Review Article Cardiology

SILENT INFORMATION REGULATOR 2 PROTEINS- SIRTUINS AND CV DISEASE

Danny Kumar MD, DM (AIIMS New Delhi). Consultant Cardiology, Grecian Hospital, Mohali.

KEYWORDS :

Medicine is ever growing and expanding. This century is about how gene controls our life and diseases. This search has become very promising in many strata. Tyrosine kinase activation by t(9,22) in CML, and and search of its inhibitor (TKI) Imatinib, saved and continue to be saving many lives. It's not only holding true in oncology but in all.

Aging is always enigma to researchers and search of sirtuins "anti-aging" protein expanded this field. Story of sirtuins started nearly two decades before, in yeast when sirtuin linked to longevity. [1] Ample work done thereafter and many physiological and pathological roles of these proteins is being studied in recent years. Many functions are related to cardiovascular system and diseases.

Silent Information Regulator 2 (SIR2) proteins—Sirtuins— are family of histone deacetylases (HDACs). Their functions are to catalyse deacetylation of both histone and non-histone lysine residues. Sirtuins are nicotinamide adenine dinucleotide (NAD+) dependant protein unlike other histone deacetylators. They do post-transcriptional modification of wide range of protein. Besides, deacetylase and deacylase activity, some sirtuins do have many other activities eg adenosine diphosphate(ADP)-ribosylase, demalonylase, desuccinylase, or glutarylase properties. Seven different sirtuins and their role have been searched. [2-5]

Basic and quick understanding of their mechanism can be learned by simple flowchart. (Figure - 1)

Calorie restriction and on exercise there is excessive NAD+, as of energy molecule $NADPH_2$ depletes and it activates sirtuins. Sirtuins by modification of various proteins had varsality in their function.

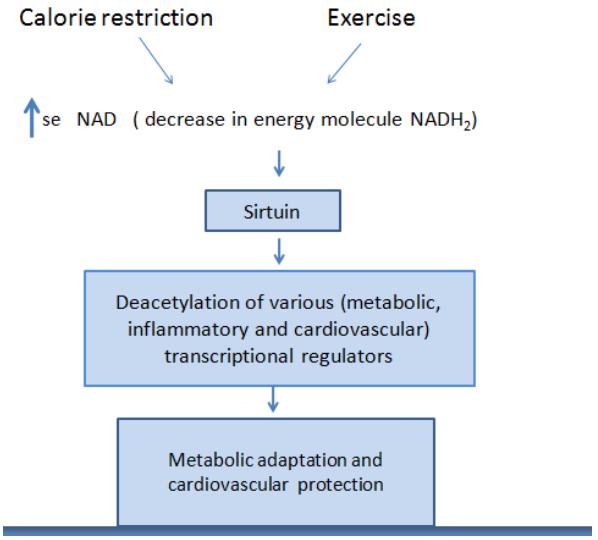

Figure 1 – Basic mechanism of sirtuins

Sirt 1, Sirt 3, Sirt 6 and Sirt 7 are chiefly studied in experimenatal mice and few in human being.

Initial description is from mice studies and followed by what yet studied in human in related to cardiovascular diseases.

Neurodegenerative disorder as Alzheimer disease and cancer are other field where sirtuins are extensively studied.

Sirt 1

This protein present both in the nucleus and cytoplasm. Sirt1 studied most among all seven sirtuin isoforms.

- Sirt1 activates endothelial nitric oxide synthase (eNOS). [6]
- It also decreases NFkB activity in endothelial cells and macrophages, NFkB major molecule of inflammation. [7-9]
- Its role as a master regulator of mitochondrial integrity. [10]
- Sirt1 activation lowers plasma LDL-C levels via
- proprotein convertase subtilisin/kexin 9 (Pcsk9) secretion inhibition.this increases hepatic LDL-receptor (LDL-R) availability and lead to decrease in LDL –C. [11]
- Its activation also suppress tissue factor and it activates cyclooxygenase-2-derived prostacyclin and PPARd that lea to decrease arterial thrombus formation. [12]

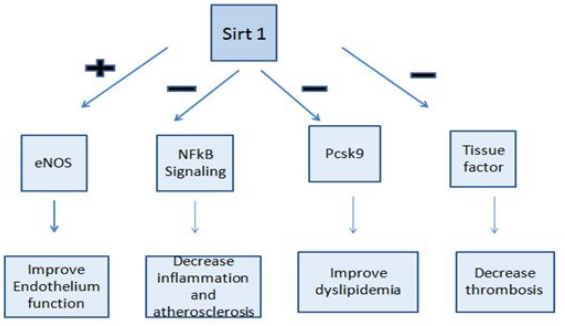

Figure 2 – Functions of Sirtuin 1

Sirt 3

- Sirt 3 is located in the mitochondria Sirt3 chiefly shown to regulate global mitochondrial lysine acetylation,thatpreserve mitochondrial function And enchance antioxidant defense. As its known that mitochondrial dysfunction is related to much cardiac illness.
- Activation of Sirt 3 - it decreases cellular levels of reactive oxygen species (ROS), by deacetylation and activation of superoxide dismutase 2 (SOD2) [14-16] diminishes cardiac hypertrophy, and may improve endothelial dysfunction and improve heart failure. [17]
- Activation of Sirt 3 activation of transcription factors (NFATc2, STAT3, and HIF1a) and prevent the development of pulmonary hypertension. [18] and preventing the development of risk factors associated with the metabolic syndrome. [15]

Sirt 6

- It is a nuclear chromatin-associated deacylase. Akin of sirt 1 it decreases NFkB activity and also lead to decrease in LDL –C via PSCK9 inhibition.
- It also had role in telomere and genome stabilization, [21] gene expression and DNA repair, [22] glucose and fat homeostasis, [23–25]

- Sirt6 is down regulator of myocardial IGF-Akt signaling pathway, a pathway whose activation causes cardiac hypertrophy.[20]

Sirt 7

Sirt7 deacetylates distinct lysine residues located in the hetero- and homodimerization domains of GA-binding protein (GABP)b1, a master regulator of nuclear-encoded mitochondrial genes, improves mitochondrial function in numerous tissues including cardiac and skeletal muscle where it protects from cardiomyopathy, lowers lactate levels, and improves exercise performance, respectively. Moreover, Sirt7 protects from hepatic micro-vesicular steatosis.[27-28]

Human studies –

Most of studies being done in mice and data on sirtuins in human cardiovascular diseases are limited. Lower sirtuins expression level is reported in different cardiovascular disease compare to healthy control.

Sirt 1 level found low in insulin resistant condition as sirt 1 mRNA level linked to insulin sensitivity.[13]

Sirt1 expression levels found lower when compared between diseased carotid arteries and non disease arteries and also found lower in monocytes of patients of ACS.[16,29]

Incretin treatment in diabetes also shown to stabilize plaque by enhanced Sirt6 expression[30] Mutation of Sirt1 (point mutation) was associated with human type 1 diabetes and ulcerative colitis.[31] Sirt3 deficiency was associated with PAH and metabolic syndrome not only in mice but also in human.[18,19].In heart failure patient also Sirt6 levels were decreased.[50]
Yet, there are no reports about genetic variants of Sirt7 and human disease.

Pharmacological modulation of sirtuin activity: Activating Drugs

Specific Sirt1-activating compounds (STACs) applied in experimental mice and improved survival and health span. They have shown mitochondrial activation and subsequent prevention of obesity with improvement in diabetes in obese mice. STACs have shown beneficial effects in mice for atherosclerosis protection[11,32]In healthy smokers for these molecule shown improving endothelial dysfunction and lowering LDL-C.[33] Sirt1-specific activators are beneficial as stated above, pan-sirtuin activators might be more effective.[34-36]

Polyphenols compound such as resveratrol and non polyphonic compound act to SIRT1 by either indirectly by other intermediate protein or by allosteric modulation of SIRT1.

Resveratrol, found in red wine and grapes, is an STACs, we still need an RCT to reach any conclusion regarding its benefit. Till now studies had shown contradictory result.[37-40] Inconsistencies of its benefit may result from the known limitations of resveratrol in bioavailability, pharmacokinetics, and target specificity.

All sirtuins requires metabolite NAD+ is an essential co-substrate for the activity. High-fat diet, DNA damage, and aging depletes its level.[35]

Sirtuin-dependent beneficial effects of increasing NAD+ levels on metabolic homeostasis suggest that this strategy provides a novel and promising concept for cardiovascular protection.

To conclude, these are unique class of proteins that link protein modification with various effects on physiology, aging and many pathology including cardiovascular, neurodegenerative and cancer. Development of drugs targeting sirtuins to treat these diseases is ongoing research and will continue further in future.

REFERENCES

1. Kaeberlein M, McVey M, Guarente L. The SIR2/3/4 complex and SIR2 alone promote longevity in Saccharomyces cerevisiae by two different mechanisms. Genes Dev 1999;13:2570–80
2. Guarente L, Franklin H. Epstein lecture: sirtuins, aging, and medicine. N Engl J Med 2011;364:2235–44
3. Houtkooper RH, Pirinen E, Auwerx J. Sirtuins as regulators of metabolism and healthspan. Nat Rev Mol Cell Biol 2012;13:225–38.
4. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res 2012;110:1097–108.
5. White AT, Schenk S. NAD(+)/NADH and skeletal muscle mitochondrial adaptations to exercise. Am J Physiol Endocrinol Metab 2012;303:308–21.
6. Nisoli E, Tonello C, Cardile A, Cozzi V, Bracale R, Tedesco L, Falcone S, Valerio A, Cantoni O, Clementi E, Moncada S, Carruba MO. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. Science 2005;310: 314–17.
7. Stein S, Schafer N, Breitenstein A, Besler C, Winnik S, Lohmann C,Heinrich K, Brokopp CE, Handschin C, Landmesser U, Tanner FC, Luscher TF, SIRT1 reduces endothelial activation without affecting vascular function in ApoE-/- mice. Aging (Albany NY) 2010;2:353- 60.
8. Stein S, Lohmann C, Schafer N, Hofmann J, Rohrer L, Besler C, Rothgiesser KM, Becher B, Hottiger MO, Boren J, McBurney MW, Landmesser U, Luscher TF, Matter CM. SIRT1 decreases Lox-1-mediated foam cell formation in atherogenesis. Eur Heart J 2010;31:2301–09.
9. Zhang QJ, Wang Z, Chen HZ, Zhou S, Zheng W, Liu G, Wei YS, Cai H, Liu DP, Liang CC. Endothelium-specific overexpression of class III deacetylase SIRT1 decreases atherosclerosis in apolipoprotein E-deficient mice. Cardiovasc Res 2008;80:191–9.
10. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 2006;127:1109–22.
11. Miranda MX, van Tits LJ, Lohmann C, Arsiwala T, Winnik S, Tailleux A, Stein S, Gomes AP, Suri V, Ellis JL, Lutz TA, Hottiger MO, Sinclair DA, Auwerx J, Schoonjans K, Staels B, Luscher TF, Matter CM. The Sirt1 activator SRT3025 provides atheroprotection in Apoe-/- mice by reducing hepatic Pcsk9 secretion and enhancing Ldlr expression. Eur Heart J 2015;36:51–9.
12. Barbieri SS, Amadio P, Gianellini S, Tarantino E, Zacchi E, Veglia F, Howe LR, Weksler BB, Mussoni L, Tremoli E. Cyclooxygenase-2-derived prostacyclin regulates arterial thrombus formation by suppressing tissue factor in a sirtuin-1-dependent-manner. Circulation 2012;126:1373–84. Rutanen J, Yaluri N, Modi S, Pihlajamaki J, Vanttinen M, Itkonen P, Kainulainen S, Yamamoto H, Lagouge M, Sinclair DA, Elliott P, Westphal C, Auwerx J, Laakso M. SIRT1 mRNA expression may be associated with energy expenditure and insulin sensitivity. Diabetes 2010;59:829–35.
13. Qiu X, Brown K, Hirschey MD, Verdin E, Chen D. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. Cell Metab 2010;12:662–7.
14. Winnik S, Gaul DS, Preitner F, Lohmann C,Weber J, Miranda MX, Liu Y, van Tits LJ, Mateos JM, Brokopp CE, Auwerx J, Thorens B, Luscher TF, Matter CM. Deletion of Sirt3 does not affect atherosclerosis but accelerates weight gain and impairs rapid metabolic adaptation in LDL receptor knockout mice: implications for cardiovascular risk factor development. Basic Res Cardiol 2014;109:399.
15. Tao R, Coleman MC, Pennington JD, Ozden O, Park SH, Jiang H, Kim HS, Flynn CR, Hill S, Hayes McDonaldW, Olivier AK, Spitz DR, Gius D. Sirt3-mediated deacetylation of evolutionarily conserved lysine 122 regulates MnSOD activity in response to stress. Mol Cell 2010;40:893–904.
16. Hafner AV, Dai J, Gomes AP, Xiao CY, Palmeira CM, Rosenzweig A, Sinclair DA. Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy. Aging (Albany NY) 2010;2:914–23.
17. Paulin R, Dromparis P, Sutendra G, Gurtu V, Zervopoulos S, Bowers L, Haromy A, Webster L, Provencher S, Bonnet S, Michelakis ED. Sirtuin 3 deficiency is associated with inhibited mitochondrial function and pulmonary arterial hypertension in rodents and humans. Cell Metab 2014;20:827–39
18. Hirschey MD, Shimazu T, Jing E, Grueter CA, Collins AM, Aouizerat B, Stancakova A, Goetzman E, Lam MM, Schwer B, Stevens RD, Muehlbauer MJ, Kakar S, Bass NM, Kuusisto J, Laakso M, Alt FW, Newgard CB, Farese RV Jr, Kahn CR, Verdin E. SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Mol Cell 2011;44: 177–90.
19. Sundaresan NR, Vasudevan P, Zhong L, Kim G, Samant S, Parekh V, Pillai VB, Ravindra PV, Gupta M, Jeevanandam V, Cunningham JM, Deng CX, Lombard DB, Mostoslavsky R, Gupta MP. The sirtuin SIRT6 blocks IGF-Akt signaling and development of cardiac hypertrophy by targeting c-Jun. Nat Med 2012;18:1643–50.
20. Michishita E, McCord RA, Berber E, Kioi M, Padilla-Nash H, Damian M, Cheung P, Kusumoto R, Kawahara TL, Barrett JC, Chang HY, Bohr VA, Ried T, Gozani O, Chua KF. SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin. Nature 2008;452:492-6.
21. McCord RA, Michishita E, Hong T, Berber E, Boxer LD, Kusumoto R, Guan S, Shi X, Gozani O, Burlingame AL, Bohr VA, Chua KF. SIRT6 stabilizes DNA-dependent protein kinase at chromatin for DNA double-strand break repair. Aging (Albany NY) 2009;1:109–21.
22. Zhong L, D'Urso A, Toiber D, Sebastian C, Henry RE, Vadysirisack DD, Guimaraes A, Marinelli B, Wikstrom JD, Nir T, Clish CB, Vaitheesvaran B, Iliopoulos O, Kurland I, Dor Y, Weissleder R, Shirihai OS, Ellisen LW, Espinosa JM, Mostoslavsky R. The histone deacetylase Sirt6 regulates glucose homeostasis via Hif1alpha. Cell 2010;140:280–93.
23. Kanfi Y, Peshti V, Gil R, Naiman S, Nahum L, Levin E, Kronfeld-Schor N, Cohen HY. SIRT6 protects against pathological damage caused by diet-induced obesity. Aging Cell 2010;9:162–73.
24. Tao R, Xiong X, DePinho RA, Deng CX, Dong XC. FoxO3 transcription factor and Sirt6 deacetylase regulate low density lipoprotein (LDL)-cholesterol homeostasis via control of the proprotein convertase subtilisin/kexin type 9 (Pcsk9) gene expression. J Biol Chem 2013;288:29252–9.
25. Kawahara TL, Michishita E, Adler AS, Damian M, Berber E, Lin M, McCord RA, Ongaigui KC, Boxer LD, Chang HY, Chua KF. SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span. Cell 2009;136:62–74.
26. Ryu D, Jo YS, Lo Sasso G, Stein S, Zhang H, Perino A, Lee JU, Zeviani M, Romand R, Hottiger MO, Schoonjans K, Auwerx J. A SIRT7-dependent acetylation switch of GABPbeta1 controls mitochondrial function. Cell Metab 2014;20:856–69.

27. Vakhrusheva O, Smolka C, Gajawada P, Kostin S, Boettger T, Kubin T, Braun T, Bober E. Sirt7 increases stress resistance of cardiomyocytes and prevents apoptosis and inflammatory cardiomyopathy in mice. Circ Res 2008;102:703–10.
28. Breitenstein A, Wyss CA, Spescha RD, Franzeck FC, Hof D, Riwanto M, Hasun M, Akhmedov A, von Eckardstein A, MaierW, Landmesser U, Luscher TF, Camici GG. Peripheral blood monocyte Sirt1 expression is reduced in patients with coronary artery disease. PLoS ONE 2013;8:e53106.
29. Balestrieri ML, Rizzo MR, Barbieri M, Paolisso P, D'Onofrio N, Giovane A, Siniscalchi M, Minicucci F, Sardu C, D'Andrea D, Mauro C, Ferraraccio F, Servillo L, Chirico F, Caiazzo P, Paolisso G, Marfella R. Sirtuin 6 expression and inflammatory activity in diabetic atherosclerotic plaques: effects of incretin treatment. Diabetes 2015;64:1395–1406.
30. Biason-Lauber A, Boni-Schnetzler M, Hubbard BP, Bouzakri K, Brunner A, Cavelti-Weder C, Keller C, Meyer-Boni M, Meier DT, Brorsson C, Timper K, Leibowitz G, Patrignani A, Bruggmann R, Boily G, Zulewski H, Geier A, Cermak JM, Elliott P, Ellis JL, Westphal C, Knobel U, Eloranta JJ, Kerr-Conte J, Pattou F, Konrad D, Matter CM, Fontana A, Rogler G, Schlapbach R, Regairaz C, Carballido JM, Glaser B, McBurney MW, Pociot F, Sinclair DA, Donath MY. Identification of a SIRT1 mutation in a family with type 1 diabetes. Cell Metab 2013;17:448–55
31. Mercken EM, Mitchell SJ, Martin-Montalvo A, Minor RK, Almeida M, Gomes AP, Scheibye-Knudsen M, Palacios HH, Licata JJ, Zhang Y, Becker KG, Khraiwesh H, Gonzalez Reyes JA, Villalba JM, Baur JA, Elliott P, Westphal C, Vlasuk GP, Ellis JL, Sinclair DA, Bernier M, de Cabo R. SRT2104 extends survival of male mice on a standard diet and preserves bone and muscle mass. Aging Cell 2014;13:787–96.
32. Venkatasubramanian S, Noh RM, Daga S, Langrish JP, Joshi NV, Mills NL, Hoffmann E, Jacobson EW, Vlasuk GP, Waterhouse BR, Lang NN, Newby DE. Cardiovascular effects of a novel SIRT1 activator, SRT2104, in otherwise healthy cigarette smokers. J Am Heart Assoc 2013;2:e000042.
33. Gomes AP, Price NL, Ling AJ, Moslehi JJ, Montgomery MK, Rajman L, White JP, Teodoro JS, Wrann CD, Hubbard BP, Mercken EM, Palmeira CM, de Cabo R, Rolo AP, Turner N, Bell EL, Sinclair DA. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear mitochondrial communication during aging. Cell 2013;155:1624–38.
34. Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D, Canto C, Mottis A, Jo YS, Viswanathan M, Schoonjans K, Guarente L, Auwerx J. The NAD(+)/Sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. Cell 2013;154:430–41.
35. Houtkooper RH, Auwerx J. Exploring the therapeutic space around NAD+. J Cell Biol 2012 ; 199:205–09.
36. Crandall JP, Oram V, Trandafirescu G, Reid M, Kishore P, et al. Pilot study of resveratrol in older adults with impaired glucose tolerance. J Gerontol A Biol Sci Med Sci. 2012;67:1307–12.
37. Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab. 2011;14:612–22
38. Yoshino J, Conte C, Fontana L, Mittendorfer B, Imai S, et al. Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. Cell Metab. 2012;16:658–64.
39. Poulsen MM, Vestergaard PF, Clasen BF, Radko Y, Christensen LP, et al. High-dose resveratrol supplementation in obese men: an investigator-initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. Diabetes. 2012;62:1186–95.