Chapter 16 Resveratrol: An Epigenetic Regulator of SIRT1 - Is It a Magic Tool to Prevent Cardiovascular Disease?

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in both men and women and has largely been attributed to genetic makeup and lifestyle factors. However, genetic regulation does not fully explain the pathophysiology. Recently, epigenetic regulation, the regulation of the genetic code by modifications that affect the transcription and translation of target genes, has been shown to be important. Silent information regulator-2 proteins or sirtuins are an epigenetic regulator family of class III histone deacetylases (HDACs), unique in their dependency on coenzyme NAD+, that are postulated to mediate the beneficial effects of calorie restriction, thus promoting longevity by reducing the incidence of chronic diseases such as cancer, diabetes, and CVD. Emerging evidence shows that SIRT1 is ubiquitously expressed throughout the body. Resveratrol, a plant polyphenol, has cardioprotective effects and its mechanism of action is attributed to regulation of SIRT1. Incoproation of resveratrol into the diet may be a powerful therapeutic option for the prevention and treatment of CVD.

INTRODUCTION

Cardiovascular Disease

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism (WHO, 2015). CVD is the

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Resveratrol

leading cause of death in most developed countries including the United States (Naghavi et al., 2015). As the leading cause of worldwide death, CVD represents nearly 30% of all deaths, and in 2008 caused 17 million deaths and led to 151 million disability-adjusted life years (Bloom, 2011). Behavioral risk factors such as physical inactivity, tobacco use, and unhealthy diet explain nearly 80% of the CVD burden. The greatest contributors to CVD mortality and morbidity are chronic heart failure, coronary heart disease, and stroke. The global cost in 2010 has been estimated at US\$ 863 billion (Bloom, 2011). Even though multiple risk factors have been identified, the current approach to treatment is only to decrease modifiable risk factors through healthy lifestyle changes and the use of medications, such as statins to lower cholesterol. Despite extensive study and efforts over many years, CVD remains the leading cause of death. This is due in part to the difficulty in adhering to lifestyle changes such as a family history of CVD. Since modifying behavioral risk factors involves individual choices, approaches such as government regulation, advertising, and public policy statements have had limited impact on CVD incidence. Innovative approaches are needed to reduce further the negative impact of CVD.

Current treatment of cardiovascular diseases requires lifestyle changes with or without medications. Evidence-based recommendations were provided in 2013 by the American College of Cardiology and the American Heart Association (Jensen et al., 2014; Stone et al., 2014). The new guidelines refined the original Framingham risk assessments with new knowledge and involve matching individuals' CVD risk with the intensity of prevention steps (Wenger, 2014).

Two decades ago, following the discovery of the double helical structure of DNA and subsequent automation of DNA sequencing, scientists held high hopes that unraveling the human genome would uncover the genetic basis of many human diseases such as cancer, and that would lead to new and effective treatments. However, early gene linkage studies revealed only rare cases of single-gene disorders. Also, analysis of many genome-wide association studies has found little contribution to disease variation to date (Bjorkegren, Kovacic, Dudley, & Schadt, 2015). Accordingly, other explanations for disease development and expression have been sought. Recently, the interaction between genes and the environment has emerged as a new frontier for studying how networks of developmentally programmed genes may lead to several major pathologies. Epigenetic studies may identify pathologic mechanisms early enough in human development to suggest ways to alter adverse gene expression in chronic disease. Humans are particularly susceptible to epigenetic influences during fertilization, gametogenesis, and early embryo development (Martinez, Gay, & Zhang, 2015). In addition, these epigenetic marks can also accumulate during adult life to increase disease susceptibility.

Sirtuins

Histone deacetylases (HDACs) are enzymes that remove acetyl groups from histone and non-histone proteins to counterbalance the activity of histone acetyltransferases (HATs). These activities control the epigenetic regulation of gene expression through post-transcriptional modifications to proteins (Z. Y. Wang, Qin, & Yi, 2015). Four classes of HDACs have been characterized according to their homology to yeast HDACs, and a total of 18 mammalian HDACs have been identified. HDACs are divided into four classes, class I (HDAC1, 2, 3, and 8), class II (HDAC4, 5, 6, 9, and 10), and class IV comprising only HDAC11 (Z. Y. Wang et al., 2015). A unique class, class III, is made up of the sirtuin family of enzymes that are not susceptible to inhibition by classical HDAC inhibitors such as vorinostat (Chavan & Somani, 2010).

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