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# Regulation of SIRT1 in aging: Roles in mitochondrial function and biogenesis

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ABSTRACT

Aging is a degenerative process associated with cumulative damage, which leads to cellular dysfunction, tissue failure, and disorders of body function. Silent information regulator-1, also known as sirtuin 1 (SIRT1), has been reported to be involved in the regulation of various important biological processes, including inflammation, mitochondrial biogenesis, as well as cell senescence and consequent aging. The level of SIRT1 is decreased in both transcriptional and postranscriptional conditions during aging, accompanied by attenuated mitochondrial biogenesis, an important component of aging-related diseases. Over the last decade, extensive studies have demonstrated that SIRT1 can activate several transcriptional factors, such as peroxisome proliferator activated receptor γ co-activator 1α (PGC-1α) and hypoxia-inducible factor 1α (HIF-1α) resulting in ameliorated mitochondria biogenesis and extended life span. In this review, we focus on the molecular regulation of SIRT1 and its role in mitochondrial biogenesis during in the context of aging and aging-related diseases.



**Contents**



*Abbreviations:* SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator activated receptor γ co-activator 1α; HIF-1α, hypoxia-inducible factor 1α; ROS, reactive oxygen species; RC, respiratory chain; NAD, nicotinamide adenine dinucleotide; mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation; TFAM, mitochondrial transcription factor A; TFB, mitochondrial transcription factor B; NRF, nuclear respiratory factors; ERRα, estrogen related receptor α; CREB, cAMP response element; YY1, ying yang 1 transcription factor; PRC, (PGC-1 related coactivator); ATP, adenosine triphosphate; NF-κB, nuclear factor-κB; ChREBP, carbohydrate response-element-binding protein; FoxO, O subclass of the forkhead family of transcription factors; SMCs, vascular smooth muscle cells; IGF-1, insulin-like growth factor-1; PI3K, phosphoinositide 3-kinase; IGF-IR, insulin-like growth factor 1 receptor; PAECs, porcine aortic endothelial cells; CDK5, cyclin-dependent kinase 5; Nampt, nicotinamide phosphoribosyltransferase; NLSs, nuclear localization sequences; NESs, nuclear export sequences; TERF2IP, telomeric repeat-binding factor 2-interacting protein 1; HIC1, hypermethylated in cancer 1; MEFs, mouse embryonic fibroblasts; CtBP, C-terminal-binding protein; 2-DG, 2-deoxyglucose; HSF, heat shock factor 1; CS, cockayne syndrome; PAS, Per-ARNT-Sim; HREs, HIF-responsive elements; PPAR, peroxisome proliferator-activated receptor; IRS-1, insulin receptor substrate1; FKHD-L, folkhead-like consensus binding site; HuR, Hu antigenR; SA-β-gal, senescence-associated β-galactosidase; JNK2, Jun N-terminal kinase-2; Cyclin B, cell cycle-dependent kinase; CK2, protein kinase 2; DYRK1A, dual specificity tyrosine phosphorylation-regulated kinase 1A; SENP, sentrin-specific protease; Set7/9, mono-methyltransferas; SNO-GAPDH, nitrosylated glyceraldehyde-3-phosphate dehydrogenase; AKT, protein kinase B (PKB); AMPK, AMP-activated protein kinase; LKB1, liverkinaseB1; GCN5, nonderepressible 5.

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## 1. Introduction

Aging is a degenerative process, manifested by the progressive decline in physiological functions in biological systems. The deleterious changes are believed to be associated with metabolic activities and are controlled by many factors including genetic traits, environmental stimuli and stochastic processes. A well-known theory of aging, presented by Denham Harman is the "free radical theory of aging". Briefly, the theory is based on the idea that free radicals, in particular reactive oxygen species (ROS) produced from normal metabolism, may be the primary cause of aging and aging-related degenerative diseases. Few years later, professor Harman updated the theory with the "mitochondrial theory of aging" (Lee and Wei, 2012) (Bereiter-Hahn, 2014), claiming that as an organism grows, mitochondria accumulate oxidative damage caused by the toxicity of ROS. Reactive species are associated with detrimental effects on mitochondrial function, leading to abnormal amounts of ROS production, and so further damage.

As an essential intracellular organelle for aerobic metabolism, mitochondria are critically relevant to energy homeostasis, since approximately 90% of cellular ATP production is associated with oxidative phosphorylation in the respiratory chain (RC) complexes located in their inner membrane (Romano et al., 2014). The decline of mitochondrial function has been reported to be important during the process of aging with distinct mitochondrial morphological changes, e.g., abnormal rounded mitochondria (Lin et al., 2015), reduction of mitochondrial DNA but increase of mutation rate (Gaziev et al., 2014; LaRocca et al., 2014), reduction of RC activity (Sudheesh et al., 2009) as well as impaired mitochondrial biogenesis (8). A decrease in mitochondrial biogenesis may reduce the turnover of mitochondrial components resulting in the accumulation of oxidized lipids, proteins and DNA (Ungvari et al., 2010). Thus, it is believed that maintenance of mitochondrial biogenesis capacity during aging is a key factor in preventing the progression of aging-related diseases.

With homology to *Saccharomyces cerevisiae* silent information regulator 2 (Sir2), the sirtuin family is a highly conserved class of nicotinamide adenine dinucleotide ($NAD^+$) dependent deacetylases and ADP-ribosyltransferase proteins. This family is composed by seven members in both prokaryotes and eukaryotes (Morris, 2013). SIRT1 is the most extensively studied sirtuin protein, probably because of its involvement in the regulations of diverse cellular physiological and pathological processes including gene silencing, stress resistance, apoptosis, inflammation and senescence, as well as its potential for therapeutic approaches (Chung et al., 2010; LaRocca et al., 2014; Revollo and Li, 2013). Interestingly, overexpression of SIRT1 in mice (Sirt1-overexpressing transgenic mice) results in significant life span extension and exhibits phenotypes associated with delayed aging, such as enhancement in physical activity, body temperature, oxygen consumption, and quality of sleep compared to age-matched control mice, whereas inhibition of SIRT1 in these mice abrogates the effect of life span extension (Satoh et al., 2013).

Recent studies demonstrated that SIRT1 promotes mitochondrial biogenesis by deacetylation of target proteins such as peroxisome proliferator activated receptor γ co-activator 1α (PGC-1α) (Wenz, 2013) and hypoxia-inducible factor 1α (HIF-1α) (Gomes et al., 2013). These findings suggested potential therapeutic benefits of SIRT1 activation for metabolic and other aging-related diseases. For the better understanding of its molecular and cellular mechanisms, we discussed the role of SIRT1 in aging focusing on the regulation of mitochondrial biogenesis in this review.

## 2. Dysregulation of mitochondrial biogenesis in aging

### 2.1. Mitochondrial biogenesis

Mitochondria are the most dynamically responsive sensing systems in eukaryotic cells, acting to satisfy metabolic energy demands, supply biosynthetic precursors, and consequently regulate diverse processes, including proliferation (Li et al., 2015a), immune responses (Kim et al., 2015), apoptosis (Kuo et al., 2015), and cell viability (Radogna et al., 2015). Cells can degrade damaged mitochondria (the process of mitophagy) and under appropriate conditions, stimulate functional mitochondria to proliferate through mitochondrial biogenesis (Peterson et al., 2012). Mitochondrial biogenesis is a complex process consisting of both growth and division of pre-existing mitochondria. It requires replication and synthesis of the mtDNA regulated mainly at transcriptional level, and import of proteins and lipids from the cytoplasm to the existing mitochondria (Scarpulla, 2011; Wenz, 2013). Expression of mitochondrial genes including structural genes and assembly factors must be coordinated with the 13 mitochondria-encoded genes (coding for oxidative phosphorylation (OXPHOS) enzymes I, II, III, IV, and V as well as 2 rRNAs and 22 tRNAs). Nuclear encoded mitochondrial proteins are synthesized in the cytoplasm and then imported into mitochondria, while the mtDNA encoded proteins are synthesized within the organelle itself (Menzies and Hood, 2012).

Mitochondrial transcription factor A (TFAM), mitochondrial transcription factor B1 and B2 (mtTFB-1 and mtTFB-2) are critical in the control of replication, transcription and maintenance in mitochondrial biogenesis (Brenmoehl and Hoeflich, 2013). Additionally, there is a set of nuclear-encoded protein factors involved in regulating the expression of nuclear encoded mitochondrial proteins. The first described transcription factors were nuclear respiratory factors1 and 2 (NRF1 and NRF2). They control the expression of nuclear-encoded mitochondrial genes and the delivery of these proteins to mitochondria (Scarpulla, 2011). Also, estrogen related receptor α (ERRα) (Li et al., 2013), cAMP response element (CREB) (Liu et al., 2014) and the Ying Yang 1 transcription factor (YY1) (Ji et al., 2015) are known to modulate mitochondrial genes. All the factors work synergeticly with transcription coactivators, the

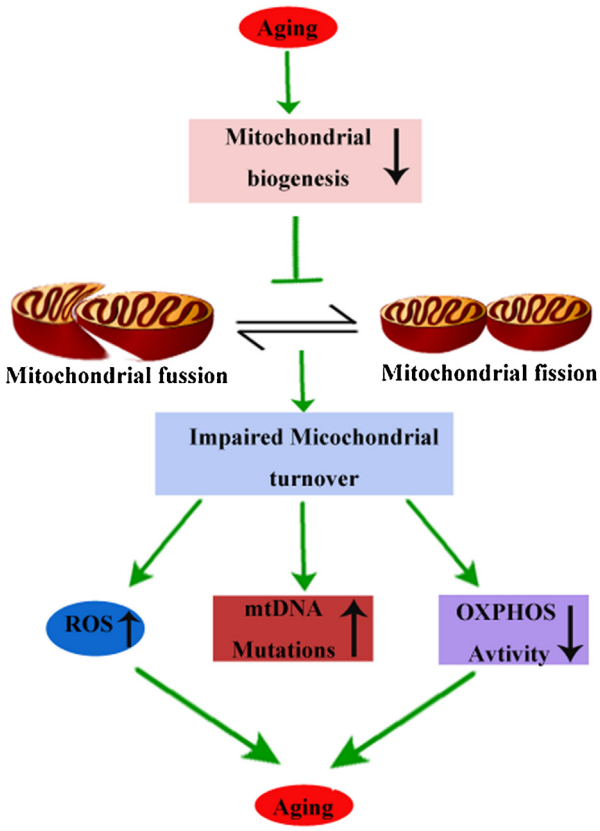


**Fig. 1.** Proposed model of mitochondrial dysfunction in aging.
Mitochondrial biogenesis indispensably supports energy-dependent cell processes, including those involved in the repair of cell and tissue damage. Mitochondrial biogenesis is coordinated with mitochondrial turnover (fission and fussion). During the aging process, the impaired mitochondrial biogenesis reduces turnover of specific mitochondrial components resulting in the accumulation of oxidized lipids, proteins, and DNA, which would lead to a gradual deterioration of various mitochondrial functions, affecting biosynthetic pathways, cellular energetics, cellular redox homeostasis, signaling, calcium buffering, and accelerating the aging.

peroxisome proliferator-activated receptor γ-coactivator-1 (PGC-1) family, consisting of PGC-1α, PGC-1β and PRC (PGC-1 related coactivator). PGC-1 family is essential for several metabolic pathways, and PGC-1α, the most well-known, has been highlighted in many studies in the last few years, primarily for its capability to regulate mitochondrial biogenesis as a co-regulator of NRFs and ERRα. (Scarpulla, 2011).

### 2.2. Mitochondrial biogenesis and its relation to aging

Aging is a multifactorial process. During aging, the decline of mitochondrial function may impair the generation of sufficient adenosine triphosphate (ATP) for homeostasis, ultimately triggering apoptosis (Biala et al., 2015), contributing to the onset and progression of aging and aging-related disorders. With regard to the pathology of mitochondrial dysfunction induced by cellular senescence, deterioration in mitochondrial biogenesis is likely to be the central event (Lopez-Lluch et al., 2008). Disruption of biogenesis will slow mitochondrial turnover (Peterson et al., 2012), accelerate the accumulation of ROS (Baldelli et al., 2014), oxidized lipids, proteins and mutant DNA (Carelli et al., 2015), and impair the OXPHOS activity (Carelli et al., 2015), further aggravate the aging situation (Fig. 1).

Recent studies have shown that, mitochondrial biogenesis was impaired in senescent endothelial cells induced by high glucose in vitro (Xu et al., 2014). In vivo, mitochondrial stress/dysfunction triggered by abnormal mitochondrial quality control (a balance

**Table 1**
Targets of SIRT1 that are regulated during aging process.

| Substrates | Models | Functions of SIRT1 | Mechanism | Reference |
|---|---|---|---|---|
| FOXO 3 | Sirt1+/− mice | Prevent chronic inflammation and premature lung aging | Deacetylate the FOXO3 though protein–protein interaction | Yao et al. (2012) |
| P53 | Overexpression of Nampt in human SMC | Delay senescence and lengthen cell lifespan | Deacetylate P53 on lysine 382 and further improve degradation of P53 | van der Veer et al. (2007) |
| | Acute IGF-1 exposure to human primary fibroblast | Attenuate IGF-1 induction of premature cellular senescence | Deacetylate P53 on lysine 382 and further improve degradation of P53 | Tran et al. (2014) |
| PPAR α | SIRT1 LKO mice | Prevent hepatic steatosis, inflammation, and ER stress on a high-fat diet | Induced PPARα expression via the association with its DBD and LBD domain | Purushotham et al. (2009) |
| NF-κB | Old mice | Ameliorate vascular endothelial dysfunction with aging in mice | Inhibition NF-κB activity though enhancing COX-2 signaling | Gano et al. (2014) |
| CREB | ob/ob mice and adipocytes exposured to TNFα | Regulate nutrient signals in mice | Deacetylate the CREB on lysine 136 | Paz et al. (2014) |

between mitochondrial biogenesis and mitophagy) contributes to artery stiffening during aging in mice (LaRocca et al., 2014). Impaired mitochondrial biogenesis has also been described in liver tissue from old rats (Picca et al., 2013). In contrast, an increase in mitochondrial biogenesis may attenuate the aging process and aging-related diseases. For example, in mutant flies, genetic ablation of *Indy* increases midgut expression of PGC-1α, resulting in increased mitochondrial biogenesis and reduced reactive oxygen species (ROS) production. Consequently elevated mitochondrial biogenesis preserves intestinal stem cell homeostasis and contributes to longevity of these flies (Rogers and Rogina, 2014). In addition, In MCKPGC-1α Mut mice (mice transgenically expressing PGC-1a under the *MCK* promoter), overexpression of PGC-1α in the skeletal and cardiac muscle from fetal stage promotes muscle mitochondrial biogenesis and eventually improves aging phenotypes and well as preventing aging-related cardiomyopathy in adults (Dillon et al., 2012b). In central neural system, improvement of mitochondrial biogenesis via increasing PGC-1α levels dramatically protects neural cells in culture from oxidative stress-mediated death in vitro, while in vivo, *PGC-1α* null mice are much more sensitive to the age-dependent neuronal damage and neurodegeneration (St-Pierre et al., 2006). Collectively, a growing body of evidence implicates that attenuated mitochondrial activity and biogenesis capacity during aging is a key factor in progression of age-related diseases.

## 3. SIRT1

### 3.1. SIRT1 and aging

SIRT1 has the capability to extend life span, delay aging and prevent aging-related diseases, mainly by catalyzing the deacetylation of histones, and regulation of transcription factors, or coactivators, such as P53, forkhead box O (FOXO), nuclear factor-κB (NF-κB), PGC-1α, and Ku70 (Table 1) (Ramis et al., 2015; Yao and Rahman, 2012). Activity is augmented by a SIRT1 activator (e.g., SRT1720), leading to attenuation of stress-induced premature cellular senescence and protection against emphysema that is induced by cigarette smoke in mice via deacetylation and activation of FOXO3 (Yao et al., 2012). van der Veer et al. (2007) reports that overexpression of nicotinamide phosphoribosyltransferase (Nampt, the rate-limiting enzyme for NAD+ salvage from nicotinamide) results in deferred senescence and significantly extended lifespan, concomitant with enhancement of SIRT1 activity and degradation of deacetylated P53 in human vascular smooth muscle cells (SMCs). This is in agreement with the findings that upregulation of SIRT1 attenuates insulin-like growth factor-1 (IGF-1)-induced primary fibroblasts senescence via P53 deacetylation (Tran et al., 2014). Additionally, in vivo, Purushotham et al. (2009) has demonstrated that the overexpression of SIRT1 in liver is able to increase expression of PPARα and activate PGC-1α, which results in improvement of oxidative metabolism and regulations of lipid metabolism in response to nutrients and hormonal signals. In a recent study, activation of SIRT1 by SRT1720 ameliorates vascular endothelial dysfunction with aging in mice by inhibition of NF-κB activation and reducing oxidative stress and inflammation (Gano et al., 2014). Moreover, in the inducible p25 transgenic mouse, a model of Alzheimer's disease and tauopathies, enhancement of SIRT1 activity by resveratrol or injection of SIRT1 recombinant lentivirus in the hippocampus resulted in significant protection against neurodegeneration by deacetylation of PGC-1α and P53 (Kim et al., 2007). Two independent studies have also convinced the protective role of SIRT1 in age-related cognitive decline such as Alzheimer's disease (Wang et al., 2013), Parkinson's disease (PD) and Lewy body dementia (Donmez et al., 2012), which is relevant to SIRT1 mediated deacetylation of PPARγ and heat shock factor 1 (HSF1). Given that, the mechanisms involved in the prevention of aging and aging-related diseases by SIRT1 may be diverse and dependent on the target proteins it regulates.

In addition, the endogenous level of SIRT1 is related to development of age-related diseases. It is reported that hyperglycemia promotes premature senescence in vascular endothelial cells by downregulating SIRT1 expression (Arunachalam et al., 2014). A similar phenomenon has been observed in an *in vivo* aging model (senescence-accelerated mouse prone 8 mice; SAM-P8). SIRT1 expression declines with age at the transcriptional and translational levels in the brain, liver, skeletal muscle and white adipose tissues. Specifically, the repressed expression of SIRT1 in the brain has been reported by Cho SH, that SIRT1 is reduced with the aging of microglia and microglial SIRT1 deficiency is a causative role in cognitive decline and neurodegeneration in aging mice (Cho et al., 2015). Besides to the importance of the protein level of SIRT1, the activity of SIRT1 is also impacted by the aging status (Gong et al., 2014). $H_2O_2$ is able to accelerate cellular senescence by decreasing $NAD^+$ levels and subsequent SIRT1 activity in human lung fibroblasts and human lung epithelial cells (Caito et al., 2010; Furukawa et al., 2007). In a cockayne syndrome (CS; an accelerated aging disorder) mouse model, due to the aberrant PARP activation, the deacetylase activity of SIRT1 decreases, leading to mitochondrial dysfunction (Fang et al., 2014). Furthermore.

### 3.2. Regulation of SIRT1 in aging

As a major regulator protein, the intracellular location, nucleocytoplasmic shuttling activity and expression regulation at both transcriptional and posttranslational levels of SIRT1 are all under tight control.

#### 3.2.1. Location and nucleocytoplasmic shutting of SIRT1

The nuclear-cytoplasmic localization of SIRT1 can be different depending on tissue type. SIRT1 was initially described as a nuclear protein in Hela cells and normal human fibroblasts (Frye, 2000; Michishita et al., 2005), but the cytoplasmic localization of SIRT1 is also observed in some neuron-like cells of the striatum and murine pancreatic β cells (Moynihan et al., 2005; Tanno et al., 2007).

Within the catalytic domain of human SIRT1, there are two nuclear localization sequences (NLSs; amino acid residues 31–38 and 223–230) and two nuclear export sequences (NESs; amino acid residues 136–262, 223–445), closing to the posttranslational modification sites of SIRT1, hence, the catalytic domain is the key in regulating the nucleocytoplasmic shuttling of SIRT1. Subcellular localization, cell differentiation and proliferation of SIRT1 are closely related (Tanno et al., 2007). In *Drosophila*, during embryonic development, SIRT1 moves from the cytoplasm to the nucleus. Other studies have found that SIRT1 is predominantly localized in cytoplasm in neonatal rat cardiomyocytes, while is nuclear when adult (Rosenberg and Parkhurst, 2002). Moreover, it has been observed in cancer cells that the cytoplasmic localization and protein stability of SIRT1 is regulated by phosphoinositide 3-kinase (PI3K)/insulin-like growth factor 1 receptor (IGF-IR) signaling, in which the localization of SIRT1 in cytoplasm is essesntial for PI3K mediated growth (Byles et al., 2010).

The nucleocytoplasmic shuttling of SIRT1 has been described in both physiological and pathological conditions in aging, nevertheless the effects of sublocalization and nucleocytoplasmic shuttling on its activity are still debated (Bai et al., 2012; Herskovits and Guarente, 2014). Tong et al. (2013) reported that in cardiomyocytes, SIRT1 is expressed predominantly as a sumoylated form (i.e., a post-translational modification) in nuclei, and the sumoylation not only contributes to the nuclear localization but also is involved in upregulation of the activity of SIRT1, which is relevant to a

tolerant capacity of the heart toward ischemic stress. Furthermore, unlike the young heart, the aged heart failed to sequester SIRT1 into the nucleus during acute ischemia, which resulted in an increase in nonsumoylated cytoplasmic SIRT1. Thus aging causes impaired nucleocytoplasmic shuttling and the cytoplasmic SIRT1 negatively regulates the activation of SIRT1 during ischemic stress. These findings are in agreement with aother study, in which the cytoplasmic localization of SIRT1 caused by inhibition of PI3K with LY294002, was associated with elevated cell susceptibility to apoptosis during toxic insult (Jin et al., 2007).

Inhibition of CDK5 promotes SIRT1 shuttling from nucleus to the cytoplasm, resulting in ameliorated anti-aging activity in vivo. Prevention of the phosphorylation of CDK5 is able to block the development of atherosclerosis in ApoE $^{-/-}$ mice though the interaction with telomeric repeat-binding factor 2-interacting protein 1 (TERF2IP; a critical regulator of NF-κB signaling) and subsequent inhibition of NF-κB signaling (Bai et al., 2012).

*3.2.2. The transcriptional regulation of SIRT1*

Under conditions of DNA damage, two transcription factors, tumor suppressor hypermethylated in cancer 1 (HIC1) and the cell cycle regulator E2F1 have been shown to modulate SIRT1 transcription. Mouse embryonic fibroblasts (MEFs) from Hic1 $^{-/-}$ mice are more resistant to double-strand DNA breaks induced by etoposide treatment in comparison to wild-type MEFs. HIC1 forms a transcriptional repression complex with SIRT1 and this complex directly binds the *SIRT1* promoter and represses its transcription (Fig. 2a) (Chen et al., 2005). In a negative-feedback loop, SIRT1 deacetylates the HIC1 at lysine 314 followed by the further SUMO modification, a crucial modification for repressive function of the HIC1 complex, which increase SIRT1 expression (Stankovic-Valentin et al., 2007). Besides DNA damage, the HIC1-CtBP suppressor complex is high sensitivity to the intracellular redox state, the complex dissociates when the glycolytic pathway is inhibited by 2-deoxyglucose (2-DG) resulting in increased $NAD^+$:NADH ratio, leading to activation of SIRT1 gene expression (Zhang et al., 2007) (Fig. 2a).

Conversely, SIRT1 transcription and its protein levels have also been shown to increase through activation of the E2F1 transcription factor in response to DNA damage. E2F1 is a crucial activator of SIRT1 expression in response to DNA damage, indeed the benefit for SIRT1 expression is abrogated in E2f1$^{-/-}$ MEFs. However, increased SIRT1 expression mediated by E2F1 seems to be temporary, since the accumulation of SIRT1 would stimulate deacetylation of E2F1, and shut down its own transcription as a feedback inhibitory mechanism, which may attenuatet the proapoptotic activities of E2F1 (Wang et al., 2006) (Fig. 2g).

Hypoxia, characterized by a general decrease in $O_2$ supply to cells and tissues, plays a critical role in the development of aging and aging-related diseases such as cardiovascular disorders and atherosclerosis (Valli et al., 2015). In response to acute hypoxia, SIRT1 transcription and activity are increased in a HIF-dependent manner. Under hypoxia, the accumulation and stability of Hypoxia-inducible factor (HIF) protein is boosted in hepatocellular carcinoma (HCC) cell lines and mice livers as is the association-binding between Hsp90 and its Per-ARNT-Sim (PAS) domain (Gradin et al., 1996). Furthermore, the increased accumulation of HIF-1α and HIF-2α bind directly to HIF-responsive elements (HREs) on the *SIRT1* promoter, which increase SIRT1 stability and expression on the transcriptional level (Fig. 2b) (Chen et al., 2011).

In addition, the peroxisome proliferator-activated receptor (PPAR) and poly (ADP-ribose) polymerase (PARP) superfamily contribute to the regulation of SIRT1 in the replication senescence process. In senescent WI-38 cells and in lung, fat and heart tissues from senescent Balb/c mice, expression of SIRT1 declines, which is associated with the binding of PPARγ to specific sites on *SIRT1* promoter. On the contrary, SIRT1 has the ability to regulate the deacetylation process of PPARγ and reduce its DNA binding capacity, further combats its suppresive impact on SIRT1 expression (Fig. 2c) (Han et al., 2010). Another member of PPAR, after the treatment of starvation, PPARβ elicits a significant stimulatory effect on the transcriptional activity of SIRT1 in human hepatocyte-derived HuH7 cells. Intereatingly, the effect of PPARβ is not directly mediated by DNA binding but through another transcription factor Sp1 comfirmed by EMSA and ChIP assays (Fig. 2d) (Salvadó et al., 2014).

The role of PARP in longevity is associated with the regulation of SIRT1. In skeletal muscle from aged mice the PARP1 activity is highly enhanced, which leads to NAD+ depletion, therefore, inhibit the activity of SIRT1 (Mohamed et al., 2014). Nevertheless, deletion of PARP1 in brown adipose tissue and muscle in Parp1$^{-/-}$ mice elevates the activation of SIRT1, which faciliates the protection against metabolic disorder (Bai et al., 2011b). Similar effect of PARP2 has been reported in a recent study, in which PARP2 deficiency in cultured myotubes increases SIRT1 activity, and Parp2 $^{-/-}$ mice are protected against diet-induced obesity because of the increased epression of SIRT1 (Fig. 2e) (Bai et al., 2011a).

Nutrient availability regulates life-span in a wide range of organisms, and nutrient withdrawal can increase life-span in both the nematode and yeast. SIRT1 levels are transcriptionally regulated by nutrient availability through interdependent regulation by cAMP response-element-binding protein (CREB) and the carbohydrate response-element-binding protein (ChREBP) with the same binding sites of the *SIRT1* promoter (Fig. 2h). Specifically, in response to fasting, the glucagon and norepinephrine stimulated activation of CREB drives CREB recruitment to the proximal *SIRT1* promoter, in turn leading to the increase of SIRT1 expression. Conversely, in the case of feeding induced nutrient excess, ChREBP binds to the *SIRT1* promoter to downregulate its expression, potentially through competition with CREB binding (Noriega et al., 2011). The conception was reinforced by Fusco S, who found that the expression of SIRT1 is dramatically reduced in CREB-deficient mice. Interestingly, CREB-dependent genes are markedly down-regulated in SIRT1 deficient cultured neurons (PC12) and in the brain of SIRT1 KO mice (Fusco et al., 2012). Recently, Paz et al. (2014) have verified that, proportion of acetylated CREB at lysine136 is low under basal conditions, due to constitutive deacetylation by SIRT1 in adipose, suggesting that CREB is also a substrate of SIRT1.

Nemoto et al. demonstrated that under normal nutritional conditions, the activation of P53, which is phosphorylatied and acetylated by CBP/p300 has been described to bind to the two P53-binding sites present at the *SIRT1* promoter, resulting in the repression of SIRT1 gene (Luo et al., 2004). While, upon starvation, the activated forkhead transcription factor (FOXO3a) shuttles to the nucleus of PC12 cells, in which it binds and removes P53 from its binding sites on the *SIRT1* promoter, and then activates SIRT1 transcription (Fig. 2i). This model is supported by studies in P53-deficient mice (*Trp*53$^{-/-}$), which express constitutively higher SIRT1-mRNA levels in several tissues under normal nutritional conditions, but lack starvation-induced SIRT1 expression, suggesting that FOXO3a/P53 plays an important role in the transcriptional regulation of SIRT1 in this stinuli (Nemoto et al., 2004). Meanwhile, deacetylation of P53 at lysine 382 mediated by SIRT1 decreases its stability and activity, and in turn prevents the inhibition of SIRT1 transcription (Vaziri et al., 2001). Besides to the FOXO3a, FOXO1, another member of FOXO family has been found an important regulator for SIRT1 gene expression. FOXO1, which can directly bind to *SIRT1* promoter region which is characterised by FOXO1 core binding repeat motifs [e.g., insulin receptor substrate1 (IRS-1) and a folkhead-like consensus binding site (FKHD-L)], leading to FOXO1 mediated SIRT1 transcription, and results in an increased expression of SIRT1 (Fig. 2f). This model is supported by a study of Shiqin Xiong et al., in which FOXO1 overexpression increased

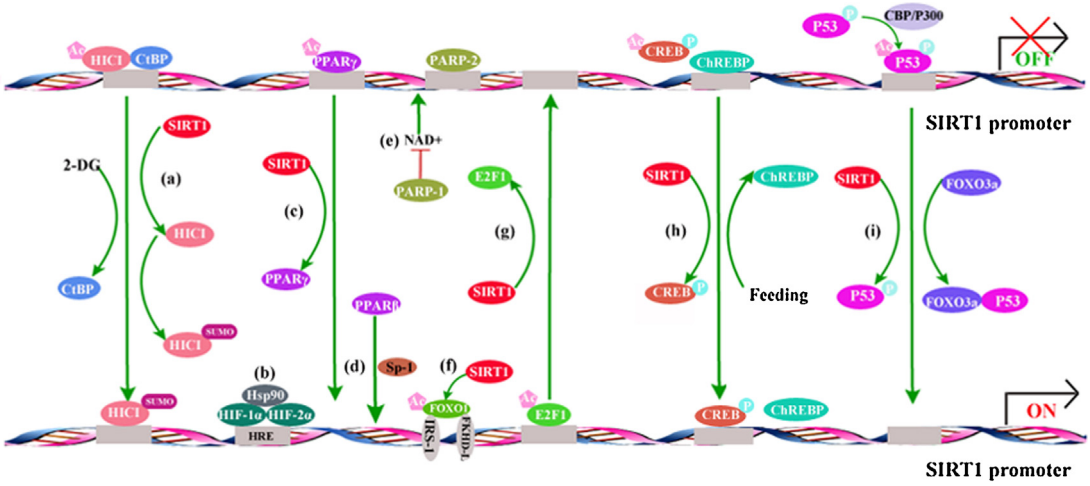


**Fig. 2.** Transcriptional regulation of SIRT1.
SIRT1-mRNA transcription is coupled with extracellular stimuli, nutrient deprivation and hypoxia during the aging process. SIRT1 associates with all of these factors and regulates their activity via deacetylation. Currently there are many feedback control mechanism regulating transcription levels of SIRT1, such as P53/FOXO3a- SIRT1 pathway; FOXO1-SIRT1 pathway; HIF-1α/HIF-2α-SIRT1 pathway. (a) The HIC1-CtBP complex associates and SIRT1 to repress SIRT1 transcription. Associated with the redox changes caused by 2-deoxyglucose, the complex was dissociated and thereby activate SIRT1 gene expression. (b) During acute hypoxia, HIF-1α and HIF-2 α accumulate stably with a combination of Hsp90, and bind directly to HIF-responsive elements (HREs) on the *SIRT1* promoter. (c, d) A repressor complex, composed of PPARγ or PPARβ and SIRT1, binds specific sites on *SIRT1* promoter and directly suppress transcriptional induction to exogenous stress. (e) Upon aging, the PPAR1 activity is highly enhanced, which leads to NAD+ depletion, therefore, inhibit the activity of SIRT1. (f) FOXO1, which can directly bind to *SIRT1* promoter region consisting of a FOXO1 core binding repeat motifs insulin receptor substrate1 (IRS-1) and a folkhead-like consensus binding site (FKHD-L), leads to a FOXO1 mediated SIRT1 transcription and results in an increase expression of SIRT1. (g) In response to DNA damage, acetylated E2F1 enhance its binding to the promoter region of SIRT1, enhanced SIRT1 transcription. (h) In response to metabolic status and nutrient availability, SIRT1 is coordinately regulated by CREB and ChREBP in an interdependent way. (i) During starvation, p53 associates with FOXO3a; this association blocks p53 inhibitory function and activates SIRT1 transcription.

SIRT1 expression, and FOXO1 depletion by siRNA reduced SIRT1 expression at both the messenger RNA and protein levels in vascular smooth muscle cells and HEK293 cells (Xiong et al., 2011).

### 3.2.3. *The posttranscriptional regulation of SIRT1*

Human antigen R (HuR), a member of the embryonic lethal abnormal-vision family of mRNA-binding proteins play a major role in stabilizing SIRT1 mRNA, by associating with the 3′ untranslated region of the mRNA (Abdelmohsen et al., 2007). During replicative senescence in WI-38 human diploid fibroblasts (HDFs), with the markedly elevated activity of senescence-associated β-galactosidase (SA-β-gal), SIRT1 and HuR are down-regulated and the HuR-SIRT1 mRNA complex is rapidly dissociated, leading to reduction of SIRT1 mRNA stability from 8 h to 12 h (Calder et al., 2007; Morgan et al., 2007; Pang et al., 2013). Moreover, other disease conditions are able to impact this reaction. Oxidative stress promotes the phosphorylation of HuR mediated by cell cycle checkpoint kinase Chk2 (Fig. 3A), resulting in the dissociation of HuR-SIRT1 complex (Abdelmohsen et al., 2007).

SIRT1 is also the target of several miRNAs, which regulate SIRT1 expression and activity directly by binding with the 3' UTR of SIRT1 or through HuR level. In cardiovascular system, miR-22 (Xu et al., 2011), miR-34 (Choi et al., 2013), miR-143/145 (Pramanik et al., 2011), miR-195 (Zhu et al., 2011), miR-199a (Zhang et al., 2013b), and miR-217 (Deng et al., 2014; Zhang et al., 2013a) are highly expressed in vascular tissues and directly inhibit SIRT1 expression, and in other tissues miR-9 (Ramachandran et al., 2011), miR-93 (Li et al., 2011), miR-100 (Tarantino et al., 2010), miR-132 (Zhang et al., 2014), miR-135a (Marasa et al., 2010), miR-137 (Tarantino et al., 2010), miR-181a/b/c (Schonrock et al., 2012), miR-199b (Newsholme et al., 1999) and miR-204 (Gao et al., 2015; Li et al., 2015b) can also directly down-regulate SIRT1 expression (Fig. 3). For example, in hearts and spleens of diet-induced obesity mice, the high level of miR-34a in 32 week old mice reduces expression of SIRT1. Overexpression of miR-34a attenuates SIRT1 expression and accelerates endothelial senescence (Ito et al., 2010). Besides these miRNAs, there are more miRNAs regulate SIRT1 though HuR, such as miR-16 (Xu et al., 2010), miR-125a (Guo et al., 2009) and miR-519 (Marasa et al., 2010). For instance, the miR-519 is highly expressed in human fibroblasts during aging, and the increasing miR-519 has shown detrimental effectson the expression and function of SIRT1 as well, and inhibiting HuR by miR-519 is a key causal factor for this effect (Marasa et al., 2010) (Fig. 3A).

### 3.2.4. *The posttranslational modifications of SIRT1*

Reversible posttranslational modifications are known to be involved in regulating the activity of a variety of enzymes and proteins. So far, mass spectrometry described 15 phosphorylation residues of SIRT1, 8 of which are localized within the C-terminus and 7 within the N-terminus (Sasaki et al., 2008). Both serine (Ser) phosphorylation sites (Ser27, Ser 47, Ser154, Ser649, Ser651, Ser683, Ser 659 and Ser 661) and threonine (Thr) phosphorylation sites (Thr530 and Thr522) on SIRT1 have been identified. In addition, one SUMOylation associated residue, one Methylation associated residue, and two S-nitrosylation associated residues have also been identified (Hwang et al., 2013).

Comparing with the abundant phosphorylation of SIRT1 on Ser27 by C-Jun N-terminal kinase-2 (JNK2) in cancer cells, phosporylation of SIRT1 Ser27 in primary human epidermal keratinocytes (NHEK) and normal diploid fibroblasts (NDF) is too low to detect. Moreover, RNAi-mediated depletion of JNK2 reduces the half-life of SIRT1 protein from >9 h to <2 h, implying that phosphorylation of SIRT1 on Ser27 by JNK2 is relevant to increased protein stability (Fig. 3Ba) (Ford et al., 2008). Similarly, phosphorylation of SIRT1 on Ser27, 47 and Thr530 mediated by JNK1 increases its nuclear localization and enzymatic activity, which contributes to the protection of SIRT1 during oxidative stress in cardiomyocytes (Nasrin et al., 2009; Vinciguerra et al., 2012). Another study has demonstrated that JNK1- dependent SIRT1 induces extensive degradation in hepatocytes in obese mice mediated by ubiquitination and proteasome activity. Degradation leads to SIRT1 inhibition in high fat diet (HFD)-induced obese mice, indicating dual effects

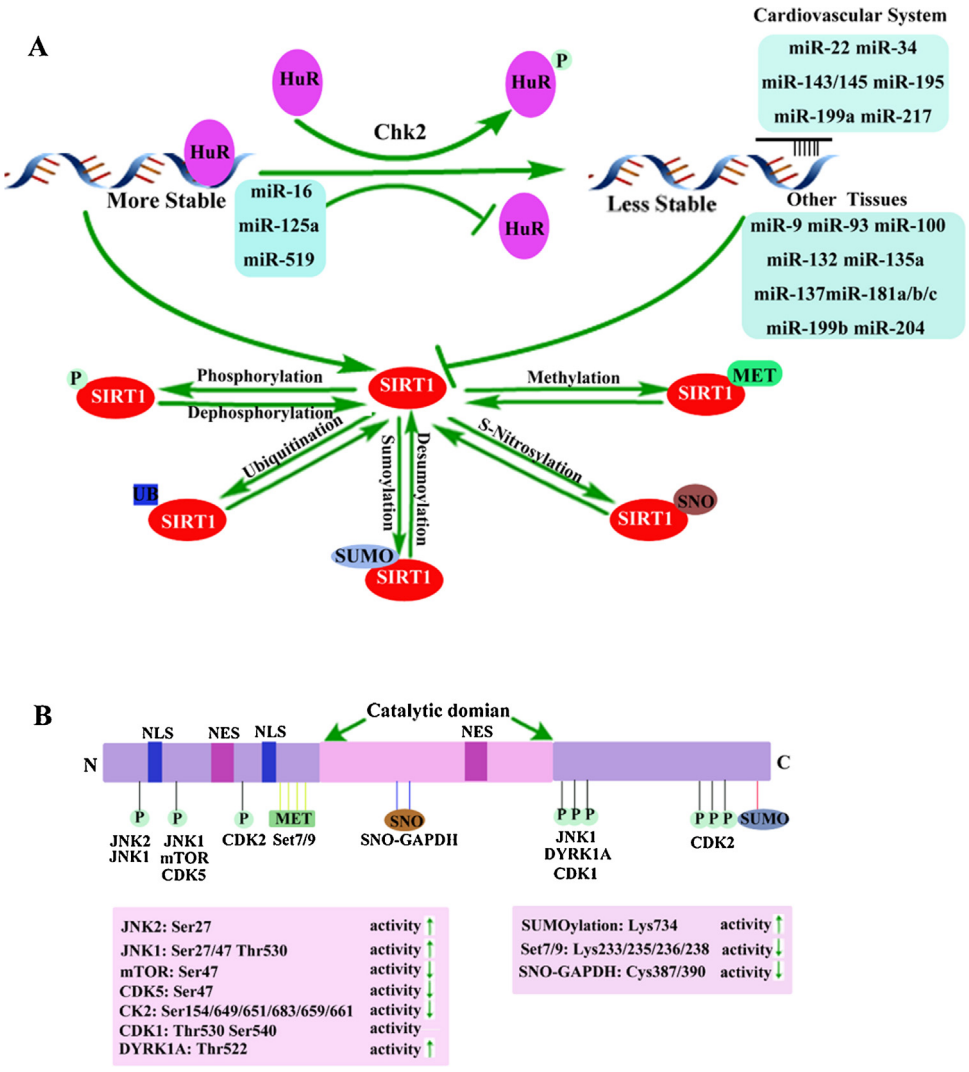


**Fig. 3.** A complex regulatory network controls SIRT1 expression and activity.
(A) SIRT1 mRNA is stabilized by binding of HuR (pink) to the SIRT1-mRNA 30 UTR. Activated Chk2 induced by oxidative stress promotes HuR phosphorylation, which results in dissociation of the HuR-SIRT1-mRNA complex. Additionly, several miRNAs also control SIRT1 transcription directly through HuR level miR-16, miR-125a and miR-519 or by binding with the 3′ UTR of SIRT1. (B) Posttranslational modifications Schematic of SIRT1 and the regualtion of its activity. Upon the aging, SIRT1 undergoes posttranslational modifications, such as phosphorylation (P), S-nitrosylation (SNO), methylation (MET), and SUMOylation (SUMO). SIRT1 deacetylase activity is affected by these posttranslational modifications.

of JNK1-dependent phosphorylation on SIRT1 (Fig. 3Ba and b) (Gao et al., 2011).

The phosphorylation on Ser47 is also regulated by the mammalian target of rapamycin (mTOR) signaling pathway and/or cyclin-dependent Kinase 5 (CDK5), and the phosphorylation is associated with decreased deactylase activity of SIRT1, leading to the development of premature senescence, observed in human carcinoma cells and porcine aortic endothelial cells. (Fig. 3Bb) (Back et al., 2011; Bai et al., 2012).

The cell cycle-dependent kinase (cyclin B/CDK1) mediates the phosphorylation of SIRT1 on Thr530 and Ser540, with effects on deacetylase activity, and is required for cell cycle progression in endothelial cells (Fig. 3Bf). Mutation of these residues disturbs normal cell cycle progression and fails to rescue proliferation defects in SIRT1-deficient cells (Sasaki et al., 2008). Protein kinase 2 (CK2), is a pleiotropic kinase, with anti-apoptotic and pro-growth activities, which can promote the phosphorylation of murine SIRT1 at Ser154, Ser649, Ser651, Ser683, and Ser659, Ser661of human SIRT1 (Fig. 3Bg). In H1299 cells, due to the phosphorylation of SIRT1 by CK2, increased SIRT1 deacetylase activity and substrate-binding affinity of SIRT1 such as P53 can suppressed etoposide-induced apoptosis by 42% (Dixit et al., 2012).

The dual specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) plays an important role in body growth and brain physiology. It has been shown that by combining with another member of the DYRK family, DYRK3, it could directly phosphorylate murine SIRT1 on Thr522 (homologous to human Thr530) (Fig. 3Bf). This posttranslational modification enhance SIRT1 deacetylase activity of P53, and promote cell proliferation and protects cell from DNA damage-induced cell death (Kang et al., 2009; Zschoernig and Mahlknecht, 2009).

Ubiquitination is clearly associated with protein degradation. In contrast, sumoylation of SIRT1 is able to increase protein stability (Herrmann et al., 2007). Sumoylated human SIRT1 on Lysine (Lys) 734 enhances deacetylae activity toward P53 and other target genes (Fig. 3Bh). In response to DNA damage induced by UV radiation, increased sumoylation of SIRT1 can protect human fibroblasts from oxidative stress by deacetylation of HIC1 and promote SIRT1 expression (Dehennaut et al., 2013). While the desumoylation of SIRT1which is mediated by enzyme sentrin-specific protease

(SENP) reduces its deacetylase activity, resulting in the consequent acetylation and activation of apoptotic proteins in the heart (Tong et al., 2013).

Methylation of SIRT1 lysine mediated by monomethyltransferas(Set7/9) has been described in several studies suggesting that the modification may influence the biological activity of SIRT1, however, the specific function of the modification is unclear (Liu et al., 2011; Schmeisser et al., 2013). One study has described that the methylation modification of SIRT1on Lys233, 235, 236, and 238 has no effect on its deacetylae activity (Fig. 3Bd), but is able to dissociate the interaction between SIRT1and P53, thus increasing p53 activity during the DNA damage response (Liu et al., 2011). Thus, we suggest that the methylation modification may modulate SIRT1 activity by regulating the affinity of SIRT1 toward its target proteins.

S-Nitrosylation is another modification that affects the function of SIRT1, in which nitric oxide (NO) is covalent bound to a cysteine thiol/sulfhydryl, leading to form an S-nitrosothiol derivative. Nitrosylated glyceraldehyde-3-phosphate dehydrogenase (SNO-GAPDH) interacts with SIRT1, and in turn mediates nitrosylation of SIRT1 through trans-nitrosylation at cysteine (Cys) 387 and 390. These residues are localized in the catalytic domain of SIRT1, therefore, their nitrosylation reduces deacetylae activity of SIRT1 toward to target protein PGC-1α (Fig. 3Be) (Kornberg et al., 2010).

## 4. Role of SIRT1 in mitochondrial biogenesis

Evidence has suggested that increased mitochondrial biogenesis mediated by SIRT1 plays a key role in improving life span and aging-related diseases (Menzies and Hood, 2012). Indeed, some studies have proven that pharmacological treatment targeting for stimulating SIRT1 such as Resveratrol (Sin et al., 2014), Metformin (Qin et al., 2014), and Tetramethylpyrazine (Xu et al., 2014), increase mitochondrial biogenesis, slowing senescence. In respect to the mechanisms involved, both PGC1α-dependent and PGC1α-independent pathways are though to play prominent roles.

### 4.1. SIRT1-PGC1α-dependent pathway

SIRT1 promoting mitochondrial biogenesis via PGC-1α occurs both in the nucleus and cytoplasm (Brenmoehl and Hoeflich, 2013). Cytoplasmic SIRT1 and PGC-1α are partly co-localized in mitochondria, which is associated with D-loop region of mtDNA, the original site for replication and transcription. In the isolated organelles and cytoplasmic fractions from brain, skeletal muscle and liver of mice, SIRT1 and PGC-1α are detected in the collected organelles rather than cytosol (Aquilano et al., 2010). Cytoplasmic SIRT1 and PGC-1α reside within the mitochondria and particularly mitochondrial matrix (Aquilano et al., 2013). SIRT1 could activate PGC-1α by deacetylation, and PGC-1α in turn co-activates TFAM in the cytoplasm, which account for import of SIRT1 and PGC-1α into mitochondria, as well as recruitment of activated TFAM to the D-loop region of mtDNA to form a tri-protein complex (Fig. 4). Ultimately, the complex drives the transcription/replication of mtDNA and consequently improves mitochondrial biogenesis (Aquilano et al., 2013). This mechanism is in accordance with the report by Tarnopolsky that a large multi-protein complex containing TFAM, SIRT1 and PGC-1α has been discovered in purified mitochondrial extracts of mouse skeletal muscle (Little et al., 2010). Also, cytoplasmic SIRT1 can directly activate PGC-1α and translocation to nuclear targets (Fig. 4), a mechanism which has been demonstrated in total cell extracts from HeLa cells, heart, and skeletal muscle cells (Zhong and Mostoslavsky, 2011).

SIRT1 can also modulate another nutrient sensor AMPK, which is also involved in several aging-associated processes, such as insulin resistance (Okazaki et al., 2010), obesity (García-Prieto et al., 2015), decreased fatty acid catabolism (Fentz et al., 2015; O'Neill et al., 2014), and deterioration of mitochondrial biogenesis (Wang et al., 2015). As an AMPK-activating protein kinase, LKB1 is able to be activated by SIRT1, and promote phosphorylation and activation of the catalytic α-subunit of AMPK. LKB1-deficient murine embryonic fibroblasts, which are associted with nearly complete loss of phosphorylation AMPK in response to energy stress, are hypersensitive to apoptosis (Fig. 4) (Shaw et al., 2004).

In skeletal muscle, exercise activated AMPK increases the phosphorylation on threonine-177, serine-538 and activity of PGC-1α in the nucleus, resulting in triggering transcription of mitochondrial genes, such as NRF1 and ERRα, and strengthened mitochondrial biogenesis (Fig. 4) (Jager et al., 2007). Meanwhile, activated AMPK also increases the protein expression of PGC-1α via a complex of SIRT1–MyoD–PGC-1α. The presence of this complex in skeletal muscle, has been described where it binds to the promoter of PGC-1α creating a positive feedback and auto-regulatory loop for PGC-1α expression (Fig. 4) (Amat et al., 2009). In contrast to SIRT1-mediated deacetylation of PGC-1α, acetylation of PGC-1α is achieved by the acetyltransferase general control nonderepressible 5 (GCN5). In response to a high-fat diet, the expression of GCN5 is upregulated, and PGC-1α is hyperacetylated, which in turn results in a release of SIRT1 and MyoD additionally recruiting its transcriptional repressor receptor interacting protein 140 to the site. Ultimately, the expression of PGC-1α is blunted, leading to the depression of mitochodrial biogenesis (Rodgers et al., 2008).

FOXO3 is also essential for the SIRT1- PGC-1α pathway during the regulation of mitochondrial biogenesis (Lutzner et al., 2012). The expression of SIRT1 and FOXO3 are downregulated during the accelerated aging in cardiac microvascular endothelial cells and the heart of the ischemic reperfusion (I/R) rat, which are characterized by elevated production of ROS and disorder of mitochondrial haemostasis (Lin et al., 2014; Peng et al., 2013). This suggests that FOXO3 may be involved in the regulation of mitochondrial function. Indeed, nuclear SIRT1 is able to deacetylate and activate FOXO3. Activated FOXO3 is found to induce transcription of PGC-1α and Nampt in endothelial cells through the protein-protein interaction. Moreover, enhancement of NAD+/NADH ratio mediated by Nampt, is required for SIRT1-dependent deacetylation and in turn causes an activation of SIRT1 in endothelial cells (Fig. 4) (Canto et al., 2009).

### 4.2. SIRT1-PGC1α-independent pathway

HIF-1a is involved in the regulation of mitochondrial biogenesis, and modulation of the nuclear-mitochondrial communication during aging independent of PGC-1α (Gomes et al., 2013). Both in adult-inducible SIRT1 knockout mice (SIRT1-iKO) and primary myoblasts subjected to SIRT1 silencing, an accumulation of HIF-1α in the nucleus is observed (Mendelsohn and Larrick, 2014). The upregulation of HIF-1α activates the Mxi1 gene, which encodes a c-Myc transcriptional repressor, resulting in interrupting the combination between c-Myc and TFAM, and further decreaseing the *TFAM* promoter activity, suppressing mitochondrial biogenesis (Fig. 5) (Gomes et al., 2013).

PGC-1β is another master regulator of mitochondrial biogenesis, oxidative metabolism as well as antioxidant defense (Dillon et al., 2012a). It is preferentially expressed in tissues with high oxidative capacity where it participates in the metabolic response to high energy demand through regulating mitochondrial biogenesis. As described by Antonio Moschetta, PGC-1β is highly expressed in the intestinal epithelium and possesses dual activities, stimulating mitochondrial biogenesis and oxygen consumption while inducing antioxidant enzymes, which further promote enterocyte lifespan (Bellafante et al., 2014). In addition to c-Myc, HIF-1α also negatively controls PGC-1β activity. It has been described that along with the

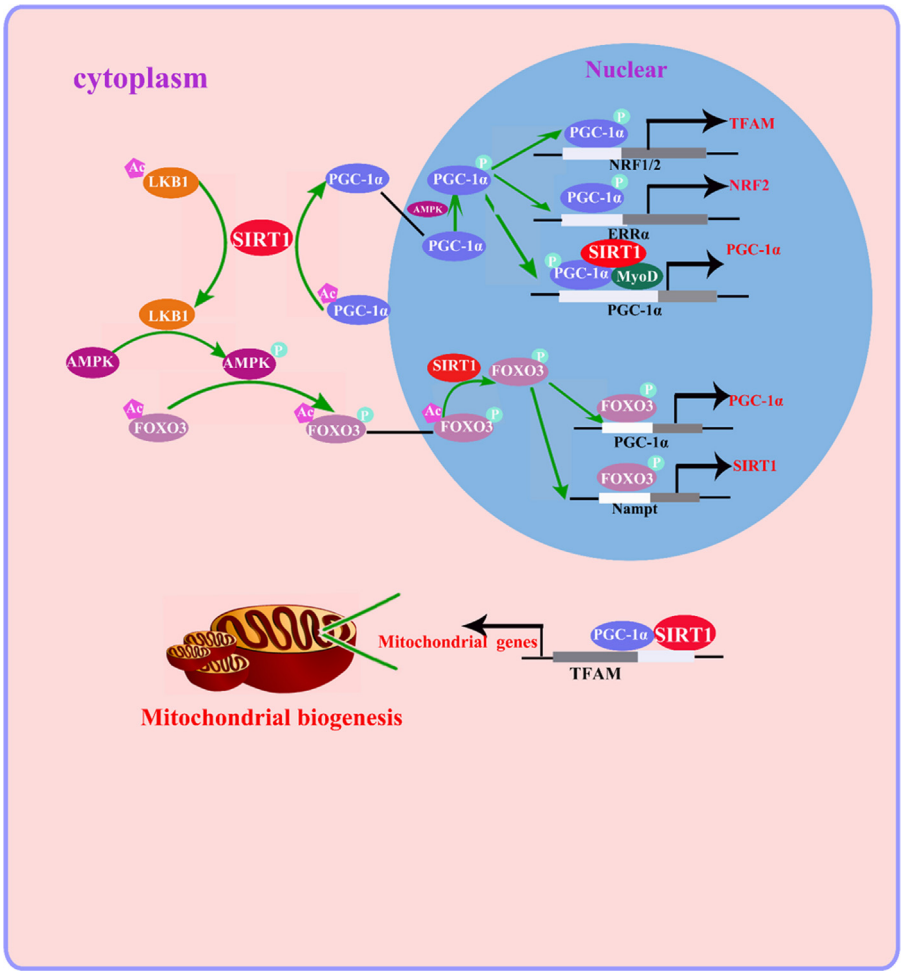


**Fig. 4.** Control of mitochondrial biogenesis by PGC1α.
Activated AMPK induced by SIRT1-mediated LKB1deacetylation, which is required for FOXO3 phosphorylation and nuclear translocation. In the nucleus, SIRT1 deacetylates FOXO3, and further induces transcription of PGC1α and Nampt. Nampt will increase NAD+ levels required for SIRT1-dependent deacetylation and thus activation of PGC1α. Deacetylated PGC-1α is translocated to the nucleus. Phosphorylated nuclear PGC-1α activated by AMPK can enhance expression of NRF-2 and TFAM, that in turn upregulate the mitochondrial biogenesis. PGC-1α also form a complex with SIRT1 and MyoD and induces its own expression.

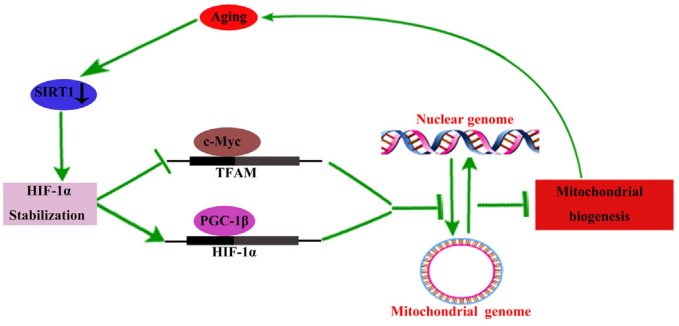


**Fig. 5.** Regulation of mitochondrial biogenesis by PGC1α-independent ways.
During aging process, with the decline of nuclear energetic state or NAD+ levels, the activity of SIRT1 in the nucleus is reduces, which causes decline of Von Hippel-Lindau (VHL) and stablization of HIF-1α. Stablized expression of HIF-1α then reduces the activity of c-Myc and prevent the transcription of TFAM. PGC-1β activity is also inhibited because of the binding with HIF-1α, which resulting in the downregualtion of mitochondrial genes.

increased expression of HIF-1α in hypoxic mice, both the mRNA and protein levels of PGC-1β in the cardiac ventricles are decreased because of the binding with HIF-1α (Fig. 5). Conversely, degradation of HIF-1α leads to the release of PGC-1β, and subsequently promotes mitochondrial biogenesis (Carabelli et al., 2011).

## 5. Conclusion

SIRT1 acts in the complex coordination of nuclear, cytosolic and mitochondrial metabolic and cell stress responses. Beside its role in metabolism, stress resistance, apoptosis, autophagy and inflammation, SIRT1 regulates senescence through deacetylation of target proteins when the NAD+/NADH balance is disturbed by ROS and oxidative stress. Through AMPK, HIF-1α and PGC1α, SIRT1 activates mitochondrial biogenesis promoting an increase in expression of mitochondrial genes critical for proliferation, fission and fusion, and ATP generation via OXPHOS. A better understanding of the transcriptional, posttranscriptional and posttranslational regulation of SIRT1 has implications for modulation and control of the mechanisms of premature cellular senescence and the pathogenesis of many chronic diseases during aging, such as cardiovascular disease, cancer, obesity, and diabetes.

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