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SIRT1: A Novel Target to Prevent Atherosclerosis

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ABSTRACT

Atherosclerosis is a chronic immuno-inflammatory disease associated with blood lipids disorder. Many studies have demonstrated that caloric restriction (CR) can prevent atherosclerosis and extend lifespan. Sir2 protein, mammal's SIRT1, has been reported to at least partly contribute to the protective effect of CR. Hence, we hypothesize that SIRT1 is a key regulator in the pathogenesis of atherosclerosis and that upregulation of SIRT1 in endothelial cells may mimic CR's beneficial effect on vascular health. The recent studies have demonstrated that endothelial SIRT1 is an anti-atherosclerosis factor and the possible mechanism may be related to inhibit oxidized low-density lipoprotein (oxLDL)-induced apoptosis, upregulate endothelial nitric oxide synthase (eNOS) expression, and improve endothelium relaxation function. We infer that SIRT1 may be a novel target for atherosclerosis prevention and treatment. J. Cell. Biochem. 108: 10–13, 2009.

KEY WORDS: ATHEROSCLEROSIS; CALORIC RESTRICTION; SIRT1

Atherosclerotic arterial disease is the leading cause of morbidity and mortality in Western countries and is rapidly increasing in the developing nations [Yusuf et al., 2001]. It is well known that atherosclerosis is a chronic immuno-inflammatory disease associated with blood lipids disorder. Though many studies have demonstrated that reduce risk factors, such as serum lipids and lipoproteins, hypertension, diabetes mellitus, high-sensitivity C-reactive protein (CRP), can delay the development of atherosclerosis, the molecular mechanisms in preventing atherosclerosis are largely unexplored. Identifying novel regulatory mediators may lead to new methods to prevent atherosclerosis.

CR PREVENT ATHEROSCLEROSIS

Recently, considerable attention has been paid to CR because of its potential role to prevent atherosclerosis. During the Second World War the shortage of food in some North European countries led to a sharp fall in mortality from coronary artery disease; when the war ended mortality rose sharply. Data obtained form the research of Verdery and Walford [1998] showed that short-term CR with a low-protein diet can improve a number of risk factors for atherosclerosis, including blood pressure (BP), serum total cholesterol (Tchol), and triglyceride (TG) levels. Studies by Fontana et al. [2004] also reported that long-term CR results in profound and sustained beneficial effects on the major atherosclerosis risk factors, serum Tchol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TG, and BP, that usually increase with advancing age. They further show that CR provides a powerful protective effect against obesity and insulin resistance, and provide evidence for a decrease in inflammation, as reflected in extremely low CRP levels. Most importantly, carotid artery intima–media thickness (IMT), which was often used to evaluate the extent of atherosclerosis, was ≈40% less in the CR group than in the comparison group [Fontana et al., 2004].

CR ACTIVATE SIRT1 IN MAMMALS

CR has been known for decades to extend lifespan of virtually all organisms from yeast to mammals. The means by which CR extends lifespan is not yet clear. Accumulating evidence has demonstrated that CR extends lifespan by increasing the activity of the Silent information regulator 2(Sir2) protein [Anderson et al., 2003; Cohen et al., 2004; Lin et al., 2004], a member of the conserved sirtuin family of nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases [Imai et al., 2000; Landry et al., 2000; Hekimi and Guarente, 2003]. In yeast, worms and flies, an extra copy of theSir2 gene or its orthologue increases lifespan by 18–50% [Kaeberlein et al., 1999; Tissenbaum and Guarente, 2001; Rogina and Helfand, 2004] whereas a deletion of the gene, in yeast, reduces lifespan [Kaeberlein et al., 1999].

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In mammals, there are seven members in the Sir2 family, termed Sirtuin1-7 (SIRT1-7) [Frye, 1999, 2000]; among these, SIRT1 is the closest homolog of yeast Sir2 protein [Frye, 2000]. In addition to histone, SIRT1 also deacetylates other proteins, including the forkhead transcription factors (FoxOs), MyoD, the tumor suppressor p53, and PGC-1α [Luo et al., 2001; Vaziri et al., 2001; Fulco et al., 2003; Brunet et al., 2004; Motta et al., 2004; Rodgers et al., 2005]. Thus, SIRT1 can mediate cellular metabolism and exert corresponding effects on gene expression. Several studies showed that SIRT1 is a key regulator of cell defenses and survival in response to stress [Brunet et al., 2004; Motta et al., 2004; Kobayashi et al., 2005]. The recent studies have demonstrated that SIRT1 is required for CR to mediate lifespan extension in mammals [Cohen et al., 2004; Chen et al., 2005; Boily et al., 2008]. Hence, we hypothesize that SIRT1 is a key regulator in the pathogenesis of atherosclerosis and that upregulation of SIRT1 in endothelial cells may mimic CR's beneficial effect on vascular health.

SIRT1 PREVENT ATHEROSCLEROSIS

At present, two main hypotheses have been explain the pathogenesis of atherosclerosis: the lipid hypothesis and the chronic endothelial injury hypothesis. Recent experimental studies have shown that SIRT1 has profound effects on these two hypothesis. Studies by Li et al. [2007] demonstrated that SIRT1 activates liver X receptor (LXR) proteins α and β. In SIRT1 knockout mice, expression of ABCA1, a well known LXR target, is reduced, resulting in defective cholesterol efflux, lower HDL-C levels, and fatty livers. Moreover, studies by Purushotham et al. [2009] also reported that when challenged with a high-fat diet, liver-specific SIRT1 knockout mice develop hepatic steatosis, hepatic inflammation, and endoplasmic reticulum stress. All these results indicated that SIRT1 play an important role in the regulation of blood lipids metabolism.

SIRT1 is highly expressed in endothelial cells and controls their angiogenic function: it is involved in vascular growth of cultured endothelium, in the formation of the vascular network of the developing zebrafish, and even in ischaemia-induced neovascularization of the adult mouse [Potente et al., 2007]. SIRT1 has also been shown to exert protective effects against endothelial dysfunction by preventing stress-induced senescence [Ota et al., 2007] and to mediate the effects of CR on endothelium-dependent vasomotor tone by deacetylating eNOS and increasing nitric oxide (NO) bioavailability [Mattagajasingh et al., 2007]. Although SIRT1 has been shown to play a critical role in the regulation of vascular function, little information is available on the function of endothelial SIRT1 during hypercholesterolaemia-induced atherosclerosis.

Recently, studies by Zhang et al. [2008] reported that endothelial SIRT1 is a bona fide anti-atherosclerosis factor in vivo. They founded that oxLDL and H_2O_2 treatment increased the SIRT1 level in Human umbilical vein endothelial cells (HUVECs). Overexpression of SIRT1 prevented the oxLDL-induced apoptosis of HUVECs, and this effect was mediated by a marked increase in the expression of eNOS. Accordingly, endothelialspecific overexpression of SIRT1 in apolipoprotein E null ($ApoE^{-}/^{-}$) mice-induced eNOS and significantly blunted the high-fat diet-induced attenuation of endothelium-dependent relaxation in isolated aortic rings. Most important of all, endothelial-specific overexpression of SIRT1 also attenuated aortic plaque development in response to the high-fat diet in $ApoE^{-}/^{-}$ mice. All these results suggest that the anti-atherosclerosis effect of SIRT1 is related to eNOS expression, which is well recognized for increasing NO to promote endothelial survival and improve endothelial function [Dimmeler and Zeiher, 1999]. However, the underlying mechanisms of how SIRT1 controls eNOS expression are still unclear. In addition, whether this effect is involved in other important proteins such as p53 and FoxOs also remains to be further elucidated.

THE METHODS TO ACTIVATE SIRT1

The activity of SIRT1 can be modulated directly by pharmacological compounds. The polyphenolic plant antioxidant resveratrol moderately increases the SIRT1 activity [Yoshida et al., 2007; Chen et al., 2009] and has been shown to slow down the development of atherosclerosis (Fig. 1) [Zang et al., 2006; Hou et al., 2008]. Recently, compounds that are 1000 times more potent than resveratrol have become available, and it has already been shown that these potential new drugs improve the glucose homeostasis [Milne et al., 2007]. In the light of all these beneficial effects, it could be speculated that

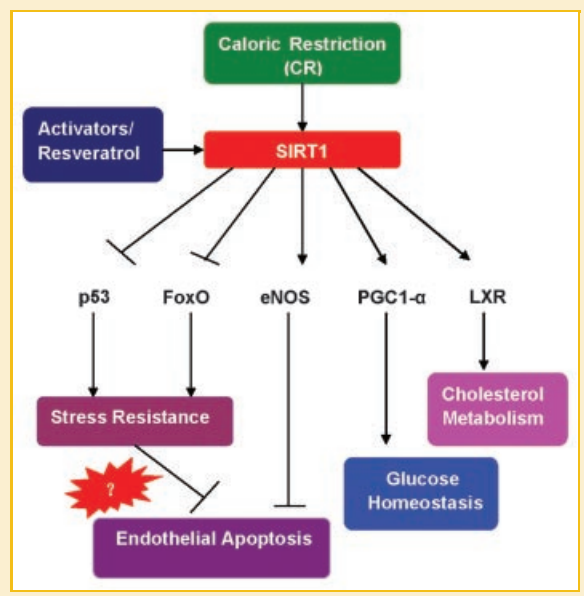

Fig. 1. SIRT1 prevents the development of atherosclerosis. CR activates SIRT1 in mammals. The overexpression of SIRT1 regulates important effectors like p53, FoxO, eNOS, preventing endothelial apoptosis and senescence. In addition, SIRT1 controls PGC-1α, LXR, improving the glucose homeostasis and cholesterol metabolism. Activators of SIRT1 such as resveratrol or endothelialspecific overexpression of this sirtuin promote eNOS expression and prevent the development of atherosclerosis. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

these compounds might also be of value as a potential anti-atherosclerotic therapy.

CONCLUDING REMARKS

SIRT1 is a key regulator in the pathogenesis of atherosclerosis and that upregulation of SIRT1 in endothelial cells may mimic CR's beneficial effect on vascular health. Though the underlying mechanisms of how SIRT1 prevent atherosclerosis are still uncertain, we have reasons to believe that SIRT1 may be a potent target for atherosclerosis prevention and treatment.

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