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SIRTUIN 3: THE MOST ADVANTAGEOUS ENZYME - A REVIEW

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ABSTRACT

Sirtuin-3 or SIRT3 belongs to the sirtuin family which are homologs of Sir2 of the yeast. It is a NAD^+ dependent deacetylase which is the regulator of mitochondrial protein functions. It can regulate cell-metabolism process, redox homeostasis and various health disorders like inflammation-related diseases. It consists of two domains: large Rossmann fold and small Zn^{2+} binding site. It interacts with many types of molecular targets like AceCS2, p53, GDH, etc. And regulate several cellular functions. The main function of SIRT3 is to exhibit protection from various neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), etc. It helps in the regulation of cellular metabolism. Based on the type of cells it acts on, SIRT3 acts as a tumour-suppressor as well as oncogene.

INTRODUCTION

Sirtuins are produced by silent information regulator genes abbreviated as SIR genes. They consist of a family of proteins present in various organisms like bacteria to mammals[1]. As *Jang et.al.*said, they are a type of enzymes which are Nicotinamide Adenine Dinucleotide (NAD^+) dependent deacetylases where NAD^+ helps in the catalysis of the biological reactions[2]. *Imai S. et. al.* stated that the *Saccharomyces cerevisiae* gene that is, yeast gene, is the primitive silent information regulator 2 or Sir2protein which was then identified as histone deacetylase that is NAD^+ dependent [3]. The human sirtuins are Sir2 homologs. *Akeidaet. al.* proposed that the mammalian sirtuin family consists of seven types of sirtuins; SIRT1 - SIRT7[4]. Each protein is encoded by the corresponding gene; for example: SIRT1 is encoded by the SIRT1 gene, SIRT2 is encoded by SIRT2 gene. Each sirtuin has its own functions. SIRT1 has tumour suppressing ability[5]. SIRT2 helps in regulating the metabolism of mammals[6]. As stated by *Bell E.L. et. al.*, SIRT3 inhibits tumour growth and is also a promoter of carcinogenesis[7]. SIRT4 regulates the activation of GDH(glutamate dehydrogenase)[8]. Nakagawa et. al. Stated that SIRT5 has an action in the animal urea cycle[9]. SIRT6 has metabolic actions. SIRT7 helps in the regulation of RNA polymerase[10]. Among these seven sirtuins, SIRT3 has much clinical relevance. Sirtuin-3 is a sirtuin enzyme

which is mainly located in mitochondria. It is a NAD^+ dependent deacetylase enzyme. Its main action is to regulate the functions of proteins in mitochondria. It is one of the important proteins seen in mitochondria that can act as a principal stress-responsive deacetylase enzyme [11-12]. It can act on mitochondrial proteins for the deacetylation of the amino acid lysine (*Y Chen. et.al.*). Another action is that it can regulate various cellular functions. It can regulate cell-metabolism process, ATP generation, redox homeostasis and various health disorders like inflammation-related diseases.

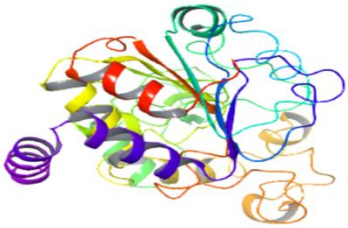

Fig. 1: Structure of Sirtuin-3

One of the first substrates that were used for SIRT3 was acetyl-CoA synthetase 2 (AceCS2). *Hallows W. C. et. al.* stated that together with glutamate dehydrogenase (GDH), AceCS2 showed that in mitochondrial metabolism, SIRT3 functions as a regulator. Here, AceCS2 undergoes activation by the deacetylation process by SIRT3 [13]. This deacetylation can be responsible for the increased enzymatic activity of glutamate dehydrogenase (GDH). This results in the oxidation of several amino acids [14].

Due to the activity of GDH and AceCS2 on SIRT3, there is independence in the liver glycolysis process and so SIRT3 has an important role in calorie restriction. MRPL10, a mitochondrial ribosomal protein is found to be a specifoc target of SIRT3. From this, it can conclude that SIRT3 has a major role in mitochondrial respiration [15]. *Ahn BH et. al.* stated that SIRT3 might have some interactions with the electron transport chain (ETC). It interacts with the subunits of ETC that are complex I and complex II. This results in the potentiated activity of both the complexes of ETC [16].

SIRT3 has a function regarding the regulation of proper mitochondrial function that is it can control oxidative stress. *Shi T. et. al.* proposed that this causes a reduction in the membrane potential of mitochondria leading to the decrease in the production of reactive oxygen species (ROS) [17].

Structural Properties of SIRT3

As we know that all human sirtuins are homologs of Sir2, they all (including SIRT3) contain core domain which consists of sequence motifs [18]. It has been reported that for human SIRT3, there is crystalline structure also [19]. It consists of different C-terminal and N-terminal regions. The SIRT3 structure has an enzymatic core having a catalytic site mainly consisting of two domains. The parts of the SIRT3 structure are; Rossman fold, the large domain, Zinc binding site, the small domain, flexible loop, inerface - catalysis site and the C-terminus and N-terminus. This depiction consists of a large domain and a small domain and an interface-catalysis site. The NAD^+ binding site is the large domain which is seen in orange colour and it is a Rossmann fold-like structure. The small domain consists of Zn^{2+} binding site which can be seen highlighted in cyan colour. The apo-structure without the substrate is given below.

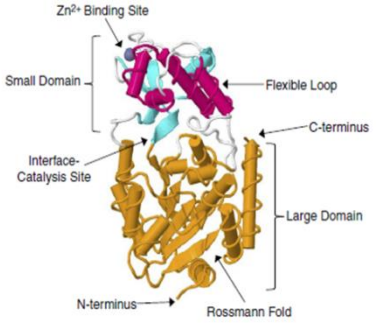

Fig. 2: Apo-structure of SIRT3

The large domain has two insertions. According to *Nguyen G. T. et. al.,* these insertions bind to the Zn atom leading to the formation of the small domain [20]. The binding of the cleft between the large and small domains occurs with presence of a peptide substrate that has undergone acetylation (*Nguyen GT et. al.*). The helical module can be seen highlighted in magenta colour. The domain interface loops are depicted in white (*Jin et al.*). The Rossmann domain is a largely super-imposable fold. The closure of this domain or lobe occurs when there is any binding interaction between the protein and a substrate [21]. The domain interface loop is a flexible loop and the separation or branching of the protein structures occurs at this loop. This loop then, closes down on the NAD^+ C-pocket. *Sanders BD et.al.*reportedthatSIRT3 consists of a co-factor binding pocket. This pocket is composed of three sites: the adenine ribose moiety of NAD^+, the nicotinamide ribose moiety and the catalytic centre located deep inside the pocket [22]. SIRT3 is composed of class I core domain sequences. Many studies like mutagenesis have proposed that the interface of the large domain and small domain acts as the catalytic site. At the N-terminal, it contains a mitochondrial processing peptide having an enzymatic core composed of two domains. *X Wen et. al.* Stated that the main sites seen on the SIRT3 protein are deacetylase sirtuin-type domain, nucleotide binding site, active site and metal binding site [23].

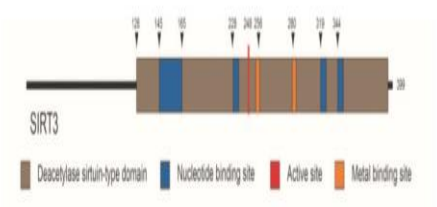

Fig. 3: Various sites of SIRT3

Localisation of SIRT3

SIRT3 is a mitochondrial deacetylase protein. It is located in the mitochondrial matrix of the cells. But, it can be seen located in the nucleus rarely. These sirtuins which are located in the nucleus can travel from the nucleus to the mitochondria during cellular stress. But, *Haigis. M. C. et. al.* stated that the main location is the mitochondria and this is because, they consist of mitochondrion-targeting sequences in their N-terminal [24].

Tissue Distribution of SIRT3

The first human sirtuin reported to be localized to mitochondria is SIRT3 [25]. The localization of the sirtuin to the mitochondrial matrix is essential for its activity. *Schweret. al.* says that the enzymatic activity is due to the cleavage of the signal of sequences [26]. There are two different isoforms of SIRT3. They are short length and full length forms. They are expressed in both humans and mice [27]. They are seen in differentially distributed tissue specific manner. According to *Cooper H. M. et. al.,* there are various types of variants present. They are M1, M2 and M3. M1 and M2 are located to the mitochondria when the M3 is located to the nucleus [28]. The localisation of both short and full length isoforms is not certain yet. Earlier, it was reported that the full length form is localised only to the mitochondria and the short length form to the nucleus and the cytoplasm. Now, *Scher M.B. et. al.* proposed that under basic conditions, it appears to be present in the nucleus and then, moves to the mitochondria under cellular stress [29]. The matter of localisation of SIRT3 has been an interesting topic sine a very long time that it became a talk. Therefore, so many studies have been done with various expressions of SIRT3. The subcellular fractionation study has also been done and it stated that no human SIRT3 could be found in the cell-nucleus failed to find hSIRT3 in the nucleus. So, it is seen particularly in mitochondria [30].

Molecular Targets and Cellular Functions of SIRT3

Many types of substrates can bind and interact with SIRT3 and can potentiate many activities of it like mitochondrial metabolism [31]. SIRT3 functions these activities by the deacetylation process [32]. These molecular targets include acetyl-CoA synthase 2, HMG-CoA synthase 2, glutamate dehydrogenase, p53, cyclophilin D, Ku70, FOXO3a, succinate dehydrogenase, manganese superoxide dismutase (MnSOD), ATP & electron transport chain, etc. For each target-protein binding, there is an activity caused by the interaction. Many cellular functions are carried out due to the interaction of SIRT3 and the molecular targets. It includes synthesis of cholesterol and fatty acids, production of ketone bodies, aging process, cardiac protection, etc. These activities of SIRT3 on various molecular targets can be studied and used for various research purposes. These are the various molecular targets acting on the sirtuin 3 protein and the functions exhibited by them are given below.

AceCS2

Acetyl-CoA synthase 2 or AceCS2 was found to be the first mitochondrial substrate of SIRT3 [33]. *Schweret. al.* said that the action of SIRT3 on AceCS2 is deacetylation and its activation. Due to this, SIRT3 has an activity on increasing the biosynthesis of cholesterol and fatty acids.

p53: SIRT3 induces the suppression of the activity of p53 that may lead to increase in cell arrest causing growth arrest and aging (*Yang J et.al.*) [34]. p300/H3-K56 - It increases the DNA repair.

Ku70: SIRT3 deacetylates Ku70 and this leads to the protection of cardiomyocytes from cell-death due to the induction of stress. So, as stated by *Sundaresan N. R. et.al.*,SIRT3 causes increase in the protection of cardiomyocytes[35].

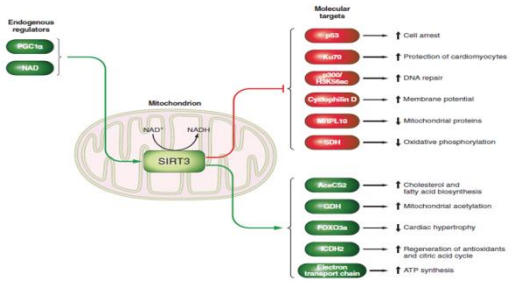

Fig. 4: Molecular targets of SIRT3

Cyclophilin D - It increases the membrane potential.

MRPL10

SIRT3 causes the deacetylation of MRPL10. As a result of this, the production of mitochondrial proteins is decreased [36].

SDH

Succinate dehydrogenase or SDH enzyme can be seen in mitochondrial oxidative phosphorylation causing it to decrease [37].

GDH

Glutamate dehydrogenase or GDH has the same effect as AceCS2 and HMGCS2. GDH is deacetylated and activated by SIRT3. This causes an increase of mitochondrial acetylation [38].

FOXO3a

FOXO3a may be present in cardiomyocytes. It is activated by SIRT3 protein increasing its activity..*Sundaresan NR et. al.* stated that the activation of FOXO3a by SIRT3 can lead to the inhibition of cardiac hypertrophy.

ICDH2: SIRT3 induces the deacetylation and activation of isocitrate dehydrogenase 2 or ICDH2. According to *Schlicker C. et. al.*,this causes an increase in the citric acid cycle and the regeneration of the anti-oxidants.

Electron Transport Chain: Complex I of electron transport chain or ETC is deacetylated by SIRT3. This increases the

rate of the synthesis of ATP in mitochondria causing the metabolism of energy (*Ahn B. H. et.al.*) [39].

MnSOD: Manganese superoxide dismutase or MnSOD is deacetylated and activated by SIRT3 [40]. This decreases the rate of cardiac hypertrophy.

HMGCS2: Hydroxyl methylglutaryl CoA synthase 2 or HMGCS2 is substrate acting on SIRT3. In mitochondria, by SIRT3, it gets deacetylated and activated in the mitochondria [41]. According to *Shimazu T. et.al.*,activation of HMGCS2 by SIRT3 leads to the production of ketone bodies.

Binding with p53, SIRT3 increases cell-arrest, with p300/H3K56ac it increases the rate of DNA repair, with cyclophilin D, it increases membrane potential, with GDH, it increases mitochondrial acetylation and with ETC, it increases the rate of ATP synthesis. Other cellular functions are protection of cardiomyocytes, decreasing oxidative phosphorylation, decreasing cardiac hypertrophy, etc. An endogenous regulator of SIRT3 is known and is PGC-1α.

VARIOUS ACTIVITIES OF SIRT3

SIRT3 and Neurodegeneration

It is an emerging area of interest that SIRT3 is connected to neurodegeneration. Many researchers have reported that activation of SIRT3 triggers the protection of neural system (*Jie Wu et. al.*). It is also said that suppression of SIRT3 causes neurodegeneration disorders. So,SIRT3 may be an essential target triggering neuroprotection. Neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and multiple sclerosis (*Procaccini C. et.al.*) [42]. The overexpression of SIRT3 may prevent neuronal disorder in various types of neurodegenerative disorders like stroke, AD,PD and HD [43]. There are mitochondrial adaptations which are dependent on SIRT3.

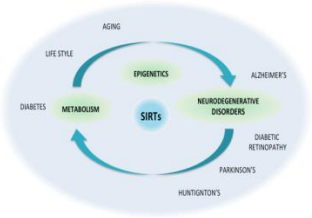

Fig. 5: Sirtuins and neurodegenerative diseases

We know that SIRT3 is localised to the mitochondrial matrix. It interacts with certain targets like AceCS2, PGC-1α,etc. and gets activated. This leads to the control of mitochondrial function and regulation of thermogenesis (*Michishita E. et.al.*) [44]. The neurodegenerative disorders leads to various stress. This regulates the mitochondrial SIRT3. During toxic stress, the level of reactive oxidative species increases and SIRT3 is up regulated which is a characteristic of neurodegenerative disorders like AD [45]. According to *Mattson et.al.,* the upregulation of SIRT3 causes caloric restriction and this reduces the possibility of neurodegenerative disorders in the case of AD and PD [46] and the expression of SIRT3 elevates the lifespan of neurons (*Weir et.al.*)[47]. Mainly, the elevated levels of ROS and also Ca^{2+} can cause neurodegeneration. SIRT3 regulates these levels. Increased oxidative stress triggers the activation of SIRT3 [48]. The upregulation of SIRT3 is an essential process to protect against the increased oxidative stress that can follow the development and progression of AD. SIRT3 gives protective effect on dopaminergic neurons in PD. This increases the activity of mitochondrial enzymes [49]. *Hasegawa et. al.* reported thatPGC-1α regulates the various changes of mitochondrial function in degenerating neurons in PD and PGC-1α is suppressed in the condition of PD. It is confirmed that SIRT3 can regulate the neurodegenerative conditions and the functionality of proteins through its deacetylation activity and modulate the mitochondrial function.

SIRT3 and Cell Metabolism

The activity of SIRT3 has a stronger association with cell-metabolism and this follows the body immune functions [50]. Because, the cell-metabolic functions and immune functions are inter related. The metabolic tissues on which SIRT3 exhibits its functions are hepatic tissue, skeletal muscle tissue and adipose tissue. The activity of SIRT3 on these tissues is depicted below.

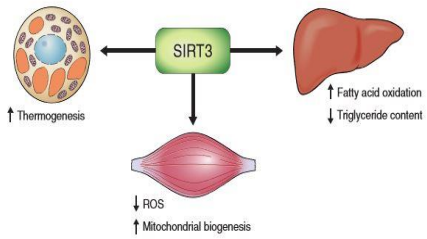

Fig. 6: Metabolic activities of SIRT3 on various tissues

SIRT3 and hepatic function: During the diet of high fat in SIRT3 model, acetylation of liver proteins occurs. This says that SIRT3 plays a major role in hepatic mitochondrial functions as stated by *Kendrick et.al.*[51]. Here, it helps in increasing the rate of fatty acid oxidation. It also helps in decreasing the triglyceride level in the body.

SIRT3 and adipose tissue: SIRT3 is usually seen in high levels in brown adipose tissue and in lower levels in white adipose tissue [52]. The activity of SIRT3 in brown adipose tissue increases the expression of PGC-1α. This leads to an increase in thermogenesis and in the consumption of oxygen. This is the action of SIRT3 on adipose tissue.

SIRT3 and skeletal muscle: During high fat diet, there may be lower levels of SIRT3 in skeletal muscle. But after caloric restriction and fasting, the levels become high [53]. It increases the mitochondrial biogenesis and decreases ROS level (*Palacios et.al.*). The SIRT3 level is increased by various activities like exercise. Low levels of SIRT3 inhibit the activity of PGC-1α.

SIRT3 and Tumourigenesis: We know that one of the main features of tumour is metabolic transformation. SIRT3 plays a major role in the occurrence of tumourigenesis in mammary glands. This leads to the fact that SIRT3 has a tumour-suppressing activity as proposed by *Kim H. et.al.*[54]. So, the action is that, it can inhibit tumourigenesis by the deacetylation and inactivation of S-phase kinase associated protein 2 (Skp2) [55]. SIRT3 function of cancer depends on the type of cells. It can be tumour-suppressing activity or oncogene activity.

As an oncogene: Carcinogenesis is related to the reprogramming of cell metabolism. It is caused by several mechanisms that include transcriptional changes led by the factor HIF-1α. After stabilizing, HIF-1α can move to the nucleus and can cause the transcriptional changes in the genes, here as it is tumour causing genes (*Semenza G.L. et.al.*) [56]. We know that SIRT3 can cause decrease in ROS levels that may lead to the destabilization of HIF-1α and its degradation [57].

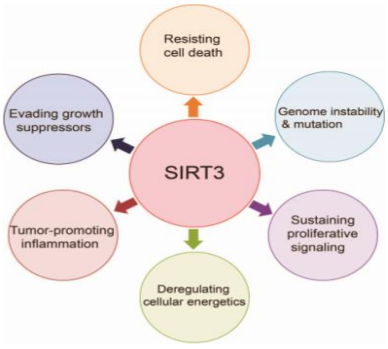

Fig. 7: SIRT3 and tumourigenic action

*Lai C.C.et.al.*stated that SIRT3 is overexpressed in the head and neck squamous cell carcinoma (HNSCC). Here, SIRT3 can control and maintain the levels of ROS at the necessary levels where the apoptosis can be prevented. This can uplift carcinogenesis [58]. SIRT3 has stress-responsive deacetylase activity so that cancer cells can be protected from cell

death. The picture depicting the mechanism of SIRT3 acting as tumourigenic agent is given below.

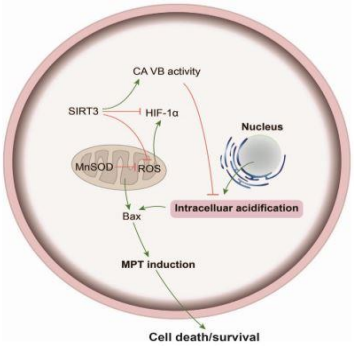

Fig. 8: Tumourogenic mechanism of SIRT3

As a tumour suppressor

SIRT3 can act as a tumour suppressor also. It exhibits this tumour-suppressing activity by reducing the levels of ROS and controlling HIF-1α (*Y Chen. et.al.*). The activation of SIRT3 can cause high levels of p53 and p21 proteins[59]. It decreases the levels of ROS. So, SIRT3 can act as a tumour suppressor in adenocarcinoma of the lungs. SIRT3 acts on various molecular targets for the activity of tumour suppression such as HIF-1α. The main molecular targets for this function of SIRT3 other than HIF-1α are Bax, Caspase 3, Bcl-2, Akt, Erk 1/2, JNK, etc. The picture depicting the mechanism of tumour suppression along with tumourgenesis is given below.

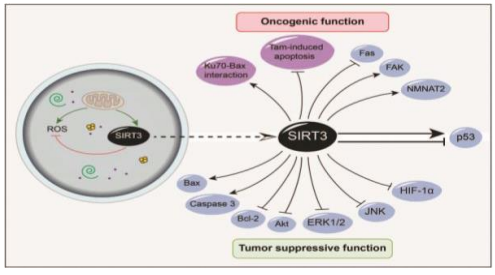

Fig. 9: Oncogenic and tumour suppressive function

CONCLUSION

Sirtuin-3 or SIRT3 is the most advantageous sirtuin member which is a NAD^+ dependent mitochondrial deacetylase. The structure consists of domains which help in the interaction with other molecular targets that leads to various cellular activities. By conducting the study on SIRT3, we could conclude that there are many actions exhibited by the sirtuin in various tissue sites. The activity of SIRT3 has a stronger association with cell-metabolism and this follows the body immune functions as cell-metabolic functions and immune functions were interrelated. Other function is that it exhibits protection against neurodegenerative diseases the knowledge that can be helpful in many occasions as the number of people who get affected with the neurodegenerative diseases is getting increased. Another important field where the action of SIRT3 is helpful is the tumourigenesis. It can inhibit tumourigenesis by the deacetylation and inactivation of S-phase kinase associated protein. Causing transcriptional changes in the genes, it gives protection to the tumour generating genes. SIRT3 can act with derivatives of thiazolidinone to exhibit many of these activities.

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