Chapter 7
Bioreactivity of Resveratrol Toward Inflammation Processes

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Keywords Cardiovascular diseases • French paradox • Functional food • Red wine • Sirtuins

1 Dietary Polyphenols

To adapt to or mount defenses against their often unfavorable environment, plants produce many non-energy compounds called secondary metabolites (e.g., flavonoids, polyphenols), numbering between 5,000 and 8,000 of such currently known substances. They protect against radiation, microbial infections, oxidizing stress, hydric, or chemical stress and even, through pigments and odorant molecules, enhance pollination, or protect against predators. Similarly, these plant microconstituents often provide valuable bioactive properties in humans and animals for essential physiological function (signaling, gene regulation, acquired or infectious disease prevention, etc.). The essential biochemical processes put in place by sometimes primitive organisms have been selected through evolution and are generally preserved in all living beings. With hindsight, this can be exemplified with the substance called resveratrol, the well-known polyphenol from grapes that plays an essential role in wine as an elicitor of the natural defenses, which, interestingly, has been shown to be a protector of health in humans. For some researchers, this is an anti-infectious agent against pathogenic microorganisms such as *Botritis cinerea.* In humans, it can delay, or even block, the appearance of predominant diseases such as atherosclerosis, diabetes, cancer and inflammation. At the same time, it is considered that regular consumption of green vegetables, fruits,

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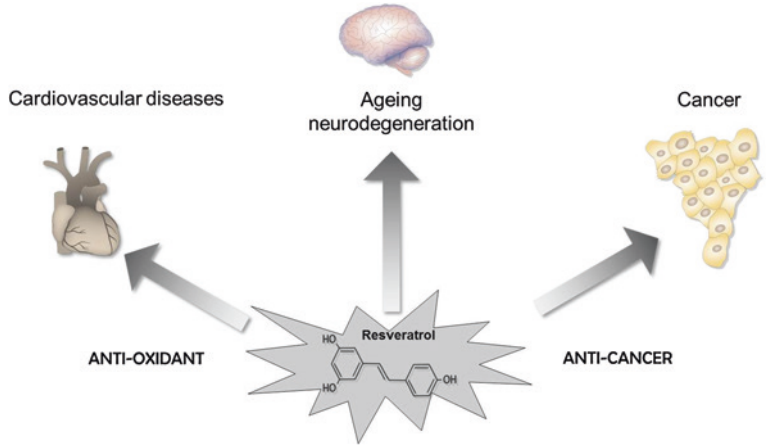

Fig. 1 Resveratrol, a beneficial molecule for human health

fiber, and fish proteins, accompanied by daily physical exercise has a protective effect against the appearance of disease and is consequently a factor of longevity. Grapes, like tea and coffee, soy, peanuts, cacao, apples, onions, cabbage, broccoli, tomato, almonds, olive oil, pomegranates, and red berries (blueberries, black currants, raspberries), etc., are rich in polyphenols (both colored and uncolored) and in vitamins possessing powerful antioxidant properties.

2 Resveratrol: A Unique Polyphenol from Vine

Resveratrol (or *trans*-3′, 4, 5′-trihydroxystilbene) (Fig. 1), as far as we know today, is the grape vine's main defense molecule (so-called phytoalexin) and is most particularly massively produced in response to a fungal attack. Although other plants belonging to around 20 other species also synthesize resveratrol including nonedible plants such as *Polygonum cuspidatum*, known to be rich in resveratrol, and *Veratrum album* (European White Hellebore or White Veratrum, found for instance in the plateaux of the Haut-Doubs region near the Jura mountain in France, from which the name resveratrol originates) (Aggarwal and Shishodia 2006). A few are edible (except for peanut plants in which resveratrol is found in the seeds, or in blueberries). Historically, Asian civilizations did not commonly cultivate grape vines and therefore were not familiar with resveratrol. Nonetheless, their pharmacopeia included extracts of *Polygonum cuspidatum* roots as a vasorelaxant and preparations based on *Yucca schidigera* for their antimutagenic properties. These two medicinal plants have been identified over the past few years as rich in resveratrol. Langcake and Pryce detected this new molecule in grapes and wine after infection of the grapevines by *Botrytis cinerea* (Langcake and Pryce 1976). The *trans (E)* isomer of resveratrol is the most abundant and active form of resveratrol as compared to the *cis (Z)* isomer. In grapes

resveratrol mainly accumulates in a glycosylated conjugated state (piceid). Some di-methoxylated derivatives are also present (pterostilbene) as well as resveratrol oligomers (ε-viniferin, a dimer, and hopeaphenol, Renaud et al., showed that a large cohort of moderate consumers of wine presented lower cancer mortality (Renaud et al. 1998). Interestingly, over the past few years new properties of resveratrol have been discovered, at least in laboratory mammals, such as its possible beneficial role in longevity, (Howitz et al. 2003) prevention of neurodegenerative disease, (Parker et al. 2005) delay of cerebral aging, (Chan et al. 2008; Ritz et al. 2008) maintenance of a high level of physical activity in mice subjected to a diet including resveratrol, (Baur et al. 2006; Lagouge et al. 2006) and the prevention of oxidative stress (OS) in ischemia-reperfusion during organ transplantation (see Explanatory Box 1. For resveratrol, Sirtuins and aging) (Hassan-Khabbar et al. 2008).

Explanatory Box 1: Aging, Epigenetics, and SIRT (Human Sirtuin)

During the last couple of decades, many beneficial effects have been ascribed to resveratrol. These include not only antioxidant properties but also various chemopreventive, anticancer properties, a beneficial influence on the cardio-vasculature and diverse antimicrobial activities to mention just a few. This chapter will address some of these activities and their underlying cellular mechanisms in more detail.

Recently, resveratrol has also fuelled a rather different debate. It seems that this compound is able to slow down aging and increase the lifespan of some mammalian test animals. Not surprisingly, these findings have stirred up a rather intense debate, given the implication that it might be possible to delay aging in humans as well, and hence to achieve longevity by taking certain natural products, either as food or food supplements or even as anti-aging drugs. Here, the debate goes well beyond the more traditional 'anti-aging' crèmes which are commonly used in cosmetics to protect against skin damage by UV-radiation or free radicals. It appears that substances such as resveratrol not only simply protect the organism from external stresses, but retard the natural aging process of cells and the organism as a whole.

Nonetheless, such 'anti-aging' pills are not just part of science-fiction or a clever decoy to transfer money down the age pyramid. There is some quite convincing scientific evidence which points towards epigenetic effects associated with resveratrol (and also other natural products, including xanthohumol from hop). In brief, such compounds interfere with key epigenetic processes. Xanthohumol, for instance, may chemically modify relevant lysine and/or arginine residues of specific histones and hence cause a state resembling (hyper-)acetylation, a detachment of DNA and an (over-)expression of certain proteins. These proteins may, for instance, assist the cell in functioning normally, to differentiate and also to enter apoptosis if any serious damage has occurred. Indeed, an increase of histone acetylation is often desired and there

are certain drugs, such as the hydroxamic acid vorinostat, which cause this state by inhibiting the enzymes responsible for the controlled removal of such acetyl groups, i.e., the histone deacetylases (HDACs). Vorinostat belongs to the SAHA-type HDAC inhibitors and is used in the treatment of cutaneous T cell lymphoma.

Resveratrol, in contrast, seems to act more indirectly by activating a specific class of HDACs, namely (some of) the sirtuins (SIRT enzymes). These enzymes remove acetyl-groups from histones and hence decrease acetylation. In contrast to the more common HDAC inhibitors, SIRT *activators* therefore decrease the acetylation status of specific histones. This results in a tighter binding of DNA and a *reduced* expression of specific proteins. As some of the proteins down-regulated by these processes actually promote aging, the sirtuins seem to delay aging (and promote DNA repair). Taken together, the activation of sirtuins by compounds such as resveratrol may therefore delay aging and hence indeed increase the lifespan of the organism affected. The notion of longevity drugs is therefore not just a pipedream, but may indeed possess a rather solid biochemical basis related to epigenetics.

3 Antioxidant Properties of Resveratrol

Antioxidants, both endogenous and supplied by the diet, are essential in the vital processes because cell aging is directly related to the presence of free radicals, oxygenated or others, presenting a lone electron that is chemically very reactive. Thus, one of the mechanisms of action of an antioxidant is to scavenge oxygen free radicals (Fig. 2). The other mechanism that an antioxidant uses is to stimulate the cell's antioxidant defenses (e.g., enzymes detoxifying free radicals). Given their content of hydroxyl chemical functional groups related to their benzene nuclei (or phenols), phytophenols have essential antioxidant properties. It should be remembered that living mammalian cells naturally produce oxidant compounds, such as some types of free radicals that present a highly reactive single electron (e.g., superoxide radical anions, etc.,) (Fig. 2). These free radicals have dual roles, one defending the body with bactericidal or antiviral effects (produced by macrophages), the other producing harmful effects by altering the essential macromolecules of life: DNA breaks, peroxidation of lipids, or oxidation of proteins. These free radicals are for the most part produced by the mitochondria in which the oxygen from breathing is corrupted to superoxide radical anion. Their toxic effect is the source of the transformation of healthy cells into cancerous cells as well as cell aging. Polyphenols therefore trap single electrons by making them mobile within the polyphenol molecule and therefore much less reactive to neighboring molecules. Concomitantly the polyphenols oxidize, however, with the phenol groups

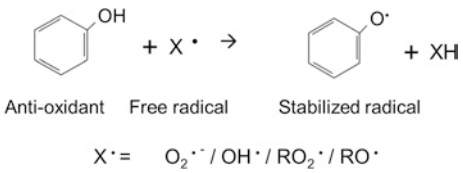

Fig. 2 Anti-oxidative properties of (poly-) phenols

becoming quinone groups, which in some cases (when polyphenols are in excess) can also become pro-oxidants. In conjunction with polyphenols, vitamins C and E also contribute to the antioxidant potential brought by fruit and vegetables. Resveratrol has been established as a powerful antioxidant with a direct impact on oxidative stress. Many tests are available to measure the antioxidant potential of a fluid or an extract, e.g., the measurement of malondialdehyde, isoprostanes, the occurrence of 8-hydroxydesoxyguanine in DNA, etc.

4 Bioavailability

In nutri-pharmacological potency or in toxicology, the notion of bioavailability is essential. This concerns the processes of absorption, transformation (metabolism), elimination (excretion), and the pharmacokinetics. It is known that resveratrol, which is found mostly in the glycosylated form in grapes and wine, undergoes deglycosylation by the intestinal flora and by glycosidases at the surface of enterocytes and is then absorbed in this form (called aglycone). Its rapid transfer through the cell membrane is mediated by a passive diffusion phenomenon accompanied by a facilitated diffusion process because resveratrol is amphiphilic (soluble in both hydrophobic medium, such as membrane phospholipids, and hydrophilic medium such as extracellular or cytoplasmic spaces) (Lancon et al. 2004). Resveratrol (all or in part) is then transformed (metabolized) by conjugating enzymes (UDP-glucuronyl-transferases, sulfotransferases) to turn it more hydrosoluble, e.g., in a glucuronide or sulfate form (Lancon et al. 2007). Resveratrol is also converted by a hydroxylated form, the piceatannol or a hydrogenated form at the conjugated double bond between the two phenolic groups. The elimination of resveratrol and its by-products by the intestinal cells, and therefore their passage in the bloodstream, involves the intervention of ATP-dependent efflux pumps called MDRs (multidrug resistance proteins) located in the cell's plasmic membrane. The passage of these by-products through the liver accentuates their metabolism and part of the conjugated forms is recycled back to the aglycone (the active form), which is distributed throughout the body. From a pharmacokinetic point of view, resveratrol is rapidly absorbed with a plasma peak between 15 and 30 min and a concentration depending on the quantity ingested, which is on the order of the micromolar (Colin, Ph.D thesis, University Bourgogne, Dijon, France, 2008). Conjugated resveratrol is found eliminated in the feces and urine.

A general, recurrent, and complex question in this research area is "can resveratrol concentrations inducing an *in vitro* effect be reached *in vivo*?" The current knowledge is as follows. (1) the plasmatic resveratrol concentrations can reach micromolar levels in animal and humans receiving pharmacological doses of resveratrol in resveratrol-supplemented diet. Moreover, the plasma level of polyphenols represents just a part of the blood content since these molecules largely accumulate in blood cells (Ginsburg et al. 2011) and (2) the plasmatic resveratrol concentration does not reflect tissue concentrations since several papers report accumulation of resveratrol in the liver (Bertelli et al. 1998). In addition, we have shown that resveratrol can accumulate in hepatic cells not only through diffusion, but also through active carrier-mediated uptake (Lancon et al. 2004). In colon intestine cells, raise up to 40 micromolar (Patel et al. 2010). This concentration is compatible with those required for resveratrol binding to and inhibition of enzymes such as COX1 (cyclo-oxygenase 1) and COX2 or for stimulating the integrin alpha V beta 3 receptor (Calamini et al. 2010; Lin et al. 2006).

5 Bioactivity of Resveratrol

Resveratrol has been established as a powerful antioxidant with a direct impact on oxidative stress. Indeed, in 1995 it was shown that the powerful antioxidant properties of resveratrol were capable of preventing the oxidation of LDL cholesterol and therefore to protect the arteries against atherosclerosis (Fig. 1) (Goldberg et al. 1995).

Resveratrol has also been shown to inhibit lipoxygenases and cyclo-oxygenases (that synthesize pro-inflammatory mediators from arachidonic acid), protein kinases (such as PKCs and PKD), receptor tyrosine kinases and lipid kinases, as well as IKKα, an activator of the pro-inflammatory NF-κB pathway (Delmas et al. 2011). In addition, resveratrol regulates apoptosis (Colin et al. 2011) and cell cycle progression and down-regulates the MAP kinase signaling pathway, the NF-κB pathway, and the AP-1 (Activator Protein 1) pathway (Delmas et al. 2002). Resveratrol interferes with many other cell functions such as phosphorylation signaling and gene regulation. This requires that mechanisms of action also include activation of membrane proteins, such as recruitment of death receptors to set off apoptosis (Delmas et al. 2003), activation of kinases, such as AMP-kinase and CDKs (cyclin-dependent kinases) (Delmas et al. 2002), or activate nuclear receptors to estrogens regulating the transcription of target genes. Recent data showed that resveratrol monosulfate and bisulfate derivatives display biological effects, such as the inhibition of COX1, COX2, $^{\bullet}$NO production and iNOS expression, or the activation of Sirtuin 1 (SIRT1) which are compatible with anticancer effects. Recently, we have discovered a resveratrol-dependent new regulatory pathway through the regulation of microRNA activities (see further below) (Hoshino et al. 2010).

6 Anti-inflammatory Properties of Resveratrol

6.1 Resveratrol and Inflammation; Systemic Effect

Inflammation is the result of a complex immune response to pathogens, allergens, damaged cells, tissue injury, or toxic molecules (Fig. 3). For the body, this inflammation is beneficial and self-contained, yet may become chronic. Chronic inflammation has been linked to many pathologies such as vascular alterations, neurodegenerative diseases, rheumatoid arthritis, chronic asthma, multiple sclerosis, psoriasis, inflammatory bowel disease, and various types of cancers. For instance, it has been established that inflammation is associated with the induction or the aggravation of more then 25 percent of cancers (Colotta et al. 2009).

The inflammation process is the result of signaling the emission of molecules and capitation of so-called chemokines. The chemokines are small and chemoattractive proteins which will mobilize leucocytes from the lymphea/plasma to the site of inflammation which is marked by chemokine emission responsible for the production of pro-inflammatory compounds (e.g., prostaglandins and leukotrienes) (Bureau et al. 2008). These chemokines (including interleukins) will bind to receptors at the membrane surface of monocytes, a process which will result in macrophage activation, consequently eliminating damaged tissues. These events are usually accompanied by pain. The inflammatory process will end when chemokines are enzymatically degraded. Numerous pathologies are linked to such an inflammatory process.

One way to limit inflammation is to inhibit chemokines production, which can be achieved by employing steroid anti-inflammatory drugs or non steroid anti-inflammatory drugs. Interestingly, resveratrol, as well as curcumin, have also been shown to exert a variety of anti-inflammatory effects through the inhibition of

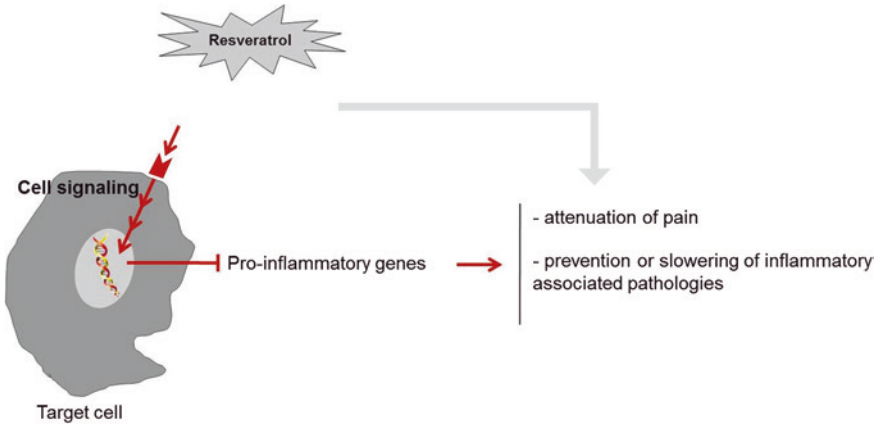

Fig. 3 Resveratrol anti-inflammatory properties

lipoxygenases and cyclo-oxygenases that synthesize pro-inflammatory mediators from arachidonic acid (Csaki et al. 2009). Inhibition of protein kinases such as PKCs and PKD, receptor tyrosine kinases and lipid kinases, as well as IKKα, an activator of the pro-inflammatory NF-κB pathway also provides some relief (Delmas et al. 2011).

6.2 *Resveratrol-Dependent Control of Inflammation Through MicroRNA Modulation*

MicroRNA (miRNA) function in the cell is an expanding new field of research. The first noncoding small regulatory RNA (*lin4*) was identified by Lee et al. as a developmental regulator in *C. elegans.* miRNAs were rapidly shown to be present not only in animals but also in plants and viruses (Lee et al. 1993). Since then, miRNAs have been implicated in the regulation of cell proliferation, differentiation and homeostasis, as well as in the innate and adaptive immune response. To date around 1,500 miRNAs have been identified in humans. miRNA misexpression has been linked to major pathologies such as cancer or cardiovascular, neurodegenerative and autoimmune diseases (Tili et al. 2007). Finally miRNAs have recently been found in blood and other body fluids. They are transported from cell to cell either through the gap junction or through blood secretion and exert their targeting capabilities in recipient cells. In blood miRNAs have been found either in microvesicles, exosomes, HDLs, or associated with RNA-binding proteins such as Ago2 or nucleophosmin 1 (Kosaka and Ochiya 2011). MiRNAs are capable of delivering an effect to distant cells, and may even be responsible for the induction of metastases at a distant location of the original tumor (Kosaka and Ochiya 2011). In contrast it is probable that some pharmaceutical compounds, including resveratrol, may possibly exert wide anti-inflammatory and antitumor effects in the body by causing the secretion of anti-inflammatory and antitumor miRNAs into the bloodstream. Excellent reviews have recently described the effects of resveratrol in animal models (Athar et al. 2007; Tili and Michaille 2011).

Despite a number of studies which have recently investigated several signaling and transcriptional pathways, the mechanisms of pleiotropic action of resveratrol is presently still poorly understood (Delmas et al. 2011). Some recent publications, however, have established that one reason resveratrol can affect so many different regulatory pathways might be due to its ability to modulate the expression, and consequently the regulatory effects, of a number of small noncoding RNAs, namely microRNAs (miRNAs) (Tili and Michaille 2011). Interestingly some polyphenols, including resveratrol, are known to exhibit anti-inflammatory properties and we recently showed that resveratrol can regulate the expression of both pro- and anti-inflammatory miRNAs (Tili et al. 2010). In human THP-1 monocytic cells as well as in human blood monocytes, for instance, resveratrol upregulates *miR-663*, an anti-inflammatory and tumor-suppressor miRNA that decreases AP-1

transcriptional activity and impairs its up-regulation by lipopolysaccharides (LPS) at least in part by targeting *JunB* and *JunD* transcripts. In contrast, resveratrol impairs the upregulation of pro-inflammatory and oncogenic *miR-155* by LPS in a *miR-663*-dependent manner. These results open the perspective of manipulating *miR-663* levels to potentiate anti-inflammatory and antitumor effects of resveratrol in pathologies associated with elevated levels of *miR-155*. In contrast to 'classical' coding transcripts noncoding RNAs have been generally much less conserved during evolution.

6.3 Resveratrol and Osteoarthritis

Osteoarthritis is a chronic and 'wear-and-tear'-associated pathology of articulations. This age-linked disease is very handicapping and painful and is characterized anatomically by the lack of articular cartilage (collagen, chondroitin sulfate) regeneration. This disregulation of cartilage production results into pain (mechanical and diurne) as well as difficulties to move the articulations. The disease can evolve into a sub-chondral bone fissuring. The osteophyte formation (bone extension), accompanied or not, of a synovite is characterized by immune cell infiltration (macrophage, neutrophiles) and accute inflammation at the synovial cavity. Currently no curative treatment is available, an inhibition of disease progression is equally difficult. The only approach to delay the handicap is to maintain regular and very moderate physical exercise, and the supplementation with chondroitin derivatives. Local and heavy pain and inflammation can be attenuated by anti-inflammatory drugs. These drugs, however, show often undesirable side effect. In contrast, some polyphenols such as resveratrol are known to be good natural anti-inflammatory molecules (Shakibaei et al. 2007, 2008; Wang et al. 2011) and interesting analgesic substances (Pham-Marcou et al. 2008).

While the anti-inflammatory effects of resveratrol as well as of other phytophenols are known the knowledge of their impact on chondrocyte model is so far limited (Shakibaei et al. 2007, 2008; Sharma et al. 2007; Wang et al. 2011). The mechanisms of action may involve signaling pathways where NF-κB and AP-1 become inhibited (Fig. 4). Alterations of chondrocytes are mainly responsible for arthritis accompanied by inflammation and pain. Resveratrol (RSV) shows anti-inflammatory properties by inhibiting IL-6, IL-8 secretion in LPS- treated cultured human chondrocytes (Ragot et al. unpublished)

Thus resveratrol a natural and safe polyphenol appears to be a good anti-inflammatory compound which could substitute partially or even completely for classical steroid anti-inflammatory drugs and non steroidal anti-inflammatory drugs. A recent review has been published by Shen et al. (2012) These new data open interesting perspectives for further studies, and aim at the prevention and the treatment (possibly co-treatment with glucocorticoids) of inflammation linked to arthritis.

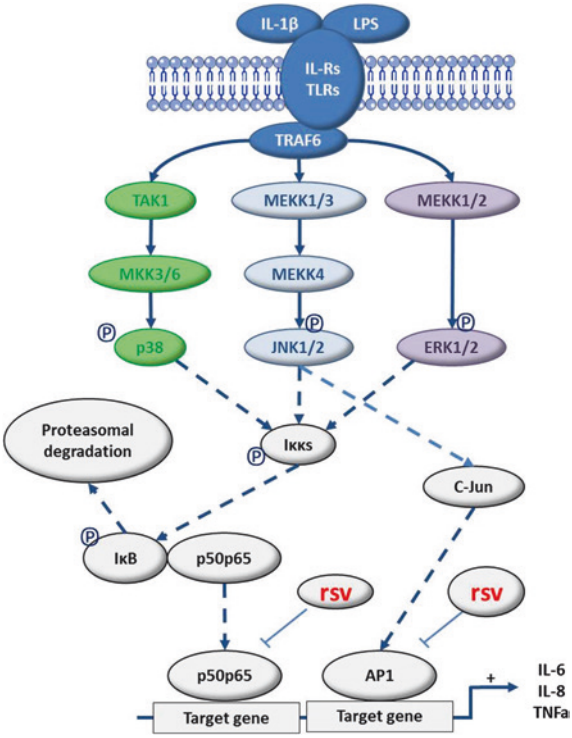

Fig. 4 Signaling pathway of the inflammatory process and possible interference(s) of resveratrol

6.4 Resveratrol and ALMD (Age-Linked Macular Degeneration)

A few years ago, it has been considered that inflammatory processes were also associated with retinal disorders such as diabetic retinopathy and ALMD (Ambati et al. 2003; Joussen et al. 2004). Later one, an *in vivo* study on mice has reported the ocular inflammation may be induced by endotoxins, and relieved in part by treatment with resveratrol (Kubota et al. 2009). This paper also demonstrated that a 5-day pretreatment with an oral resveratrol supplementation leads to the inhibition of ICAM-1 and MCP-1, two important proteins in the inflammatory process. MCP-1 (Monocyte Chimoattractant Protein 1) is a chemokine expressed by endothelial cells covering the vascular wall. Its role is to attract immune cells such as leukocytes to the inflammatory site. ICAM-1 (Inter-Cellular Adhesion Molecule 1) is expressed at the endothelial surface. Its role is to extract leukocytes from the bloodstream to allow them to diffuse at the tissue target.

In diabetes, the sustained high level of blood glucose leads to a chronic inflammation accompanied by a slow but regular degradation of Retine Pigmentar Epithelial cells (RPE) leading to the alteration of the blood-retinal

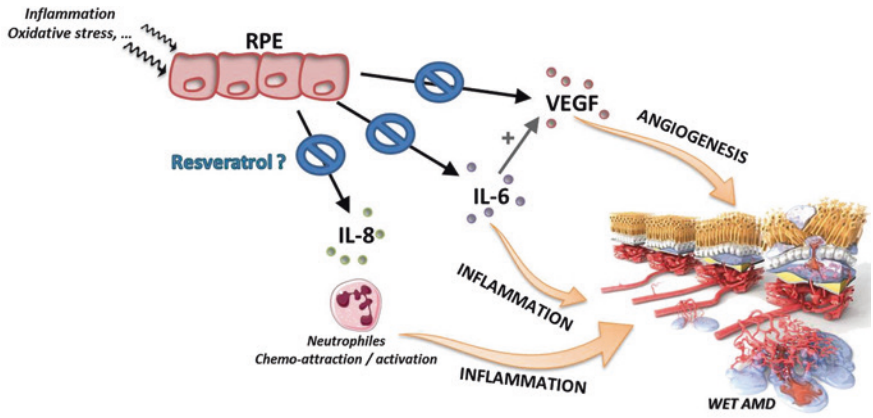

Fig. 5 Hypothetical inhibition effect(s) of resveratrol in the context of the pathogenesis of wet AMD

barrier and the loss of the central vision. Recently, an *in vitro* study on retinal pigmented cells analyzed the inflammatory phenomena to hyperglycemia conditions (Losso et al. 2010). The authors have shown that cells submitted to the diabetes test are producing pro-inflammatory cytokines like interleukin 6 and interleukin 8 and that resveratrol was able to inhibit this reaction in a dose-dependent manner. At the same time cyclo-oxygenase-2 (COX2) activity, which is responsible for the pro-inflammatory prostaglandin production, is also inhibited by resveratrol while the expression of Connexin 43 and Gap-junction, two proteins involved in cell–cell interaction is conserved. The cell cohesion is maintained thus preventing retinal-blood barrier degradation. A tentative explanation of the hypothetical inhibition effect of resveratrol in the context of the pathogenesis of wet AMD is presented in Fig. 5.

It has been shown that resveratrol inhibits ROS production leading to a protection of trabecular net cells which are submitted to OS following hyperoxygenation, a factor which can initiate glaucoma. A similar study shows that resveratrol is able to decrease the expression of interleukin-6 (IL-6), interleukin-8 (IL-8), messenger of interleukin-1α (IL-1α) as well as selectin-E, all of which are markers of inflammation. Selectin-E, also called ELAM-1 (endothelial-leukocyte adhesion molecule-1) is involved in the recruitment of leucocytes on the inflammation site, similar to ICAM-1 (Hua et al. 2011).

Resveratrol exhibits *in vitro* and *in vivo* anti-inflammatory capabilities at the molecular level by limiting the expression of pro-inflammatory factors such us interleukins and prostaglandins, but also at the cellular dimension by decreasing the chemoattraction and the recruitment on cells of the immune system to the inflammatory site.

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Authors Biography

Norbert Latruffe studied at the University of Besançon and the University of Lyon I and obtained his PhD in 1977. He was appointed as Professor in 1989 and is currently Full Professor of Biochemistry at the University of Burgundy. He has established and, until 2006, headed the Laboratory of Molecular and Cellular Biology. He was in charge of the group of Biochemistry of Metabolism and Nutrition at the INSERM research center, UMR 866 of Dijon until 2011. Early in his career, Norbert has been interested in the following research topics: energetic metabolism of lipids (UA CNRS 531, Besançon); phospholipid-dependent membrane enzymes (Postdoc at Vanderbilt University, Nashville TN, USA); toxicology of peroxisome proliferators (at Dijon). He has also collaborated in various projects as visitor at different international universities (e.g., Stockholm, Bern, Himeji). Starting in 1998, he launched a new challenge on the preventing role of resveratrol, a well-known phytophenol, against age-related pathologies, such as cancer, inflammation, and cardiovascular diseases. With his collaborators, he was one of the first to explore resveratrol metabolism (2004), its pro-apoptotic properties (2004), and recently discovered a new resveratrol signaling pathway through the modulation of micro RNAs (2010). To date, Norbert is the author of more than 150 international, peer-reviewed publications and of more than 120 lectures. He is a current (or past) expert member of several national

evaluation councils (e.g., CNRS, AFSSA, AERES, CNU) and at international level (EU). He has been awarded several distinctions, such as the Prize at the 16th Oncology and Molecular Medicine Meeting at Rhodes, is a laureate of the APICIL foundation, and recipient of the Academic Medal.

Allan Lançon holds a PhD in Biochemistry, Molecular and Cell Biology from the University of Burgundy, Dijon, France, which he obtained in 2006 with a thesis on a "Study of the tvransport and the metabolism of resveratrol in human hepatic cells". At this time, he also explored the cellular uptake of compounds, the biological activities of polyphenols and endocrine disruptors From 2007 until 2013, Allan has carried out several postdoctoral projects at the Laboratory of Nutritional and Metabolic Biochemistry (Dijon). These projects have been concerned with the prevention of age-related macular degeneration, the fight against metabolic syndrome, the fight against Type 2 diabetes and associated inflammation, to limit joint inflammation in osteoarthritis and to strengthen the antioxidant capacity of the body. In 2009, Allan also received training in the field of Management, especially for the creation and running of companies. Allan is currently a co-author of 11 publications.

Emeric Limagne is currently a PhD student at the INSERM research center number 866 in Dijon where he conducts his studies in the field of cancer research. Emeric previously worked as a research technician in a project on the prevention of inflammation in osteoarthritis using chondrocyte–monocyte co-cultures. Emeric has already published several manuscripts in international journals.

Jean-Jacques Michaille is Full Professor in Cell Biology at the University of Burgundy. He graduated from the University of Lyon and subsequently was appointed as Assistant Professor at the University of Grenoble and Lyon I, before being recruited as Professor at the University of Burgundy. Initially, Jean-Jacques' prime research interest was the Biology of Development. Currently, he is an expert in the field of molecular biology of mircoRNAs. Jean-Jacques collaborates closely with Professor Carlo Croce at the University of Columbus, Ohio, USA, where he regularly spends several months each year to conduct his studies in this emerging field of research. Jean-Jacques is the author or co-author of numerous publications in internationally leading journals.