Editorial

Manganese superoxide dismutase: guardian of the heart dysfunction

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Volume 1 Issue 2 - 2015

Mini Chandra, Manikandan Panchatcharam, Sumitra Miriyala
Department of Cellular Biology and Anatomy, Louisiana State University- Health Sciences Center, USA

Correspondence: Sumitra Miriyala, Department of Cellular Biology and Anatomy, Louisiana State University- Health Sciences Center, USA, Tel (318)5184518, Fax (318)675, Email smiriy@lsuhsc.edu

Received: August 12, 2015 | **Published:** August 18, 2015

Manganese superoxide dismutase (MnSOD) is an antioxidant enzyme located in the mitochondrial matrix and is responsible for protecting against the damaging effects of reactive oxygen species (ROS). Superoxide's (O_2.-) are the first oxidant produced by the metabolism of oxygen in the mitochondria of eukaryotic cells, and MnSOD plays an important role in sequestering this free radical. The increased levels of ROS whether due to over production or decreased removal leads to oxidative stress, leading to the development of cardiovascular diseases. Mitochondria are the major organelle for the metabolic activities of the body that involve ROS production, and MnSOD regulates mitochondrial function by quenching ROS production. The importance of MnSOD in aerobic life has been shown in knockout mice models[1] and in drosophila melanogaster fruit flies,[2] where deficiency of MnSOD in mice was neonatal lethal. Due to background modifications, a small percentage of knockout mice showed dilated cardiomyopathy indicating increased vulnerability to oxidative injury in the cardiac myocytes Ikegami et al.[3] Successfully generated tissue-specific MnSOD conditional knockout mice that would provide a useful tool for the analysis of the pathological role of O_2. Injuries in adult tissues.[3] Studies have also been done on heterozygous mice to observe the effect of low MnSOD activity throughout life due to increased oxidative damage, progressing with age.[4] MnSOD has also been shown to play an important role in cardiac tissue protection. A study done in 2005 by Sam et al.[5] on failing myocardium showed increase in mRNA expression but decreased activity of MnSOD, which is consistent with the fact that increased oxidative stress leads to higher production of MnSOD.[5] Another study by Lai et al.[6] showed increased oxidative stress in cardiomyocytes by overexpression of adenylyl cyclase 5 which was mediated by decreased MnSOD transcription. These effects were overcome by overexpression of MnSOD with improved cardiac function.[6] Similarly, signal transducer and activator of transcription 3 (STAT3) protects cardiomyocytes against ROS by up regulating MnSOD[7] in hypoxic cardiomyocyte.

Deficiency of MnSOD has also been implicated in carotid artery endothelial dysfunction in Apo E deficient mice. Endothelial function is affected by oxidative stress in chronic heart failure and MnSOD has been shown to protect against oxidative stress in blood vessels.[8] MnSOD's role in protection of endothelial function was studied by Miller and colleagues, and they have shown that MnSOD deficiency is associated with impaired endothelial function in mice with chronic heart failure. Oxidative stress leads to endothelial dysfunction by cyclooxygenase-1, which has been shown to be heightened in mouse models with MnSOD deficiency.[9] MnSOD also seems to enhance the cardio protective effects of various drugs such as tamoxifen[10] and phenyl butyrate,[11] which may be explained by to its increased activity. The beneficial effects of MnSOD's over expression on reversing adriamycin induced cardiotoxicity in the cardiac mitochondria have been demonstrated.[12] These findings will open up the possibility of preventing cardiotoxicity that occurs during cancer treatment. The expression of MnSOD is improved with exercise as per a study by Kavazis et al.,[13] leading to increased activity in myocytes.[13] French et al.[14] also showed that exercise increases the activity of myocardial MnSOD and thus provides cardio protection against cardiomyocyte apoptosis.[14] A study done by Yamashita et al.[15] has demonstrated the directly favorable effect of exercise on the myocardial ischemia-reperfusion injury illustrating that the increase in cardiac MnSOD due to exercise is important for protection against myocardial infarction.[15] Another study done by McCommis et al.,[16] demonstrates the positive effect of exercise on subjects in decreasing the production ROS, wherein the reduced expression of MnSOD returned to normal after exercise. It also shows the effect of chronic exercise on hypercholesterolemia by increasing the antioxidant expression.[16]

The decreased activity of MnSOD in some disease states have been attributed to post translational modification of MnSOD.[17,18] Cardiac transplants studies have suggested that acute graft rejection and concomitant high oxidative stress may be due to the decreased activity of MnSOD caused by the post-translational modification brought on by inducible nitric oxide.[19] Nitration of the aorta in aging rats secondary to high production of O_2.-has also been demonstrated.[18] The decreased activity or inactivation of MnSOD leads to the accumulation of O_2.-and peroxynitrite. The role of inducible nitric oxide synthase in increasing oxidative stress and increasing the risk of heart damage in the aging population has been implicated in hypertension and congestive heart failure.[20] O_2 has also been shown to inactivate nitric oxide (NO) by binding with it. Since NO is a vasodilator and anticoagulant, the inactivation of NO leads to the production of oxidant peroxynitrite which causes endothelial dysfunction, leading to diseases like hypercholesterolemia and atherosclerosis.[21] MnSOD is essential in the prevention of ill effects caused by peroxynitrite by precluding the inactivation of NO in the mitochondria. Aging is associated with increased incidence of cardiovascular disease. Age dependent increase in O_2.-causes reduced NO secondary to inactivation by O_2. The resulting increase in mitochondrial oxidative stress causes age related vascular dysfunction. Aging mice models show MnSOD is also impaired with the increase in O_2 and peroxynitrite.[22] A study by Roos et al. shows that decrease in the mitochondrial antioxidant capabilities due to age is one of the factors for the development of cardiovascular disease but not necessarily the reason for their development.[23] Cardiac arrhythmia can be secondary to oxidative damage, and as studies have shown, the beneficial effect of MnSOD in reducing oxidative stress makes us think that MnSOD may have a

role in preventing arrhythmia. Overall, the studies that focus on the process of reversing the post-translational modification of MnSOD may make its role clearer in disease states and thus their prevention. In conclusion, to progress the diagnosis of patients with heart diseases, we need to develop therapeutic approaches based on an innovative insight into the pathophysiology of myocardial remodelling and heart failure.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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