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The Relationship Between Cardiovascular Diseases and Cancer Through Understanding the Molecular Roles of p53

[1]Mohamad I. Jarrah, [2]Mahasen S. AL-Najar,
[1]Sulaiman Al Momany and [1]Ashraf O. Owais
[1]Department of Internal Medicine, Faculty of Medicine,
Jordan University of Science and Technology, Jordan
[2]Department of Diagnostic Radiology, Faculty of Medicine,
University of Jordan, Jordan

Abstract: This review study focused the attention on understanding the similarities between cardiac diseases and cancer through molecular mechanisms. We investigated the molecular effects of suppressor gene *p53*. The p53 is a tumor suppressor gene and its role is to maintain normal growth control and genomic stability. The importance of p53 comes from the fact that its mutations are involved in all major human cancers. In case of uncontrolled growth, p53 acts as a transcription factor for several genes to promote apoptosis. It has also been shown that p53 has important non-transcriptional effects on apoptosis which implies the involvement of its ability to repress anti-apoptotic or activate pro-apoptotic Bcl-2 family members. Studies have pointed to a link between cardiac diseases and cancer through displaying an imbalance of progrowth mechanisms.

Key words: Cardiac disease, cancer, p53, suppression gene, apoptosis, angiogenesis

INTRODUCTION

Molecular features of p53: p53 is a tumor suppressor gene and its role to maintain normal growth control and genomic stability. The importance of p53 comes from the fact that its mutations are involved in all major human cancers (Poyurovsky and Prives, 2006). In case of uncontrolled growth, p53 acts as a transcription factor for several genes to promote apoptosis. It has also been shown that p53 has important non-transcriptional effects on apoptosis which implies the involvement of its ability to repress anti-apoptotic or activate pro-apoptotic Bcl-2 family members (Moll *et al*., 2005).

THE ROLE OF p53 IN CARDIAC CELLS

The expression of p53 has been shown to increase in cells as a response to DNA damage and other cellular stressing conditions such as hypoxia (Greaber *et al*., 1994).

Several studies have shown that p53 protein levels increase in non myocyte cell lines in response to hypoxia (Greaber *et al*., 1994). It has also been indicated that hypoxia has the ability to induce cell death of cultured cardiomyocytes (Tanaka *et al*., 1994). In another study, Long *et al*. (1997) showed that there is an increased expression of p53 following hypoxia in cardiomyocytes and that this increase is thought to occur associated with myocyte cell death. These findings have also been confirmed by the study of Toth *et al*. (2006) who reported increased p53 expression and cell death in cardiomyocytes exposed to hypoxia.

In a study by Bialik *et al*. (1997), it has been investigated that if the p53 knockout mouse model can induce apoptosis that occur 48 h after imposition of ischemia caused by coronary arterial ligation, the results did not reveal differences in the level of apoptosis (measured either by DNA laddering or TUNEL staining) between wild-type and knockout mice.

In their study, Bishopric *et al*. (1999) used *ex vivo* Model to study Langendorff perfused hearts taken from p53+/+ and p53-/- mice which were exposed to 20 min of global ischemia (no flow) and 3 h of reperfusion, the results of this study did not show significant differences in DNA laddering.

Matsusaka *et al*. (2006) conducted a study using the wild-type and p53-deficient mice to examine the effects of p53 on the induction of death due to cardiac rupture as response to coronary artery ligation. The study results pointed to production of 60% large infarctions as well as large number of deaths due to cardiac rupture-8 out of 29 animals following the first 5 days of ligation in wild-type

Corresponding Author: Mohamad I Jarrah, Department of Internal Medicine, Faculty of Medicine,
Jordan University of Science and Technology, Jordan

(p53+/+) mice. On the other hand, it was found that p53+/- mice had reduced rate in death (2 out of 28 animals) following the same period. It was interestingly found that p53-/- mice exhibited no deaths.

In their study, Matsumura *et al.* (2005) reported various effects associated with p53 including average infarct size, hemodynamic performance, tissue fibrosis or Matrix Metalloproteinase (MMP) content. Researchers also reported that the absence of any difference in infarct size can be attributed to necrosis and the role of p53 has been associated with apoptosis.

Xie *et al.* (2000) reported that heart ischemia is a common pathology that associated with hypoxia. It induces the apoptotic death of cardiomyocytes and is considered as an important reason for fatal heart failure. That researchers have pointed to the phenomenon of accumulating data showing the role of p53 in the regulation of cardiomyocyte death. However, the accumulation of p53 protein and occurrence of apoptosis was shown in reperfused ventricular heart tissue after coronary occlusion (Xie *et al.*, 2000).

p53 AND MYOCARDIAL ANGIOGENESIS

According to Sano *et al.* (2007), angiogenesis adaptation mechanism is involved significantly in cases of hypertrophy to increase tolerance for pressure overload. Increased secretion of factors involved in angiogenesis including VEGF by heart with hypertrophy attributes to improved angiogenesis (Shiojima *et al.*, 2005; Sano *et al.*, 2007). If angiogenesis is defected, the adaptive cardiac hypertrophy develops to heart failure (Sano *et al.*, 2007).

Other studies have pointed to the importance of Renin-Angiotensin System (RAS) which upon its activation contributes in induction of cardiac hypertrophy following pressure overload (Masuda *et al.*, 2012). Angiotensin II (AngII) has various functions including formation of cardiomyocyte hypertrophy, cardiac fibrosis and dysregulation of myocardial angiogenesis (Belabbas *et al.*, 2008).

Using rat as an experimental model showed that the infusion of AngII deceases the density of cardiac vessels besides altering the angiogenetic capacity of aorta and coronary artery rings (Belabbas *et al.*, 2008). No precise mechanisms have been proposed so far to explain the way by which AngII defects myocardial angiogenesis irrespective to the consideration that a large number of studies have been conducted to investigate the molecular mechanisms by which AngII induces cardiomyocyte hypertrophy and growth of cardiac fibroblasts (Guan *et al.*, 2013).

It has been indicated that there is an effect of sustained pressure overload in induction the accumulation of p53 which suppresses Hypoxia inducing transcription factor (Hif-1) activity and by thus it alters the angiogenesis in cardiac tissue through the induction of cardiac hypertrophy (Sano *et al.*, 2007; Zou *et al.*, 2011).

Gaulton *et al.* (2008) conducted a huge scale association study on candidate genes in type 2 diabetes and found a strong association of p53 codon 72 polymorphism with T2D. Furthermore in another study, it has been experimentally found that the expression of p53 in adipose tissue to play a role in the development of insulin resistance and the inhibition of the reactivity of p53 in adipose tissue has been indicated to enhance insulin resistance (Minamino *et al.*, 2009).

COMMON MECHANISMS BETWEEN CARDIAC DISEASE AND CANCER

Mouraret *et al.* (2013) showed that tumor suppression as an anti-survival mechanism has impacts on hypertension resulting in a vascular smooth muscle progrowth imbalance. Furthermore, it has been pointed to the induction of senescence via Nutlin-3a to inhibit ubiquitin ligase MDM2, a negative regulator from interacting with the long established tumor suppressor p53, accordingly, this inhibits proliferation of pulmonary arterial smooth muscle cells.

According to a published study by Haldar *et al.* (2010), cardiac and vascular diseases are presented as co-morbid conditions. An illustrating example is that hypertension accompanied with cardiac hypertrophy represents an imbalance of progrowth mechanisms that also is displayed in cancer. Researcher also pointed to shared pro-apoptotic, antisurvival mechanisms to explain such comorbid features as heart failure with aneurysm formation. Researcher also showed that the transcriptional regulator Kruppel-like factor 15 (Klf15) levels were markedly reduced in heart failure and aortic aneurysm.

CONCLUSION

Taken together, the present study focused on providing an overview of p53 and its involvement in cardiac diseases and angiogenesis as well as the common features between cardiac diseases and cancer.

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