative stress in chronic neurodegeneration, such as the case of levodopa in patients with Parkinson's disease (Müller et al., 2014).

Although the different neurodegenerative diseases manifest in distinct neuronal cell types, oxidative stress and suppression of neuronal survival signals are common to many of these pathological conditions and appear to be highly relevant targets for treatment. Growing evidences suggest that at the pathological level, almost all neurodegenerative diseases share common features such as the iron accumulation and the generation of misfolded protein deposits. Furthermore, it was shown that the oxidative stress markers precede the pathological lesions of neurodegeneration, see **Figure 1**.

The vulnerability of the nervous system to reactive oxygen species (ROS) is due to its high bioenergetics and oxygen requirements. In fact neurons have high adenosine triphosphate (ATP) demand and they are largely responsible for the brain's massive consumption of oxygen in the respiratory chain; this coupled with the high content of lipid and easily mobilizable iron from several areas of the brain can stimulate the generation of ROS. The above motivates research efforts to identify new antioxidants as neuroprotective drugs, because strategies aimed at limiting free radical production reducing oxidative stress and its damage may slow the progression of neurodegenerative diseases. We have studied the antioxidant properties of various molecules on red blood cells and taking advantage of these findings, we tried to correlate the antioxidant effects found with potential beneficial effects against neurodegenerative diseases (Galtieri et al., 2010; Tellone et al., 2012, 2014, 2015).

Recently, we have focused on the potential therapeutic effects of an antioxidant compound as resveratrol (RV) or 3,5,4′-trihidroxy-trans-stilbene an antifungal molecule of the stilbene family produced in a variety of plant species. RV chemical structure, is characterized by two phenol groups in which the presence of conjugated double bond makes the electrons more delocalized and easily transferable. Just the ability to transfer hydrogen atoms or electrons to the free radicals makes RV an efficient free radical scavenger and a potent antioxidant, see **Figure 2** (Hussein, 2011; Iuga et al., 2012).

Interestingly, RV location in the cellular compartments is strictly related and increases the antioxidant properties of the drug, because the polyphenol interaction with the membrane bilayer prevents lipid peroxidation and in blood, intraerythrocyte RV by interacting with hemoglobin, may protect the protein against oxidative damage (Tellone et al., 2014). In addition, RV mediates the activation of sirtuin-1 (SIRT1) a deacetylase protein with potential therapeutic targets in a variety of human diseases (Herskovits and Guarente, 2013).

In Tellone et al. (2015), we collected knowledge on many RV molecular targets and tried to explain or partly support the effectiveness of the drug a therapeutic agent for neurodegenerative diseases, see **Figure 3**.
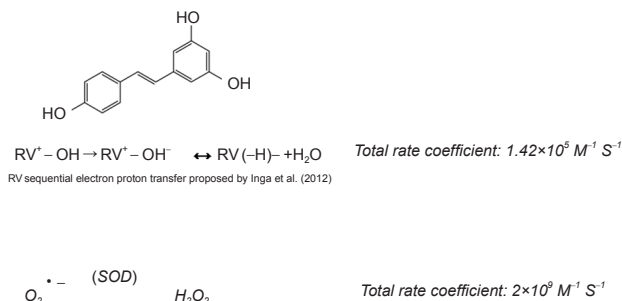
In this light, the interaction of the drug with SIRT1 certainly produces several beneficial effects against Alzheimer's disease (AD). In fact RV, potentiating SIRT1 activity positively regulates α-secretase promoter transcription, a protease which processes the amyloid precursor protein (APP) along a non amyloidogenic pathway precluding Aβ generation. Additionally, SIRT1 can directly deacetylate Tau protein, the main constituent of neurofibrillary tangles and primary marker of AD. The removal of these acetyl groups exposes Lys residues to ubiquitin ligases so that Tau protein could be marked for proteasomal degradation. A further protective role of RV-SIRT1 is the deacetylation and the subsequent inhibition of p53 tumor suppressor gene, whose upregulation and overexpression is commonly associated with Tau hyperphosphorylation, neuronal damage and cell death (Cohen et al., 2011). Besides, the p53 reduced activity affects and in turn inhibits GSK-3β, one of the major glycogen synthase kinase involved in the Tau modification and neurofibrillary degeneration. Tau pathophysiological phosphorylation is also limited by activation of calcium/calmodulin-dependent protein kinase kinase-β (CamKKβ) promoted by RV through the increase of intracellular calcium levels and activation of AMP protein kinase (AMPK).

Inhibition of p53 and the enhancement of SIRT1 activity by RV is also important for the protection of neuronal cells against the mutant polyglutamine huntingtin protein (m-htt) toxic effects occurring in Huntington's disease (HD). People with HD have an abnormally high number of DNA sequence called "CAG", in the coding region of the gene on chromosome 4. The expanded CAG segment leads to the production of an abnormally long version of the htt. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons. Overexpression of these htt fragments and p53 activation in HD increase mitochondrial oxidation and result in a gain of function mechanosensory defect that is the main cause of the pathology. RV treatment can effectively counteract the progression of HD also improving the mitochondrial function *via* a pathway in which SIRT1-AMPK and peroxisome proliferator-activated receptor-α coactivator 1α (PGC-1α) play a pivotal role (Tellone et al., 2015). RV stimulates PGC-1α, the peroxisome proliferator-activated receptor gamma coactivator-1 alpha a potent stimulator of mithocondrial biogenesis and respiration through its interaction with SIRT1. PGC1α when stimulated, regulates the expression and activities of ROS scavenging antioxidant enzymes and therefore counteracts oxidative stress (Higashida et al., 2013).

Besides, RV inducing activation and expression of SIRT1 also protects against pathological α-synuclein aggregation in Parkinson's disease (PD). α-Synuclein is a little protein encoded by a gene located in chromosome 4. Mutation in this gene leads to the overexpression of the α-synuclein protein, and its aggregates were found to be the major components of Lewy bodies, the
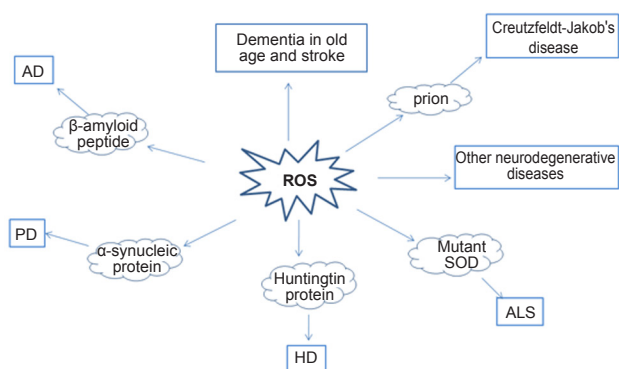
Figure 1 Oxidative stress and main neurological lesions.
AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; HD: Huntington's disease; PD: Parkinson's disease; ROS: reactive oxygen species; SOD: superoxide dismutase.

$$RV^+ - OH \rightarrow RV^+ - OH^- \leftrightarrow RV(-H) - +H_2O$$

Total rate coefficient: $1.42 \times 10^5\ M^{-1}\ S^{-1}$

RV sequential electron proton transfer proposed by Inga et al. (2012)

$$O_2{}^{\bullet -} \quad \overset{(SOD)}{\longrightarrow} \quad H_2O_2$$

Total rate coefficient: $2 \times 10^9\ M^{-1}\ S^{-1}$

Figure 2 Scavenger ability of RV for hydroxyl radical (rate constant) compared with natural antioxidant SOD.
RV: Resveratrol; SOD: superoxide dismutase.
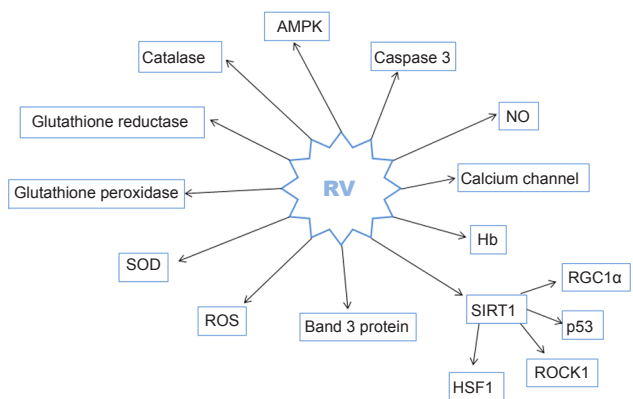
Figure 3 RV main targets for neuronal protection.
AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; HSF1: heat shock factor 1; NO: nitric oxide; PGC1α: peroxisome proliferator-activated receptor-γ coactivator 1α; ROCK1: Rho-associated coiled-coil-containing protein kinase 1; ROS: reactive oxygen species; SOD: superoxide dismutase; SIRT1: sirtuin-1.

hallmarks of PD.

In detail, SIRT1 activates heat shock factor 1 (HSF1), which in turns affects heat shock proteins 70 (hsp70); hsp70 regulates homeostasis of cellular proteins decreasing the formation of abnormal α-synuclein aggregates. Another path of RV beneficial modulation in cellular model of PD is implemented through the downregulation and partial inhibition of GSK-3β because

α-synuclein is a substrate for GSK-3β phosphorylation (Li et al., 2014).

Activation of SIRT1 by RV treatment has been shown to decrease proteotoxic stress derived from misfolded superoxide dismutase 1 (SOD1) aggregates in amyotrophic lateral sclerosis (ALS) (Herskovits and Guarente, 2013). Zhao et al. (2011) reported that RV through the overexpression of PGC1α improved motor performance and survival in a mouse model of ALS.

In conclusions, all these studies provide the proof that the RV has a strong scientific support to develop as a new therapy treatment for neurodegenerative diseases. Given that, the drug is not only active scavenger of free radicals but also acts as modulator of pro-survival or pro-apoptotic signaling pathways. As a result, this compound may have a greater potential for therapeutic success than drugs with only one mechanism of action.

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