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Regulation of redox signalling and autophagy during cardiovascular diseases-role of resveratrol

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Abstract. – Cardiovascular diseases remain one of the major health problems worldwide. The worldwide research against cardio-vascular diseases as well as genome wide association studies were successful in indentifying the loci associated with these prominent life threatening diseases but still a substantial amount of casualty remains unexplained. Over the last decade, the thorough understanding of molecular and biochemical mechanisms of cardiac disorders lead to the knowledge of various mechanisms of action of polyphenols to target inflammation during cardiac disorders. The present review article is focused on role of phytochemical resveratrol in regulation of redox signalling, autophagy and inflammation during cardiovascular pathology.

Key Words:
Reactive oxygen species (ROS), Cardiac disorders, Resveratrol, Autophagy, Redox, Signalling.

Introduction

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]. Resveratrol (trans-3,5,4-Trihydroxystilbene) (Figure 1) is a naturally occurring polyphenolicphytoalexin found in grapes and medicinal plants of the *Polygonum* species (Polygonaceae)[2]. Resveratrol belongs to subtype of phytochemicals called flavonoids which evolve from a common synthesis pathway in plants. 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 *Bothryti scinerea*, it is found in red wine in substantial amounts[3]. Extensive research in recent past confirms the modulatory role of resveratrol in multiple pathways involved in cell growth, apoptosis, and inflammation[4].

The role of reactive oxygen species (ROS) as a intracellular messenger is a known fact now and a lot of research has been conducted in past to prove the above point. Besides this, many scientists worldwide are focusing further to explore ground level mechanistic information of ROS signalling especially in the case of cardiac disorders[5]. The overproduction of ROS is associated with coronary heart disease. Most of the cardiac heart diseases including ischemic heart disease cause cardiomyocytes to face oxidative stress. The enzymes present in these cardiomyocytes are programmed to produce reactive oxygen species as well as intracellular redox buffer in order to get rid of stress due to diseased states including cardiac disorders. Moreover, the ultimate fate of ROS in a cell is to attain physiological homeostasis which depends upon the antioxidant reserve of the system as these antioxidants have ability to regulate ROS concentration[6]. The significant increase of ROS in a cell during a pathological state or due to decline in antioxidant reserve, usually leads to cell death. On the other hand, in minimal concentration with mild activity ROS act as signalling molecules and in such conditions they act as saviours.

Moreover, resveratrol can provide antioxidant reserve for regulation of ROS in cell as its protective effects appear to be closely associated with its antioxidant activity. Evidence from numerous *in vitro* and *in vivo* studies has confirmed the ability of resveratrol to modulate various targets and signalling pathways. This review discusses the potential of resveratrol in regulation of redox signalling and other associated mechanisms during cardiac disorders.

Physiological Importance of Redox Signalling

In the normal physiologic setting, regulation of cell survival is mediated by reactive oxygen species (ROS) and reactive nitrogen species

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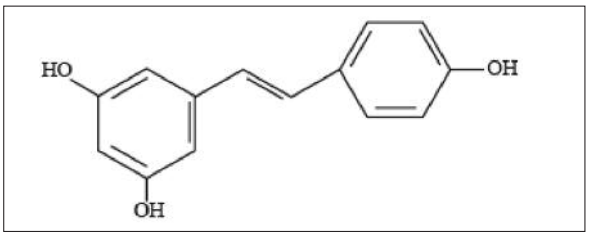

Figure 1. Resveratrol.

(RNS). In general, moderate levels of ROS/RNS functions as signals to promote cell proliferation and survival, whereas severe increase of ROS/RNS can induce cell death. Under physiologic conditions, the balance between generation and elimination of ROS/RNS maintains the proper function of redox-sensitive signaling proteins. Normally, the redox homeostasis ensures that cells respond properly to endogenous and exogenous stimuli. However, when the redox homeostasis is disturbed, oxidative stress may lead to aberrant cell death and contribute to diseased state like that of cardiac pathology[7].

Reactive species had been also described as second messenger molecules and their interaction with molecules is identified as a post-translational modification (i.e. S-nitrosylation of proteins) that can trigger a specific intracellular signal. The tight regulation of pro-oxidative species levels is essential for cellular homeostasis and such a regulatory mechanism is fundamental to maintain a safe redox state as well as to activate related redox signaling pathways[8].

Autophagy and Cardiac Disorders

The natural physiological process for nonspecific degradation of redundant or faulty cell components is called autophagy[9]. It is a conserved catabolic process for long-lived proteins and organelles of the cell[10,11]. In the heart, it has important role in mycocardium where it is active in basal cells and is fundamental for maintenance of contractile function of heart. Any mutation or fault in autophagic process results in cardiac dysfunction that ultimately leads to heart failure. It acts as a necessary source of energy during early neonatal starvation period[12]. Moreover, extensive research on autophagy inferred collectively that autophagy contributes significantly to the metabolic balance sheet of the heart and its elevation leads to an improved myocardial energy profile via changing the cardiac substrate preference.

Redox Signalling, Autophagy and Cardiac Disorders

Redox signalling has been recently reported to be associated with autophagy[13]. Anand-Srivastava et al[14] has reported recently the role redox signalling and ROS in regulating hypertension via studying modulation of Gi proteins through the activation of mitogen activated protein (MAP) kinase activity. Moreover, importance of redox reactions was also emphasized by observation of improvement in cardio-vascular functions after treatment with redox sensitive resveratrol in hypersensitive rats[15]. In cardiac ischemia, role of Hypoxia inducible factor 1 (HIF-1) and oxygen sensing has been also reported to be associated with redox signalling[16].

Oxidative stress is the key culprit for the cardiac function compromise during prolonged ischemia reperfusion injury (I/R injury). This ischemia reperfusion leads to ROS generation which further causes damage to the myocardium and results in subcellular organelle remodelling. However, in a recent study, ischemic pre-conditioning (IPC) produced by redox sensitive phytochemical resveratrol has been shown toprovide cardio protection by regulation of redox state of cardiomyocytes[17]. Resveratrol also provides cardioprotection via redox signalling through switching of IR-induced death signals into survival signals through the activation of Akt and Bcl-2[18]. As resveratrol generated a survival signal at are relatively low concentration, they hypothesized that resveratrol might induce autophagy for the protection of myocardium against IR injury and they have confirmed that resveratrol mediated autophagy in myocardium is through the activation of mammalian target of rapamycin (mTOR)[19].

Major redox-Sensitive Mechanisms of Action of Resveratrol

The prime redox sensitive pathway followed by resveratrol is of regulation of glutathione synthesis through regulation of redox sensitive transcription factors like Nrfr and NF-kB/AP1. Transcriptional factors NF-kB/AP1 are involved in the direct regulation of glutathione synthesis via transcriptional control over catalytic subunit of GCS (γ-glutamylcysteine synthetase). These in turn are mediated by several response elements, including AP-1 sites, one NF-κB site, and several antioxidant/electrophil response elements (AREs/EpREs). On the other hand, Nrf2 is a member of the "cap *n* collar" family of tran-

scription factors that binds to nuclear factor-erythroid derived 2 (NF-E2) binding sites, essential for the regulation of erythroid specific genes. The NF-E2 binding site is a subset of the antioxidant response elements (ARE) and AREs are regulatory sequences found on promoters of several phase 2 detoxification genes and are inducible by xenobiotics and antioxidants. Nrf2 is expressed in a wide range of tissues, many of which are sites of expression for phase 2 detoxification genes. Also, release and subsequent translocation of Nrf2 to the nucleus are presumably sensitive to cellular oxidative stress, thiol-reactive compounds, and antioxidants[20]. There are studies that reported stimulation of Nrf2 in PC12 cells through MAP kinase signal transduction pathways by resveratrol.

Polyphenols like resveratrol promotes autophagy as discussed before by activating (mTOR)[19]. Furthermore, the autophagy contributes significantly to myocardium energy metabolism. During stressful conditions, cardiac myocyte is unable to preserve its self preservation ability of myocardial ATP homeostasis. During normal circumstances adult heart derives 80% of energy from fatty acid metabolism and rest from glycolysis, so fatty acids are the main energy substrates responsible for maintaining cardiac function[22-24]. However, during ischemic conditions due to high concentrations of fatty acids which are detrimental due to their ability to inhibit glucose oxidation during the reperfusion period[25]. However, a growing body of evidence strongly suggests that another fundamental level of substrate inter regulation exists. Proteomics of the oxygenated myocardium reveals that 11% of the proteins identified are involved in electron transport, 11% in carbohydrate metabolism, and 10% in protein metabolism[26]. So, when ATP becomes limited during cardiac pathology, resveratrol helps in degradation of long-lived cytoplasmic proteins and organelles through autophagy[27].

Impaired autophagy in case of some cardiac disorders further results in accumulation of damaged mitochondria as well as stimulates reactive oxygen species (ROS) generation and enhanced lipofuscinogenesis[28]. Interestingly, continuous autophagic intra lysosomal degradation leads to the release of harmful lysosomal enzymes[29]. These events collectively make the cardiac cells sensitive enough to undergo apoptosis because released lysosomal enzymes can attack other proteins and mitochondria, triggering cytochrome c release and an amplification of the apoptotic program. Recent evidence suggests that pressure overload, a major risk factor for cardiac hypertrophy and heart failure, triggers basal autophagy, particularly in the basal septum[30].

Versatility of Resveratrol

Resveratrol is such a versatile phytochemical that it has been called as multipurpose agent that acts as an antioxidant, antimutagen, induces phase II drug-metabolizing enzymes (anti-initiation activity), mediates anti-inflammatory effect, inhibits cyclooxygenase and hydroperoxidase functions (anti-promotion activity and induces human promyelocytic leukemia cell differentiation (anti-progression activity). Resveratrol is also a competitive antagonist for the AhR and efficiently blocks CYP 1A1 induction *ex vivo* and *in vivo* in various organs including heart[31]. Further, resveratrol has been reported to inhibit the enzyme activities of cyclooxygenase-1 (COX1)[32], COX2[33] as well as expression of COX2 gene[34]. Cyclooxygenases produce prostaglandins from arachidonic acid. These compounds regulate cardiomyocytes proliferation, angiogenesis and immune suppression. More recently, the anti inflammatory activity of resveratrol has been also linked to its ability to block the NF-κappaB pathway through IkappaB kinase inhibition[35].

Key Molecular Pathways of Resveratrol

The extensively reported molecular target of resveratrol is blockade of activation of Nf-κB process[36]. NF-κB is a family of closely related protein dimers that bind to a common sequence motif in the DNA called the κB site. NF-κB is an inducible transcription factor for genes involved in cell survival, cell adhesion, inflammation, differentiation and growth[37]. In most resting cells, NF-κB is sequestered in the cytoplasm by binding to the inhibitory IκB proteins which blocks the nuclear localization sequences of NF-κB. NF-κB is activated by a variety of stimuli such as carcinogens, inflammatory agents, tumor promoters including cigarette smoke, phorbol esters, okadaic acid, H_2O_2 and TNF[38]. These stimuli promote dissociation of IκB-α through phosphorylation, ubiquitinylation and its ultimate degradation in the proteasomes. This process unmasks the nuclear localization sequence of NF-κB, facilitating its nuclear entry, binding to κB regulatory elements and activation of transcription of target genes[39]. Many of the target genes that are activated are critical to the establishment of early and

late stages of aggressive cancers such as expression of cyclin D1, apoptosis suppressor proteins such as bcl-2 and bcl-XL and those required for metastasis and angiogenesis such as matrix metalloproteinases (MMP) and vascular endothelial growth factor (VEGF)[40,41].

The maintenance of appropriate levels of NF-κB activity is crucial for normal cardiomyocyte proliferation; however, constitutive NF-κB activation is involved in the enhanced growth properties as seen in several cardiac disorders[42]. Dietary intake of resveratrol may, thus, be beneficial for cardiac patients who express persistently high levels of activated NF-κB.

The second major molecular target of resveratrol is Activated protein-1 (AP-1) which is a transcription factor that regulates the expression of several genes that are involved in cell differentiation and proliferation. Further, this AP-1 blockade leads to interference with the transmission of proliferative signals induced by peptide growth factors or steroid growth factors[43]. This complex consists of either homo or heterodimers of the members of the JUN and FOS family of proteins. Some of the target genes that are activated by AP-1 transcription complex mirror those activated by NF-κB and include Cyclin D1, bcl-2, bcl-XL, VEGF, MMP and urokinase plasminogen activator (uPA). Expression of genes such as MMP and uPA especially promotes angiogenesis.

Third major pathway involves the direct involvement of resveratrol in regulation of apoptosis. It directly gets involved in the activation of the genes like cyclin dependent kinase inhibitor P16, suppressor p53 which are responsible for down regulation of the cell proliferation and growth including cardiomyocytes.

Resveratrol Targeted Hallmarks of Cardiac Pathology

Aβ deposition and hyperphosphoprylation of tau are somehow now considered as cardiac pathology hallmarks. Resveratrol has been reported in recent past to inhibit Aβ fibrils formation[44]. Furthermore, resveratrol prevent amlyoid toxicity by directly affecting Aβ production (Figure 2) through activation of disintegrins as well as metalloproteinase domain-containing protein 10 by sirtuin induction[45]. The antioxidative nature and anti-inflammatory ability of resveratrol allows it to interfere directly into amyloid cascade thereby reducing Aβ induced production of ROS as well as cardiomyocytes inflammation[46]. Also, resveratrol induced activation of sirtuin-I promotes proteasomal degradation of tau that in turn further helps to check growing oxidative stress due to overproduction of ROS during cardiac disorders.

Caloric restriction adopted to boost cellular metabolism has been noticed to promote beneficial effects on cardiac physiology and overall life

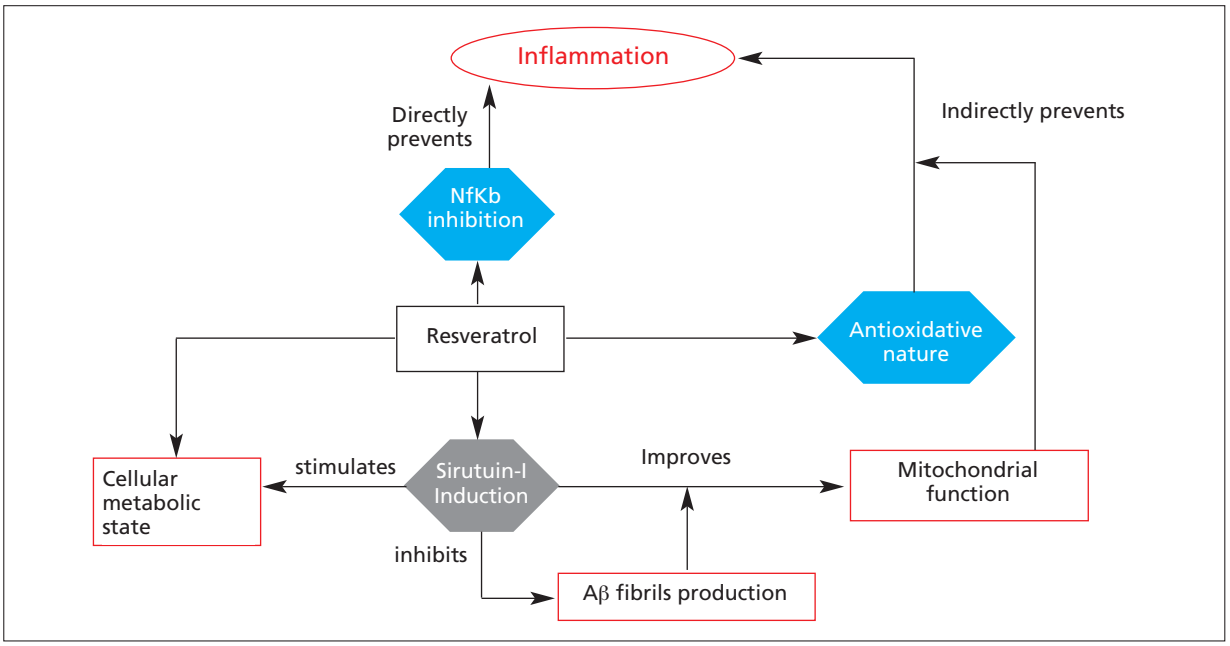

Figure 2. Resveratrol and hallmarks of cardiac pathology.

span of the living system. In the similar context, resveratrol has been also reproved to boost cellular metabolic state (Figure 2) by mimicking caloric restriction pathway via induction of of expression of sirtuin-I. This sirtuin-I further helps to improve mitochondrial functions and biogenesis. Thus, improved mitochondrial performance contributes towards efficient ROS scavenging and control[47]. Besides this, mitochondrial electron leakage also contributes towards production of mitochondrial reactive oxygen species that further results in lipid peroxidation, nucleic acid damage, protein oxidation, etc. Resveratrol also prevents the production of mitochondrial ROS by scavenging of metal induced radicals[48] or by boosting of mitochondrial bioenergetic efficiency[49].

Inflammation is also one of the prominent root causes of pathology of many vicious disease including cancer as well as cardiac disorders. It is in fact the prime site of progression for a disease to catch hold of whole physiological regulatory system. Resveratrol has been reported to reduce inflammation effectively[50]. The major contributors in resveratrol regulation of inflammation are sirtuin dependent arrest of nuclear factor kappa-light-chain enhancer of activated B cells (NFkB) signalling cascades[51].

Conclusions

The present review summarized major molecular mechanisms behind the protection potential of polyphenol resveratrol against cardiac disorders. It could be inferred from above studies that regulation of redox signalling, autophagy and generation of ROS are the prime molecular mechanisms adopted by resveratrol to efficiently target and prevent cardiac disorders.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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