LUPINE PUBLISHERS

Advancements in Cardiology Research & Reports

DOI: 10.32474/ACRR.2022.04.000176

ISSN: 2770-5447

Review Article

A Novel Molecular Pathway Linking BRCA1 Dysfunction To High Risk for Cardiac Disease

Nicholas Wilson[1], Chataigne Michara[1], Jingyao Xu[1], Alexis Clark[1], Omojolaade Akintade[1], Vaishali Reddy[2], Antoine Andreya[1], Dinesh Shiwlochan[1], Lee S Caplan[3], Joel Okoli[4], E Shyam P Reddy[1] and Veena N Rao[1]*

[1] *Cancer Biology Program, Department of OB/GYN,*

[2] *Internal Medicine,*

[3] *Community Health and Preventive Medicine,*

[4] *Surgery, Morehouse School of Medicine, Atlanta, Georgia 30310-1495*

***Corresponding author:** Veena N Rao, Professor and Co-Director Cancer Biology Program, GCC, Distinguished Cancer Scholar, Department of OB/GYN, Morehouse School of Medicine. RW D-335, 720 Westview Drive, Atlanta, Georgia 30310, USA

Received: August 10, 2022 **Published:** August 16, 2022

Abstract

Cardiovascular disease is a collection of pathologies related to the heart and surrounding blood vessels. A recent study demonstrated a link between BRCA1 gene mutation and the pathogenesis of cardiovascular disease, but the molecular mechanism is not understood. African American women with BRCA1 mutations tend to develop aggressive TNBC associated with a high mortality rate. Our previous work showed BRCA1 to bind to a downstream target Ubc9 resulting in increased SIRT1 expression which facilitated BRCA1 and SIRT1 to translocate to the nucleus and activate ER-α. However, BRCA1 mutations in TNBC impaired tethering to Ubc9 resulting in cytoplasmic localization of these proteins. Loss of Ubc9 function as seen in myocardial ischemia translates to the development of myocardial infarction, cardiovascular disease, and tumorigenesis. Furthermore, a deleterious effect of Ubc9 further manifests as increased activity of VEGF and endothelial cells which influences the progression of cardiovascular disease. VEGF activity is also influenced by the down regulation of Caveolin-1 and SIRT1 which translates to hypertension and tumorigenesis. In healthy individuals, SIRT1 works to prevent arterial stiffness and regulates the apoptosis of cardiomyocytes. SIRT1 also works to localize BRCA1 within the nucleus, and its repression has been linked to cardiovascular dysfunction. Both ER-α and ER-β contribute to cardiovascular function by upregulating protective effects against infarction and reperfusion injury. Specifically, mutation of ER-α leads to increased cardiomyocyte apoptosis. This study proposes a novel molecular pathway linking BRCA1 mutation to cardiovascular disease and proposes potential novel targets to treat BRCA1-associated TNBC with heart dysfunction.

Keywords: BRCA1; Ubc9; Caveolin-1; VEGF; SIRT1

Introduction

Cardiovascular disease is a category of diseases characterized by abnormal pathology in the heart or circulatory system; these diseases include arterial disease, heart failures, and cardiac dysrhythmias. Based on National Health and Nutrition Examination Survey data collected from 2016, approximately 48% of Americans over the age of 20 years were diagnosed with cardiovascular disease [1]. Considering the recent COVID-19 pandemic, COVID-19 patients with cardiovascular disease had a higher mortality risk compared to COVID-19 patients without cardiovascular disease [2]. These findings highlight the role of expanded treatment options for cardiovascular disease to lower mortality risk and increase patient quality of life. In our study, we worked to increase treatment options by understanding the relationship between the Breast Cancer Gene (BRCA1) mutation and cardiovascular disease. In understanding the interplay between the onset of cardiovascular disease and the BRCA1 gene, we highlighted the role of several mediators involved in this relationship including vascular endothelial growth factor, small ubiquitin-like modifier proteins, Ubc9, Caveolin-1, and SIRT1.

BRCA1

Breast cancer is the leading cause of death in American women. In 2022, it is expected that there will be over 280,000 new invasive breast cancer diagnoses, equivalent to 15% of all new cancer cases [3]. Breast cancer is often associated with mutations in tumor suppressor genes such as BRCA1 and BRCA2. and sensitivity to hormones in response to its quantity of receptors. BRCA1 is a human tumor suppressor gene associated with the etiology of breast and ovarian cancers. It is located on chromosome 17q21 and plays a role in DNA repair, regulation of cellular proliferation, and cardiovascular disease [4,5]. The BRCA1 gene codes for an 1863 amino acid full-length BRCA1 protein [6]. Our lab has identified two splice variants BRCA1a/p110 and BRCA1b/p100 in breast carcinoma [7]. BRCA1 is an essential mediator for homologous recombination by the recruitment of recombinases and double-strand break repairs [8]. Studies have shown that mutations in BRCA1 contribute to genetic instability, dysfunctional DNA repair mechanisms, and an increased risk for developing chronic diseases such as cancers and cardiovascular disease [9,10].

BRCA1 mutation leads to the highest mortality for cardiovascular disease

Breast cancer genes have been shown to be a gatekeeper in cardiovascular health. A recent study has shown that functional BRCA1 proteins have a protective effect on cardiomyocytes by reducing cardiac hypertrophy [11]. BRCA1 is known to be involved in DNA double-strand recombination repair. Studies have also shown that BRCA1 may be associated with other proteins involved in DNA repair mechanisms such as oxidative DNA repair [12]. In a BRCA1 +/+ mouse model treated with induced DNA damage, BRCA1 promoted the shuttle of subnuclear RAD51 foci and homologous recombination repair mechanisms [13]. Upregulated BRCA1 promoted increased RAD51 nuclear localization and recombination repair in cardiovascular tissue [5]. On the other hand, ablation of the BRCA1 gene led to adverse cardiovascular function [5]. Faulty DNA repair mechanisms are a hallmark of various chronic diseases such as cancer and cardiovascular disease. In addition to cancer progression, BRCA1-haploinsufficiency has been shown to cause an increase in epithelial progenitor cells and subsequent vascular dysfunction [14]. Correspondingly, BRCA1 mutations induce suppression of vascular remodeling and increase mortality due to cumulative DNA damage and the induction of p53 apoptotic pathways in cardiomyocytes [5].

BRCA1 and Triple Negative Breast Cancer

Mutations in tumor suppressor genes such as BRCA1 and BRCA2 are an indicator of a predisposition to certain types of breast, ovarian and other cancers [15]. BRCA1 mutation-associated triple-negative breast cancer (TNBC) is an invasive and highly aggressive type of breast cancer. In TNBC, malignant breast cancer cells lack receptors for progesterone, estrogen, and HER2, thus eliciting proliferation and distant metastasis. African American women have disproportional mortality rates due to BRCA1 mutations, TNBC, and cardiovascular disease [16,17].

BRCA1 downstream targets Ubc9, Caveolin-1, and VEGF

BRCA1 activity regulates downstream targets Ubc9, Caveolin-1, and vascular endothelial growth factor (VEGF). Small ubiquitin-like modifier proteins (SUMO) are conjugated in a posttranslational modification resulting in the SUMOylation of the lysine residues on the target protein [18]. SUMOylation has been shown to have protective effects against proteasomal degradation in pathological disease manifestations [19]. SUMO proteins are activated, conjugated, and ligated by E1, E2, and E3 ligase enzymes, respectively. SUMO conjugation is catalyzed by the SUMO- conjugating enzyme, Ubc9. The SUMOylation and deSUMOylation processes contributes to the stability and subcellular localization of factors in chronic disease [20]. In addition, these processes were shown to be modulators in breast cancer and cardiovascular disease [18]. In our previous studies, we found the amino-terminal of BRCA1, BRCA1a, and BRCA1b bind Ubc9, a SUMO-E2 conjugating enzyme [21]. In normal conditions, BRCA1 binds Ubc9 in conjunction with the nuclear localization signal, resulting in the nuclear localization of BRCA1 proteins [22]. However, a BRCA1 disease associated mutation fails to bind to Ubc9 resulting in cytoplasmic localization of BRCA1 proteins [22]. Furthermore, BRCA1 was shown to possess a SUMO-1 and Ubc9 – dependent E3 ubiquitin ligase activity on ER-α. Ubc9 binding mutants have repressed growth inhibition found in ER-α negative breast cancer and TNBC. SUMO proteins are also shown to be involved in cardiomyocyte development, protection, and cardiac gene expression [23]. Myocardial ischemia and oxidative stress decreases Ubc9 activity and subsequently, SUMO-specific cysteine proteases (SENP1 and SENP2) are activated. This results in deSUMOylation in ischemic infarction, cardiovascular disease, and tumorigenesis [24,25]. Hypoxia-inducible factor 1-alpha, HIF-1a, is upregulated inducing the expression of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) as well as endothelial cell (EC) activity. VEGF interruption is associated with vascular toxicity, arterial stiffness, blood pressure, and inflammation [26,27]. Decreased Ubc9 activity contributes to pro-apoptotic pathways and activation of endothelial cells (EC) in cardiovascular tissue. EC activation and ischemic stress are regulated by SUMO conjugated-E2 enzymes in the myocardium, influencing the progression of cardiovascular diseases [28]. Sirtuin-1 (SIRT1) is an NAD+ dependent histone deacetylase that plays a major role in metabolism, tumorigenesis, genomic instability, and cancer metastasis [29,30]. BRCA1 binds Ubc9, shuttling BRCA1 proteins to the nucleus. BRCA1 proteins bind to the promoter region of SIRT1 to inhibit Survivin expression thus mediating cellular proliferation. Correspondingly, Caveolin-1 is also activated which regulates vascular endothelial growth factor (VEGF) and angiogenesis [31]. It is observed that SIRT1 activity increases in the normal heart and has protective effects against inflammation, heart disease, and atherosclerotic plaque formation [32]. SIRT1 activation also attenuates arterial stiffness and hypertension [33].

Mutation carriers at higher risk of cardiovascular disease

BRCA1 mutations that are associated with TNBC, impair the tethering of Ubc9 and shuttling of BRCA1 proteins. Consequently, SIRT1 and Caveolin-1 are repressed. Knockdown of Caveolin-1 and SIRT1 are shown to induce the expression of VEGF, increase vascular permeability, decrease vascular remodeling, and increase hypertension [32,34,35]. Recent studies have shown that BRCA1 plays a role in the maintenance of cardiovascular health [5]. BRCA1 mutations have been shown to induce defective cardiomyocyte function, cardiac toxicity, and ischemic stress [5,36]. African American women have a high incidence of BRCA1 mutations, TNBC, and cardiovascular disease [16,17].

Myocardial distress in response to ischemia and reperfusion are leading risk factors in cardiovascular disease mortality [37,38]. SIRT1 regulates inflammation responses in myocardial ischemia and reperfusion [37]. Thus, SIRT1 regulation is essential for cardiovascular protection and prevention of cardiac cell apoptosis [39]. SUMOylated SIRT1 is localized in the cardiomyocyte nuclei [40]. However, in ischemia, the overproduction of deSUMOylase and SENP2 contribute to reduced nuclear localization of SIRT1. Investigations on the role of Ubc9-deSUMOylation pathways indicate overexpression of SENP2 which contributes to cardiac dysfunction, congenital heart defects, and pro-atherogenesis [41,42]. Therefore, BRCA1 mutation-associated knockdown of SIRT1 expression has negative implications on cardiovascular health. SIRT1 activation is seen as a novel therapeutic target for cardiac ischemia and reperfusion due to its involvement in essential cardiometabolic processes [40].

Role of ER-α, VEGF, and Caveolin-1 in cardiovascular disease

An increase in SIRT1 expression promotes the subcellular nuclear transport of BRCA1 through Ubc9 tethered pathways which are essential in cardiovascular protection and breast cancer modulation. On the other hand, decreased SIRT1 binding affinity promotes cytosolic localization of BRCA1 proteins and cardiovascular dysfunction. In accordance, there is impaired regulation of HIF1-α, VEGF, and Caveolin-1 in BRCA1 mutation-associated cardiovascular disease. As a result, cardiomyocytes have dysfunctional nucleocytoplasmic shuttle mechanisms and cardiac gene expression, as well as pro-apoptotic pathways that ultimately contribute to cardiovascular disease. Hormonal factors such as estrogen are shown to have cardioprotective effects in ischemia and reperfusion through genomic signaling mechanisms [43]. Two of the most common nuclear estrogen receptors are ER-α and ER-β [44]. Estrogen binding to ER-α results in pleiotropic effects that regulate cardiac function [43,44]. ER-α promotes up-regulation of anti-apoptotic gene expression in cardiomyocytes [45,46]. Likewise, in estrogen receptor-negative cancers such as TNBC, these cardioprotective effects are prospectively decreased.

Conclusions

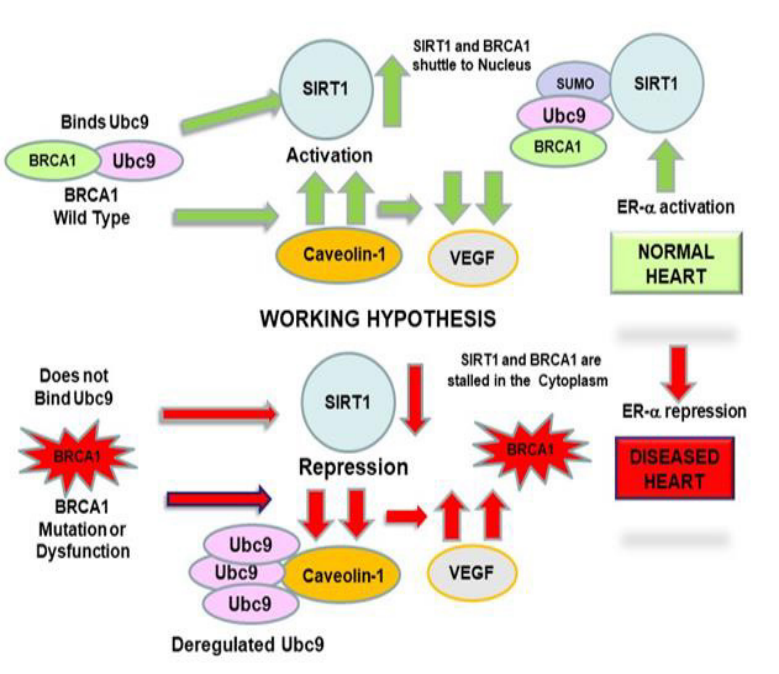

Figure 1: A novel molecular mechanism to show how BRCA1 regulates heart function. BRCA1, by binding Ubc9, facilitates nuclear cytoplasmic shuttling of SIRT1 and ER -α. activation. BRCA1 mutation / dysfunction (as seen in TNBC patients) results in loss of Ubc9 binding cytoplasmic mis-localization of SIRT1, deregulated levels of Ubc9, and ER- α repression resulting in defective heart function.

The BRCA1 tumor suppressor gene has long been affiliated with the differential diagnosis of breast and ovarian cancer; however, there is also an interconnection between BRCA1 gene mutations and a high risk for developing cardiovascular diseases in patients. Along with its many functions, studies have found that the BRCA1 gene has a protective mechanism that contributes to sustaining cardiovascular health, which when disrupted will lead to defective cardiac function. Disturbances in this mechanism are brought about by mutations in the BRCA1 gene, which is unable to bind Ubc9, resulting in down regulation of SIRT1, and Caveolin-1, as well as increasing VEGF levels, thus causing a higher risk for cardiovascular diseases. More research in the future is still needed regarding the mechanism and its implications, which will provide novel ways to treat cardiac diseases as well as TNBC that result from the loss of function of the BRCA1 gene (Figure 1).

ACKNOWLEDGEMENTS:

This work was supported in part by Georgia Cancer Coalition Distinguished Cancer Scholar Award, NIHMD research endowment award 2S21MD000101, U54 MD007602, and U54 CA118638 to V.N.R. V.N.R's lab was also supported in part by funds from the VOYA foundation, EAD Foundation and Breast cancer partnership grant It's the Journey Inc, a Cure in our lifetime and Georgia CORE.

References

1. Benjamin E (2020) Correction to heart disease and stroke statistics-2019 update: A report from the American Heart Association. Circulation 141(2): 33.
2. Azevedo RB, Botelho BG, Hollanda JVG de, Ferreira LVL, Junqueira de Andrade et al. (2021) Covid-19 and the cardiovascular system: a comprehensive review. J Hum Hypertens 35(1): 4-11.
3. 2022 Cancer of the breast (female) - cancer stat facts, SEER.
4. Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA et al. (1990) Linkage of early-onset familial breast cancer to chromosome 17q21. Science 250(4988): 1684-1689.
5. Shukla PC, Singh KK, Quan A, Al-Omran M, Teoh H et al. (2011) BRCA1 is an essential regulator of heart function and survival following myocardial infarction. Nat Commun 2: 593.
6. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, et al. (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266(5182): 66-71.
7. Cui JQ, Shao N, Chai Y, Wang H, Reddy ES et al. (1998) BRCA1 splice variants BRCA1a and BRCA1b associate with CBP co-activator. Oncol Rep 5(3): 591-595.
8. Narod SA, L Salmena (2011) BRCA1 and BRCA2 mutations and breast cancer. Discov Med 12(66): 445-453.
9. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE (1994) Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 343(8899): 692-955.
10. Botto N, Rizza A, Colombo MG, Mazzone AM, Manfredi S et al. (2001) Evidence for DNA damage in patients with coronary artery disease. Mutat Res 493(1-2): 23-30.
11. Lin D, Izadpanah R, Braun SE, Alt E (2018) A novel model to characterize structure and function of BRCA1. Cell Biol Int 42(1): 34-44.
12. Fridlich R, Annamalai D, Roy R, Bernheim G, Powell SN (2015) BRCA1 and BRCA2 protect against oxidative DNA damage converted into double-strand breaks during DNA replication. DNA Repair 30: 11-20.
13. Maser RS, Monsen KJ, Nelms BE, Petrini JH (1997) hMre11 and hRad50 nuclear foci are induced during the normal cellular response to DNA double-strand breaks. Molecular and Cellular Biology 17(10): 6087-6096.
14. Witberg G, Lev E, Ber Y, Tabachnik T, Sela S et al. (2019) Vascular endothelium function among male carriers of BRCA 1&2 germline mutation. Oncotarget 10(49): 5041-5051.
15. Fackenthal JD, Olopade OI (2007) Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev Cancer 7(12): 937-948.
16. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD et al. (2011) Heart disease and stroke statistics-2011 update: a report from the American Heart Association. Circulation 123(4): E18-e209.
17. Dietze EC, Sistrunk C, Miranda-Carboni G, O Regan R, Seewaldt VL (2015) Triple-negative breast cancer in African-American women: disparities versus biology. Nat Rev Cancer 15(4): 248-254.
18. Mendler L, Braun T, Muller S (2016) The Ubiquitin-Like SUMO System and Heart Function: From Development to Disease. Circ Res 118(1): 132-144.
19. Floris A, Mazarei M, Yang X, Robinson AE, Zhou J et al. (2020) SUMOylation Protects FASN Against Proteasomal Degradation in Breast Cancer Cells Treated with Grape Leaf Extract. Biomolecules 10(4): 529
20. Talamillo A, Ajuria L, Grillo M, Barroso-Gomila O, Mayor U et al. (2020) SUMOylation in the control of cholesterol homeostasis. Open Biol 10(5): 200054.
21. Xu J, Watkins T, Reddy A, Reddy ESP, Rao VN, A novel mechanism whereby BRCA1/1a/1b fine tunes the dynamic complex interplay between SUMO dependent/independent activities of Ubc9 on E2-induced ERalpha activation/repression and degradation in breast cancer cells. Int J Oncol 34(4): 939-949.
22. Qin Y, Xu J, Aysola K, Begum N, Reddy V et al. (2011) Ubc9 mediates nuclear localization and growth suppression of BRCA1 and BRCA1a proteins. J Cell Physiol 226(12): 3355-3367.
23. Bian X, Xu J, Zhao H, Zheng Q, Xiao X et al. (2019) Zinc-Induced SUMOylation of Dynamin-Related Protein 1 Protects the Heart against Ischemia-Reperfusion Injury. Oxid Med Cell Longev 2019: 1232146.
24. Rawlings N, Lee L, Nakamura Y, Wilkinson KA, Henley JM (2019) Protective role of the deSUMOylating enzyme SENP3 in myocardial ischemia-reperfusion injury. PLoS One 14(4): E0213331.
25. Heo KS (2019) Regulation of post-translational modification in breast cancer treatment. BMB Rep 52(2): 113-118.
26. Zito C, Manganaro R, Carerj S, Antonini Canterin F, Benedetto F (2020) Peripheral Artery Disease and Stroke. J Cardiovasc Echogr 30(1): S17-s25.
27. Stupin, Mihalj, Kolobaric, Susnjara, Luka Kolar et al. (2020) Anti-Inflammatory Potential of n-3 Polyunsaturated Fatty Acids Enriched Hen Eggs Consumption in Improving Microvascular Endothelial Function of Healthy Individuals-Clinical Trial. Int J Mol Sci 21(11): 4149.
28. Abe JI, Ko KA, Kotla S, Wang Y, Paez Mayorga J et al. (2019) MAGI1 as a link between endothelial activation and ER stress drives atherosclerosis. JCI Insight 4(7): e125570.
29. Rifai K, Judes G, Idrissou M, Daures M, Bignon YJ et al. (2018) SIRT1-dependent epigenetic regulation of H3 and H4 histone acetylation in human breast cancer. Oncotarget 9(55): 30661-30678.
30. Wang J, Schwartz RJ (2010) Sumoylation and regulation of cardiac gene expression. Circ Res 107(1): 19-29.
31. Glait C, Ravid D, Lee SW, Liscovitch M, Werner H (2006) Caveolin-1 controls BRCA1 gene expression and cellular localization in human breast cancer cells. FEBS Lett 580(22): 5268-5274.

32. D'Onofrio N, Servillo L, Balestrieri ML (2018) SIRT1 and SIRT6 Signaling Pathways in Cardiovascular Disease Protection. Antioxid Redox Signal 28(8): 711-732.

33. Gao D, Zuo Z, Tian J, Ali Q, Lin Y, et al. (2016) Activation of SIRT1 Attenuates Klotho Deficiency-Induced Arterial Stiffness and Hypertension by Enhancing AMP-Activated Protein Kinase Activity. Hypertension 68(5): 1191-1199.

34. Forrester SJ, Elliott KJ, Kawai T, Obama T, Boyer MJ et al. (2017) Caveolin-1 Deletion Prevents Hypertensive Vascular Remodeling Induced by Angiotensin II. Hypertension 69(1): 79-86.

35. Xu J, Shumate C, Qin Y, Reddy V, Burnam Y et al. (2017) A novel Ubc9 -dependent pathway regulates SIRT1- ER-α Axis and BRCA1-associated TNBC lung metastasis. Integr Mol Med 4(4).

36. Zbuk K, Xie C, Young R, Heydarpour M, Pare G et al. (2012) BRCA2 variants and cardiovascular disease in a multi-ethnic study. BMC Med Genet 13: 56.

37. Zhang X, Li Y, Wang Y, Zhuang Y, Ren X et al. (2020) Dexmedetomidine postconditioning suppresses myocardial ischemia/reperfusion injury by activating the SIRT1/mTOR axis. Biosci Rep 40(5).

38. Powers SK, Smuder AJ, Kavazis AN, Quindry JC (2014) Mechanisms of exercise-induced cardioprotection. Physiology (Bethesda) 29(1): 27-38.

39. Tong C, Morrison A, Mattison S, Qian S, Bryniarski M et al. (2013) Impaired SIRT1 nucleocytoplasmic shuttling in the senescent heart during ischemic stress. Faseb J 27(11): 4332-4342.

40. Han D, Wang J, Ma S, Chen Y, Cao F (2017) SIRT1 as a Promising Novel Therapeutic Target for Myocardial Ischemia Reperfusion Injury and Cardiometabolic Disease. Curr Drug Targets 18 (15): 1746-1753.

41. Kim EY, Chen L, Ma Y, Yu W, Chang J et al. (2012) Enhanced desumoylation in murine hearts by overexpressed SENP2 leads to congenital heart defects and cardiac dysfunction. J Mol Cell Cardiol 52(3): 638-649.

42. Heo KS, Chang E, Le NT, Cushman H, Yeh ETH et al. (2013) De-SUMOylation enzyme of sentrin/SUMO-specific protease 2 regulates disturbed flow-induced SUMOylation of ERK5 and p53 that leads to endothelial dysfunction and atherosclerosis. Circ Res 112(6): 911-923.

43. Deschamps AM, Murphy E, Sun J (2010) Estrogen receptor activation and cardio protection in ischemia reperfusion injury. Trends Cardiovasc Med 20(3): 73-78.

44. Aryan L, Younessi D, Zargari M, Banerjee S, Agopian J et al. (2020) The Role of Estrogen Receptors in Cardiovascular Disease. Int J Mol Sci 21(12): 4314.

45. Lizotte E, Grandy SA, Tremblay A, Allen BG, Fiset (2009) Expression, distribution and regulation of sex steroid hormone receptors in mouse heart. Cell Physiol Biochem 23(1-3): 75-86.

46. Ropero AB, Eghbali M, Minosyan TY, Tang G, Toro L et al. (2006) Heart estrogen receptor alpha: distinct membrane and nuclear distribution patterns and regulation by estrogen. J Mol Cell Cardiol 41(3): 496-510.

DOI: 10.32474/ACRR.2022.04.000176