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Targeting cell signaling and apoptotic pathways by EGCG: A potential role in the prevention and treatment of ischemic heart disease

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Abstract— Ischemic heart disease is the leading cause of morbidity and mortality in developed countries. Epidemiological studies have provided strong evidence in support of improved cardiovascular health in populations with consumption of diets rich in polyphenols. Many potential mechanisms have been proposed including both anti-inflammation and antioxidant effects, but questions remain regarding how the anti apoptotic pathways effect in ischemia reperfusion injury. To develop EGCG as an anti apoptotic agent, more clear understanding of the cell signaling pathways and the molecular targets responsible for cardioprotection and therapeutic effects are needed. We summarize recent researches on the EGCG-induced cellular signal transduction events which implicate in ischemic heart disease management. This prospect provides an insight on the cellular and molecular mechanism(s) by EGCG modulate multiple signaling and apoptotic pathways in ischemia reperfusion injury and elucidate the role in the prevention and treatment of ischemic heart disease.

Keywords— Egcg; Apoptosis; Ischemia Reperfusion Injury; Ischemic Heart Disease

I. INTRODUCTION

Ischemic heart disease is the leading cause of morbidity and mortality in developed countries. Although rapid reperfusion has achieved significant success in terms of large-scale reductions in patient mortality and morbidity, reperfusion of the ischemic myocardium is inevitably accompanied by the loss of myocytes, a phenomenon resulting from lethal reperfusion-induced injury [1]. Recently, apoptosis has become increasingly recognized as one of the important mechanisms of cell death during ischemia/reperfusion (I/R) injury in cultured cardiac myocytes [2,3] and the inhibition of this apoptosis can prevent I/R injury[4]. Reperfusion-induced apoptosis is now established as an important component of cardiac remodeling, particularly in the transition towards overt heart failure [5], and a greater understanding of the apoptotic events in cardiomyocyte apoptosis is imperative. Green tea, a worldwide consuming beverage, has been thought to possess significant health-promoting effects, polyphenol (-)-epigallocatechin gallate (EGCG), the predominant catechin from tea, is known to exert a variety of cardiovascular beneficial effects by affecting the activity of receptor and signal transduction kinases. Actually the intake of green tea in human is proposed to be associated with a lower incidence of coronary artery disease [6]. Identifying novel regulatory mediators may lead to new methods to prevent ischemic heart disease.

II. I/R IN ISCHEMIC HEART DISEASE

Myocardial ischemia refers to a clinical state characterized by low coronary blood flow arising from various causes but resulting in a lack of myocardial oxygen supply which can damage myocardial structure and heart function. Revascularization and restoration of blood flow as soon as possible remains the mainstay of all current therapeutic approaches to ischemia. Myocardial ischemic reperfusion injury induces irreversible myocardial damage despite reliving the myocardial ischemia, which in turn leads to cardiac remodeling characterized by dilation of the ventricle and reduced contractility [7]. Minimizing I/R injury would dramatically attenuate cardiac remodeling and improve the prognosis of patients. Therefore, it is necessary for the development of cardio protective agents to improve myocardial function, decrease the incidence of cardiovascular events and limit the total extent of infarction during ischemia reperfusion injury.

III. APOPTOSIS IS A SIGNIFICANT PATHOGENESIS OF ISCHEMIC REPERFUSION INJURY

Ischemia and reperfusion result in more than one mode of cellular injury and death: necrosis and apoptosis are thought to be key plays. However, necrosis is the pathologic death of cells resulting in irreversible damage. On the other hand, apoptosis is a highly regulated process that is activated via death receptors in the plasma membrane or via permeabilization of the mitochondria, which offers potential targets for therapeutic interventions. Until now it has been thought that myocardial apoptosis during I/R is mainly involved in the following signaling pathways: phosphatidylinositol-3-kinase/Akt (PI3K/Akt), mitogen-activated protein kinases (MAPKs), caspase, janus kinase/signal transducer and activator of transcription (JAK/STAT), cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) and lectin-like oxidized low-density lipoprotein receptor-1(LOX-1). By the way, the PI3K/Akt pathway, the MAPKs pathway, and the JAK/STAT pathway are usually known as protective pathways; these

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pathways are also involved in regulating cell apoptosis [8]. Besides the above mentioned common signaling pathways, more and more evidence has shown that there are other signaling pathways involved in the myocardial apoptosis during I/R, including NF-κB, small G proteins and protein kinase C (PKC). Despite these signaling pathways seldom being mentioned in the literature, their affect on I/R myocardial apoptosis has been confirmed [9, 10, 11]. Gene regulation of apoptosis involves promotion and inhibition. Bcl-2 is one of the most important apoptosis inhibitors, and Bax is a promoter. The Bcl-2/Bax ratio is considered to be a key factor of cell activity. Meanwhile, the upregulation of Bcl-2 expression can suppress the expression of caspase-8 and caspase-3, resulting in anti-apoptosis [11].

IV. EGCG INHIBIT APOPTOTIC PATHWAYS IN MYOCARDIAL I/R MODEL

EGCG is the major catechin in green tea and accounts for 50% to 80% representing 200 to 300 mg/brewed cup of green tea [12]. Epidemiological studies have suggested the preventive effect of green tea consumption against atherosclerosis and coronary heart disease [13,14,15]. In primary cultures of cardiac myocytes exposed to simulated I/R injury as well as in the intact rat heart subjected to I/R injury, Townsend PA et al reported that EGCG inhibits STAT-1 activation and protects isolated neonatal cardiac myocytes from I/R-induced apoptosis. STAT-1 is known to induce expression of pro-apoptotic genes such as caspase-1, Fas, and FasL[16,17], as well as down-regulate the expression of anti-apoptotic genes such as Bcl-2 and Bcl-x [18]. I/R induce cardiomyocyte apoptosis, and the inhibition of this apoptosis can prevent ischemia/reperfusion injury. Apoptosis is mediated by an activation cascade of the caspase family of cysteine proteases and ends with activation of the terminal effector caspase, caspase-3[19]. Studies by Piao CS et al showed that EGCG increased the expression of Bcl-2 protein and decreased that of Bax protein in isolated rat hearts, in addition to decreasing cleaved caspase-3 activity. They found that administration of EGCG in vitro could prevent apoptosis of cardiomyocytes by regulating pro-apoptotic and anti-apoptotic proteins such as Bax and Bcl-2, and by simultaneously regulating caspase-3 in isolated rat hearts [20]. Reperfusion of ischemic myocardium produces reactive oxygen species (ROS) and results in apoptotic cell death and DNA fragmentation. Several redox-sensitive anti- and pro-apoptotic transcription factors including nuclear factor kB (NF-kB) and heterodimeric transcription factor AP-1 progressively and steadily increase in the heart as a function of the duration of ischemia and reperfusion [21]. Aneja R et al. [22] showed that in vivo treatment with EGCG reduced ischemia/reperfusion injury by inhibiting the NF-kB and AP-1 pathways in rat hearts. This beneficial effect of EGCG was associated with reduction of nuclear factor-κB and activator protein-1 DNA binding. Recent experimental studies have shown that EGCG might suppress oxidative stress-induced cardiomyocyte apoptosis through inhibiting telomere dependent apoptotic pathway [23]. They found that EGCG significantly inhibited H_2O_2-induced apoptotic morphological changes and apoptotic rate. When H9c2 cells were incubated with H_2O_2, the telomere length shortened and the protein expression of telomere repeat-binding factor 2 (TRF2) decreased gradually, while the protein levels of p53 and p21 increased. EGCG significantly inhibited telomere attrition, TRF2 loss and p53, p21 upregulation induced by H_2O_2. However, the underlying mechanisms of whether EGCG may effect on telomere attrition in cardiomyocytes in ischemic reperfusion injury are still unclear. In addition, whether this effect is involved in other important proteins such as p27 and FoxOs also remains to be further elucidated.

V. CONCLUDING REMARKS

Large epidemiological studies linking consumption of green tea with improved cardiovascular outcomes are intriguing. Although tea polyphenols, including EGCG are often touted as antioxidants, their mechanisms of action with respect to antiapoptotic effect on I/R injury are poorly understand. Signaling crosstalk means the interaction of two or more different pathways. It is already known that apoptosis is a good target for therapeutic intervention [24]. An understanding of potential molecular mechanisms targeted by EGCG is essential to design better therapeutic strategies for cardioprotection in ischemia reperfusion injury. And further investigation is required to establish the optimal concentrations of catechins and/or their metabolites for potential therapeutics or prophylactic use.

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