CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.18434305

Available online at: http://www.iajps.com *Research Article*

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR COACTIVATOR-1A'S FUNCTION IN HEART ISCHEMIA

[1]Miss. Divyanshi Kushwah, [2]Mr. Shashiranjan Yadav, [3]Mr. Shivang Sharma
[1]Assistant Professor, Department of Pharmaceutics;
[2]Assistant Professor, Department of Pharmaceutical Chemistry
[3]Assistant Professor, Department of Pharmaceutics

Abstract:
Cardiovascular disease remains one of the principle cause of death in both developed and developing countries. It may present as a typical myocardial infarction. Increase in cardiac workload impairs myocardial flow and when oxygen supply becomes inadequate to maintain the prevailing work load, relative ischemia develops and this condition is called Myocardial Infarction. Peroxisome proliferator-activated receptor coactivator-1α (PGC-1 α) is a master regulator of oxidative metabolism and mitochondrial function. PGC-1α lacks DNA-binding activity but interacts with nuclear receptors such as peroxisome proliferated activated receptors (PPARs) and co-activates numerous transcription factors like nuclear respiratory factors (NRFs) and estrogen related receptors (ERRs) that are involved in mitochondrial biogenesis, energy metabolism, fatty acid oxidation, antioxidant activity and angiogenesis.

Keywords: *Myocardial Infarction, PGC-1 α, PPAR, NRF, ERR*

Corresponding author:
Divyanshi Kushwah,
Aman Pharmacy Collage, Bus Stand, SH 37,
Near Dholakhera, Udaipurwati-333307, Rajasthan.
Shri Ram College Of Pharmacy, Banmore-476444,
Madhya Pradesh.
E-mail address: Pharmy786@gmail.com

QR CODE

Please cite this article in press Divyanshi Kushwah et al., Peroxisome Proliferator-Activated Receptor Coactivator-1α's Function In Heart Ischemia, Indo Am. J. P. Sci, 2026; 13(01).

1. INTRODUCTION:

1.2. Myocardial Ischaemia-Reperfusion Injury

Rapid reperfusion of the heart by thrombolysis, percutaneous transluminal coronary angioplasty, coronary bypass surgery and cardiac transplantation are the optimal methods to salvage a previously ischemic myocardium resulting in the improvement of myocardial damage and cardiac dysfunction (myocardial stunning) (Baronet al.,).However, reperfusion leads to detrimental myocardial damage i.e. reperfusion injury (RI) that occur due to release of oxygenderived free radicals that opens the mitochondrial permeability transition pore (MPTP) leading to apoptosis, lipid peroxidation leading to breakdown of the sarcolemmal membrane and cell necrosis (Walters et al., ; Kramer et al., ; Hoffman et al.,),dys-regulation of intracellular and mitochondrial calcium, and micro-vascular dysfunction (Baron et al.,).Reperfusion restores the energy required for the completion of apoptosis and can accelerate the apoptotic process (Dumont et al., ; Dumont et al.,; Gottlieb et al.,).

1.3. Mechanisms of Ischaemia-Reperfusion injury

Molecular and cellular events that occur after Ischaemia-Reperfusion injury are very complex. Ischemia induces accumulation of intracellular sodium, hydrogen, and calcium ions that culminates in tissue acidosis. Reperfusion, in turn, elicits rapid alterations in ion flux and rapid renormalization of pH that paradoxically leads to increased cytotoxicity (Bond et al., ; Lemasters et al.,).Sodium-dependent pH regulatory mechanisms, including the Na+ -H + exchanger and the Na+ -HCO3 − transporter, are activated, which lead to intracellular sodium accumulation which increases sarcoplasmic reticular Ca2+ via the Na+ -Ca2+ exchange (Taniet al.,) that promote Ca2+ overload and results in myofibrillar hyper-contractility, ATP depletion, ultra structural damage to mitochondria, and myocardial stunning (Kusuokaet al., ; Nayler, ; Zimmerman et al.,).Cardiac myocytes require large quantities of energy and hence require a high density of mitochondria containing energy-generating organelles, filled with reactive intermediates and pro-apoptotic signals which are involved in Ischaemia-Reperfusion injury. The inner mitochondrial membrane, that maintains mitochondrial trans-membrane potential, is normally impermeable to ions and proteins and dissipation of the electrical potential across this membrane is termed “permeability transition” which is mediated through the mPTP. Formation of the pore creates a non-selective channel between the inner membrane of the mitochondria and the sarcoplasm which results in loss of the electrochemical gradient, release of reactive oxygen species (ROS) and apoptosome formation. Triggers for mPTP include Ca2+ overload (Orreniuset al.,) rapid normalization of pH (Kim et al.,) and oxidative stress (Kim et al., ; Rajesh et al., ; Schild et al.,).

1.3.1. PGC-1 α AS Regulator of Mitochondrial Function

The transcriptional co-activator, PGC-1α was originally identified as peroxisome proliferatoractivated receptor gamma (PPAR-γ) co-activating protein from brown adipose tissue regulating adaptive thermo genesis in response to cold (Cannon et al.,). Later on, it was identified that main function of PGC-1α is to increase oxidative phosphorylation by increasing mitochondrial biogenesis (Clapier et al.,). PGC-1αis also known as human accelerated region20 (HAR20) and is encoded by PPARGC1 gene in humans (Esterbaueret al.,). PGC-1α is highly expressed in tissues with high oxidative capacity or energy demand such as heart, brown adipose tissue, skeletal muscle, kidney and brain (Puigserver et al.,). PGC-1β and PRC are other members of PGC-1α family.

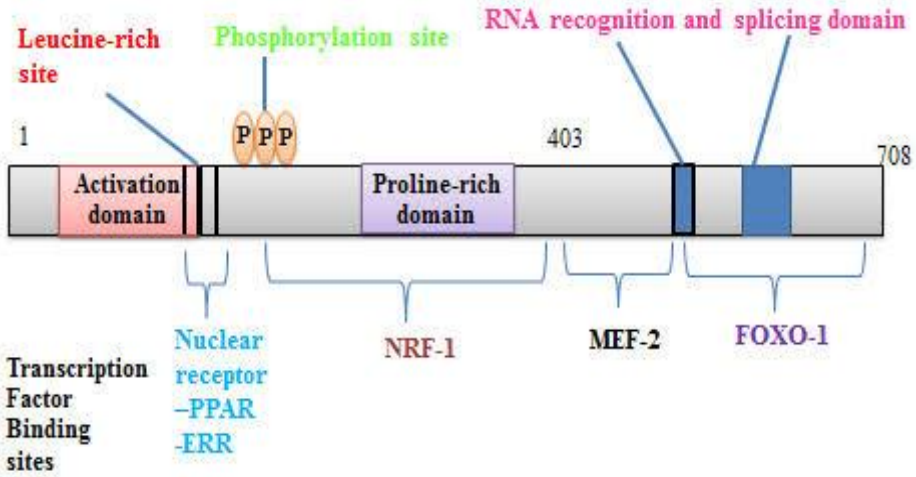

Fig 1: The key functional domains involved in the interaction of PGC-1α with transcription factors.

PGC1α induces mitochondrial biogenesis by co-activation and increase in expression of nuclear respiratory factors (NRF1 and NRF2) (Gigue`re,) leading to increased expression of mitochondrial transcription factor A (mtTFA/Tfam) (Wu et al.,),as well as numerous nuclear genes encoding mitochondrial proteins involved in oxidative phosphorylation (OXPHOS) such as ATP synthase, cytochrome c, and cytochrome c oxidase IV (Barr et al.,).mtTFA translocates to the mitochondrion, where it coordinate transcription and replication of the mitochondrial genome (mtDNA) and resulting in mitochondrial biogenesis i.e. increase in number of mitochondria (Wu et al.,).

PGC-1α has also been implicated in the oxidative stress response by regulating the expression of ROS scavenging enzymes such as catalase, glutathione peroxidase and superoxide dismutase (SOD-1/2) (Pierre et al.,). Moreover, PGC-1α deficient mice have reduced levels of these scavengers (Leone et al.,). Interestingly, over expression of PGC-1α in endothelial cells reduced the accumulation of ROS and reduced cell death (Valle et al., ; Arany et al.,). Transgenic over expression of PGC-1α in skeletal muscle induces angiogenesis, and accelerates recovery of blood flow after surgically-induced hind limb ischemia (Lehman et al.,).PGC-1α regulates angiogenesis in skeletal muscle by driving the expression of angiogenic factors like VEGF (Arany et al., ; Chinsomboon et al.,).Endurance exercise induces both mitochondrial proliferation and new blood vessel formation in skeletal muscle, and is one of the few examples of physiological angiogenesis in adult tissues (Esterbaueret al.,).

1.3.2. Mechanism of transcriptional co-activation by PGC-1α

The N-amino terminal region of PGC-1α provides the platform for proteins containing histone acetyltransferase (HAT) activity including p300/ cAMP response element binding protein (CREB) -binding protein and steroid receptor coactivator-1 (SRC-1) (Puigserveret al.,). The carboxy terminal region allows for the interaction with a second activating complex, the thyroid hormone receptor-associated protein/vitamin D receptor-interacting protein (TRAP/DRIP) complex (Wallberg et al.,). To initiate gene transcription, the transcription factor binds to the nuclear receptor response element/DNA response element in the promoter region of the target gene. Recruitment of PGC-1α allows association of the p300/CREB-binding protein and causes chromatin remodeling by histone acetylation. The subsequent and direct interaction with TRAP/DRIP provides a molecular bridge between the coactivator complex and RNA polymerase II. Remodeling of chromatin increases the accessibility of this transcriptional machinery and aids gene transcription. PGC-1α alone does not possess this ability but it acts as a scaffold for recruiting these proteins (Wallberg et al.,). Of note, PGC-1α also possesses an RNA processing domain at the Carboxy terminus that may contribute to further transcriptional regulation (Monsalve et al.,). A generalized scheme demonstrating the docking of protein regulatory complexes to PGC-1α and subsequent gene transcription .

1.4. Regulation of PGC-1 α Expression

The expression of PGC-1 α is highly and rapidly induced by physiological conditions that increase the demand for mitochondrial ATP production such as cold, exercise and fasting (Lehman et al., ; Baar et al.,). In response to cold exposure, PGC-1α expression is increased, with the induction being mediated through β3-adrenergic receptor/cAMP pathway of sympathetic nervous system (Puigserveret al.,). Induction of PGC-1α is often mediated by p38MAPK and cyclic AMP (cAMP) signaling that can be initiated by glucagon signaling (in hepatocytes) or adrenergic signaling via G-protein coupled receptors, ultimately acting on a conserved cAMP responsive element (CRE) in the PGC-1α promoter (Yoon et al., ; Herzig et al., ; Cao et al., ; Robidoux et al., ; Pogozelski et al.,).PGC-1α gene expression is also sensitive to muscle-specific factors like MEF (Buroker et al., ; Czubryt et al., ; Nakagawa et al.,) calcineurin signaling (Lin et al., ; Schaeffer et al., ; Handschin et al.,),metabolic sensors like the adenosine monophosphate-activated protein kinase (AMPK) (Jager,),nitric oxide (Nisoli et al., ; Carraway et al., ; Borniquel et al.,),p53, calcium/calmodulin-dependent protein kinase, (Handschin et al., ; Wu et al.,) and auto-regulatory positive feedback by PGC-1α itself (Handschin et al.,). PGC-1α expression is thus affected by numerous signals integrating important metabolic and neurohormonal states (Rowe et al.,).

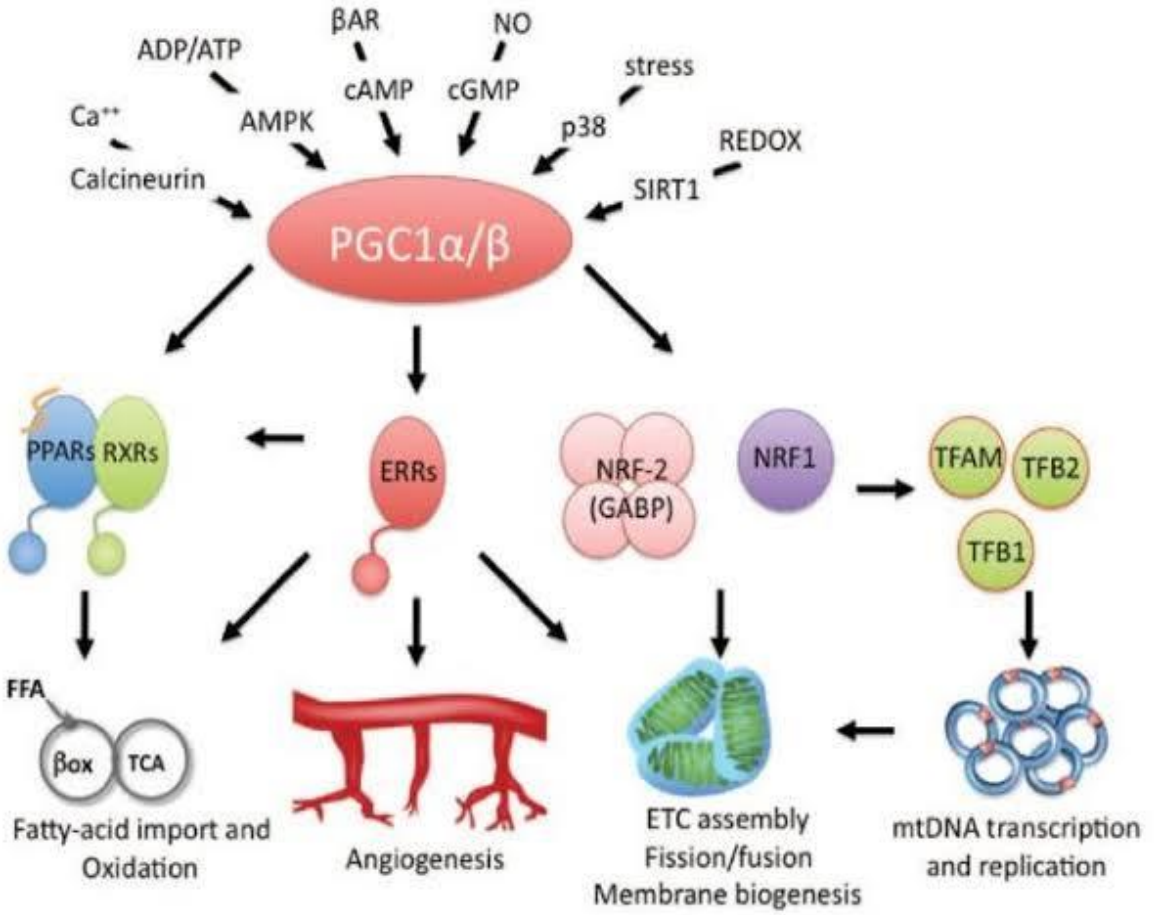

Fig 3: Transcriptional networks and regulation of PGC-1α

1.5. PGC-1α in Cardiac Physiology

PGC-1α is abundantly expressed in the heart. In fetal and neonatal heart, glucose is the primary energy substrate and ATP is produced mainly by glycolysis (Lopaschuk et al.,). After birth, as heart shifts to fatty acid oxidation (FAO) as the main source of energy, PGC-1α expression is increased (Lai et al., ; Finck et al.,). The expression of PGC-1α is also increased in other physiological conditions such as fasting, as the heart relies on FAO for the production of ATP (Finck et al., ; Lehman et al.,). Moreover, over-expression of PGC-1α in cardiomyocytes in cell culture and in vivo markedly increases fatty acid oxidation (Lehman et al.,).Glucose oxidation is decreased due to induction of PDK4, a potent inhibitor of PDH activity (Wende et al.,).

The PPARα and PPARβ are nuclear receptors that play a role in regulation of fatty acid oxidation (Ralte et al., . Both PPARα and PPARβ are highly expressed in myocardium (Glide et al.,). PGC-1α interacts with and co-activates PPARα and PPARβ (Wang et al.,) thereby inducing numerous genes critical for fatty acid metabolism, including CD36 (import into cell), CPT1b (import into mitochondria), PDK4 (reciprocal inhibition of pyruvate entry into mitochondria), and MCAD (rate-limiting step in medium chain fatty acid β oxidation). PPARγ, is expressed at substantially lower levels in the heart (Hsieh et al.,)

The estrogen receptor related receptor (ERRα),an orphan nuclear receptor is another major target of PGC-1α. PGC-1α binds to and co-activates ERRα in cardiomyocytes (Hus et al.,). Over expression of ERRα in rat neonatal cardio myocytes results in strong induction of genes involved in glucose utilization (e.g. PDK4, HK2, GLUT4),fatty-acid oxidation (MCAD, CD36) and the OXPHOS program (ATP5b, CYCS) (Huss et al). Estradiol mediated restoration of cardiac function following trauma-haemorrhage is due in part to ER-β dependent up-regulation of PGC1αthrough PPAR-α (Hsieh, et al.,). Whereas, inhibition of cardiac PGC1αexpressionabolishes ER-β agonist mediated cardio protection following trauma-hemorrhage (Hsieh et al.,).

In neonatal mice, over expression of PGC-1α promotes cardiac mitochondrial biogenesis (robust mitochondrial proliferation) and activation of known markers of the mitochondrial biogenesis, NRF-1 and its downstream target mtTFA (Russel et al.,). While in adult mice, only modest increase in

cellular mitochondrial density was observed. Moreover, chronic induction of PGC-1α expression in adult mice results in the development of a reversible cardiomyopathy (Russel et al.,). Spiegelman group demonstrated using PGC1α -/- mice that a moderate decline in cardiac function with age is associated with diminished expression of genes associated with mitochondrial FAO, oxidative phosphorylation and the Krebs cycle which led to a modest impairment of ATP maintenance (Arany et al.,).Thus, PPARs, NRFs and ERRs together form a coordinated transcriptional network governed by PGC1α to regulate energy homeostasis within cardiac tissue.

PGC-1α interacts with fork head transcription factor 1 (FoxO1) and co-activates FoxO1- dependent gene expression (Puigserver et al., ; Handschin et al., ; Lin et al.,). FoxO transcription factors are downstream targets of Akt, and their over expression protects against oxidative stress (Kops et al.,) and inhibits cardiac hypertrophy (Ni et al., ; Skurk et al.,) by transcriptionally activating catalase (Tan et al.,).

1.6. PGC-1 α in myocardial infarction and Ischaemia reperfusion injury

PGC-1α levels are reduced in the heart following MI by coronary artery ligation in rats (Sun et al.,) while treatment with angiotensin II receptor blockers (ARB) and PPAR agonists (pioglitazone and rosiglitazone),preserve both ventricular function and PGC-1α levels, and have been demonstrated to attenuate myocardial ischemia-reperfusion injury (Honda et al., ; Shiomi et al., ; Yue et al.,).Low dose metformin administered at the time of reperfusion daily improves survival and affords significant cardio protection against ischemiainduced heart failure by improving mitochondrial function via activation of AMPK and the downstream signaling pathway involving eNOS and PGC-1α (Gundewar et al.,) In delayed cardiac ischemic preconditioning, PGC-1α is temporarily induced during the transient ischemic stress which is then associated with subsequent enhanced myocardial ischemiareperfusion tolerance (McLeod et al.,).Pretreatment with diazoxide, a mitochondrial ATPsensitive potassium channel (mito K+ATP) opener, was found to protect the rat heart against Ischaemia-Reperfusion (I/R) injury by mimicking ischaemic preconditioning (IPC). Protection mechanism was found to be involvement of peroxisome proliferator-activated receptor gamma coactivator-1-1alpha (PGC-1alpha) in the effect of IPC and diazoxide preconditioning (DPC) with regard to its role in protection against Ischaemia-Reperfusion injury (Han ; Garlid et al., ; Iwai et al.,).

Disruption in oxidative phosphorylation and excessive reactive oxidative species contribute to myocardial Ischaemia-Reperfusion injury, mitochondrial biogenesis has emerged as an important regulator of mitochondrial function and a putative target for therapeutic intervention against cardiac IRI (Benard et al., ; McLeodet al.,). A down-regulation of the entire pathway of mitochondrial biogenesis was reported both in AMI and in HF evolution (Garnier et al., ; Watson et al.,). It has been shown that in heart, pathological stressors such as ischemia are associated with a down-regulation of mitochondrial biogenesis due decreased PGC-1α activity (Ahuja et al.,),and that impairment of the PGC-1α-mediatedmitochondrial biogenesis increased heart vulnerability to IRI (Yan et al.,). Accordingly, up-regulation of PGC-1α pathway confers protection against simulated Ischaemia-Reperfusion in cardio-myoblast cells (Sun et al.,). Moreover, the induction of PGC-1α protein up-regulates a broad spectrum of ROS detoxification systems, such as superoxide dismutase 2 (SOD2) and glutathione peroxidase1 (St-Pierre et al.,). Hence, a putative mechanism whereby the mitochondrial biogenesis program may additionally augment tolerance to cardiac ischemia is via ROS detoxification. During mitochondrial biogenesis, the coordinated transcription and replication of the mitochondrial genome is carried out via the nuclear-encoded mitochondrial transcription factor A (mtTFA), a downstream effect or of PGC1-α signaling. It has long been recognized that postischemic adverse remodeling is frequently associated with qualitative and quantitative defects in mtDNA (Kajander et al., ; Naya et al., ; Lebrecht et al.,),and that a decline in mitochondrial function and mtDNA copy number play a major role in the development of postischemic heart disease (Ide et al., ; Ide et al.,). In accordance, targeted disruption of mtTFA specifically within cardiac tissue resulted in a significant decrease in electron transport capacity, spontaneous cardiomyopathy, and cardiac disease (Liet al., ; Wang et al.,). Conversely, increasing the expression of mtTFA within cardiac tissue offered protection from adverse remodeling induced by myocardial infarction (Ikeuchi et al.,). PGC-1α is rapidly and strongly induced by TH. PGC-1α expression and protein levels are increased 6 h after administration of T3, and this action is mediated by a TH responsive element (TRE) in the promoter (Weitzel et al., ; Venditti et al., ; Wulf et al.,). In a rat model of post-ischemic HF, a low-T3Scorrelated with PGC-1α and mtTFA down-regulation, which corresponded to decreased mitochondrial function in the border zone; T3 replacement rescued myocardial contractility and hemodynamic parameters, while maintaining the expression of PGC-1α and mtTFA and mitochondrial function (Forini et al.,).Since the PGC-1α pathway is down-regulated by p53 activation under oxidative stress conditions, the inhibitoryrole of T3 on p53 expression may be part of an additional and indirect mechanism by which TH controls PGC1-α levels in the post-cardiac

ischemia setting (Villeneuve et al.,).The reduced PGC1-α level in the post-ischemic low-T3S is consistent with the activation of a fetal metabolic pathway observed in cardiomyopathy that is characterized by a preference for glucose over fat as a substrate for oxidative phosphorylation. Although such changes lower the oxygen consumed per ATP produced, the yield of ATP per substrate also decreases. Such inefficient metabolism powers ATP and phosphocreatine levels and decreases metabolic reserve and flexibility, leading to pump dysfunction (Ingwall et al., Ardehali et al.,). Therefore, T3 supplementation in low T3 post-ischemic cardiomyopathy may favor the normal mitochondrial homeostasis and metabolic flexibility of the heart, preventing adverse cardiac remodeling and HF evolution. Thyroid-stimulated mitochondrial biogenesis appears to be mediated via specific TRs located in both the nuclear and mitochondrial compartments (Wrutniak et al., Goldentha let al.,).

1.7. Acetylation of PGC-1α by GCN-5

Acetylation is a post-translational modification that regulates PGC-1α activity. PGC-1α is a multi component complex and interacts with several acetyl-transferases including p300, SRC-1, TIP60 and GCN-5 (Coste et al., ; Lerin et al., ; Puigserveret al.,),but only GCN-5 was found to induce acetylation of PGC-1α (Lerin).GCN-5 (general control non derepressible 5) was discovered as a histone acetyl-transferase (HAT) in Tetrahymena and shown to be the homolog of yeast GCN-5 (Brownell et al.,). Histone acetylation results in unwinding the chromatin making it accessible for the transcriptional machinery to initiate transcription (Kouzarides,).GCN-5 belongs to GNAT (GCN-5 related N-acetyl-transferase) family of histone acetyl-transferases, that transfer acetyl group from acetyl Coenzyme A to the primary amine of a wide range of substrates, including glucosamine 6-phosphate, aminoglycoside antibiotics, spermine, and spermidine (Dyda et al., ; Vetting et al.,).Moreover, GNATs are involved in both N-terminal (N−α) acetylation and N- ε acetylation of internal lysine residues of non-histone non-histone cellular proteins such as α-tubulin, importin-α and heat shock protein 90 (Hsp90) (Glozak et al., ; Zhang et al.,).

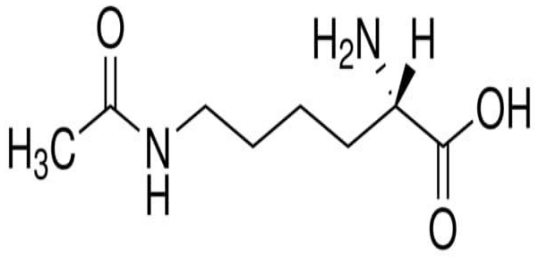

Fig 3: Acetylation of lysine residue of proteins.

GCN-5 has been shown to acetylate a large array of transcription factors (Nagy and Tora,) including the transcriptional cofactors, PGC-1α (Lerin et al.,) and PGC-1β (Kelly et al.,).Acetylation of transcription factors may increase or decrease their DNA binding affinity depending on whether the specific acetylation sites fall directly adjacent or within the DNAbinding domain, respectively (Kouzarides,). GCN-5 acetyl transferase is identified as a component of PGC-1α transcriptional pathway, that negatively regulates expression of gluconeogeni genes through direct acetylation & nuclear localization of PGC-1α (Lerinet al.,).Whereas PGC-1α deacetylation by SIRT1 (silent mating type information regulation two homolog 1) promotes PGC-1α activity (Nemoto et al., Rodgers et al.,).

PGC-1α requires acetyl-CoA as a substrate for the acetylation reaction.PGC-1α acetylation status by GCN-5 is regulated by the amounts of nuclear acetyl-CoA in the cell. A recent report suggests that, in mammals, the nuclear amounts of acetyl-CoA are controlled by the enzyme ATP-citrate lyase (ACL), which generates acetyl-CoA from tri-carboxylic acid–derived citrate both in the cytoplasm and in the nucleus (Wellen et al.,). Accordingly, knockdown of ACL blocks histone acetylation in a wide set of cell types in vitro, a mechanism highly dependent on nuclear acetyl-CoA. Interestingly, the effects on histone acetylation after silencing of ACL were very similar to those observed after silencing GCN-5, suggesting that GCN-5 is the main acetyltransferase responsible for ACL-induced histone acetylation (Wellen et al.,). Therefore, it is tempting to speculate (although it has not yet been proven) that not only histone acetylation but also PGC-1α acetylation could be gated by nuclear acetyl-CoA amounts.

GCN-5 and SIRT1act as important sensors of the energy status of the cell by regulation of acetylation and deacetylation of peroxisome proliferator-activated receptor coactivator 1α (PGC1α), respectively. Sirt1 require the coenzyme nicotinamide adenine dinucleotide (NAD+) as a substrate (Houtkooper et al.,). Sirt1 activity generally increases on fasting, exercise, or redox stress. PGC-1α deacetylation by Sirt1 increases the co-activation of its target transcription factors. Sirt1 is most active in times of energy demand, when NAD+ amounts or the NAD+/NADH ratio are at their highest levels. In conditions of low energy ATP level is decreased, AMP-activated protein kinase (AMPK) gets activated and increases NAD+ amounts by fatty acid oxidation (Canto et al.,) or enhanced its biogenesis through Nampt (Fulco et al.,),thereby enhancing Sirt1 activity and leads to the activation of deacetylation of PGC-1α and increased mitochondrial biogenesis and function. AMPK induces PGC-1α expression and directly enhances its activity through phosphorylation (Jager et al.,).

In conditions of large amounts of energy in the cell, GCN-5 (general control of amino acid synthesis) acetylates and inhibits PGC-1α; whereas reduced PGC-1α acetylation was described after a single session of exercise (Canto et al.,). PGC-1α is largely acetylated on at least 13 lysine residues which in turn are deacetylated by SIRT1 in response to low glucose. The mechanism by which acetylated PGC-1α is less active is largely unknown but may involve altered subnuclear protein localization and reduced occupancy at gene promoters (Lerin et al.,).

Hormonal and nutrient regulation of hepatic gluconeogenesis mainly occurs through modulation of the transcriptional coactivator PGC-1α (Carradori et al., ; Sakai et al.,). Adenoviralmediated expression of GCN-5 in cultured hepatocytes and in mouse liver largely represses activation of gluconeogenic enzymes and decreases hepatic glucose production (Carradori et al., ; Sakai et al.,). SIRT1 activation of PGC-1α enhances mitochondrial biogenesis, reduce ROS production, and increase antioxidant defense (Aquilano et al., ; Nemoto et al.,). Several lines of evidence show that SIRT1 has pivotal roles in cardiovascular function. Transgenic mice that over express SIRT1 in the heart are resistant to oxidative stress-related cardiac hypertrophy and ischemia/reperfusion injury (Alcendor et al., ; Hsu et al.,).In addition, the putative SIRT1 activator, resveratrol, a recognized mediator of mitochondrial biogenesis, can ameliorate heart ischemia or reperfusion injury, improve vascular functions, and ameliorate Ang II-induced cardiac remodeling (Orallo et al., ; Biala et al.,).

2. ACKNOWLEDGEMENT

Authors are thankful to Chairman , Secretary and Principal of Shatabdi Institute of Pharmacy, Nandurbar for their support and providing facilities for this work.

3. REFERENCES:

1. Arany, Z., He, H., Lin, J., Hoyer, K., Handschin, C., Toka, O., et al., (2005), "Transcriptional coactivator PGC-1 alpha controls the energy state and contractile function of cardiac muscle,"Cell Metab., 1, pp. 259-27.

2. Carradori, S., Secci, D, Mai, A., "Epigenetic modulation of PGC-1α activity by GCN5 inhibitors: WO2010007085," Expert Opin Ther Pat., 21(10), pp. 1651-1656.

3. Esterbauer, H., Oberkofler, H., Krempler, F., Patsch, W.,, "Human peroxisome proliferator activated receptor gamma coactivator 1 (PPARGC1) gene: cDNA sequence, genomic organization, chromosomal localization, and tissue expression," Genomics., 62(1), pp. 98–102.

4. Goldenthal, MJ., Ananthakrishnan, R., Marín-García, J., "Nuclear-mitochondrial cross-talk in cardiomyocyte T3 signaling: A time-course analysis,"J Mol Cell Cardiol., 39, pp. 319–326.

5. Gundewar, S., Calvert, JW., Jha, S., Toedt-Pingel, Ji., Sy Nunez, D., et al., ,"Activation of Amp-Activated Protein Kinase By Metformin Improves Left Ventricular Function And Survival In Heart Failure," Circ. Res., 104, pp. 403–441.

6. Han et al., "Myocardial ischaemic and diazoxide preconditioning both increase PGC-1alpha and reduce mitochondrial damage,"Acta Cardiol., 65(6), pp. 639-644.

7. Houtkooper, RH., Canto, C., Wanders, RJ., Auwerx, J., "The secret life of NAD+: an old metabolite controlling new metabolic signaling pathways," Endocr Rev., 31, pp. 194–223.

8. Hsieh, Y.C., Choudhry M.A., Yu, H.P., Shimizu, T., Yang, S., Suzuki, T., et al., "Inhibition of cardiac PGC-1alpha expression abolishes ER beta agonist-mediated cardioprotection following trauma–hemorrhage," FASEB J., 20, 1109–1117.

9. Jager, S., et al., , "AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha Proc Natl Acad Sci U S A., 104, pp. 12017– 12022.Kim, JS., Jin, Y., Lemasters, JJ.,, "Reactive oxygen species but not Ca2+ overloading trigger pH- and mitochondrial permeability transition-dependent death of adult rat myocytes after ischemiareperfusion," Am J Physiol. Heart Circ. Physiol., 290, pp. 2024–2034

. 10. Lerin, C., Rodgers, JT., Kalume, DE., Kim, SH., Pandey, A., Puigserver, P.,,"GCN-5 acetyltransferase complex controls glucose metabolism through transcriptional repression of PGC-1a," Cell Metabolism., 3, pp .429–438.

11. Lopaschuk, GD., et al., "Myocardial fatty acid metabolism in health and disease,"Physiol Rev.90, pp. 207-258.

12. Orrenius, S., Zhivotovsky, B., Nicotera, P.,, "Regulation of cell death: the calciumapoptosis link," Nat. Rev. Mol. Cell Biol., 4, pp. 552–565.

13. Rodgers, JT., Lerin, C., Haas, W., Gygi, SP., Spiegelman, BM., Puigserver, P., "Nutrient control of glucose homeostasis through a complex of PGC-1 alpha and SIRT1," Nature., 434, pp. 113–118.

14. Rowe, GC., "PGC-1 coactivators in cardiac development and disease", Circ. Res., 106, pp. 1559 –1569.

15. Tan W Q Wang K Lv D Y and Li P F , "Novel cardiac apoptotic pathway: the dephosphorylation of apoptosis repressor with caspase recruitment domain by calcineurin,"J Biol Chem., 283, pp. 29730–29739.

16. Villeneuve, CL., Guilbeau-Frugier, C., et al., , "p53-PGC-1α pathway mediates oxidative mitochondrial damage and cardiomyocyte necrosis induced by monoamine oxidase-A up-regulation: Role in chronic left ventricular dysfunction in mice," Antioxid Redox Signal.,18,pp. 5–18.

17. Wellen, KE., Hatzivassiliou, G., Sachdeva, UM., Bui, TV., Cross, JR., Thompson, CB.,, "ATP-

citrate lyase links cellular metabolism to histone acetylation," Science., 324, pp. 1076–1080