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REVIEW ARTICLE

Spatio-Temporal Control of Cellular and Organismal Physiology by Sirtuins

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Abstract | The survival of an organism is intricately dependent upon its ability to sense and respond to both extracellular and intracellular cues. In the context of metabolic or nutrient sensing while intracellular signaling ensures synchronization of various metabolic pathways, inter-tissue communication enables the organism to couple energetic needs of all the organ systems and in a concerted manner. In this review, we highlight the role of evolutionarily conserved sirtuins (NAD-dependent deacylases) in synchronizing inter-organellar and inter-tissue cross-talk that is needed to orchestrate organism-wide metabolic homeostasis.

1 Introduction

Organismal physiology and hence survival is dependent on the ability to perceive and respond to various stimuli, both intrinsic and extrinsic. While the need to respond to extracellular and intracellular signals is inherent, the ability to decode the inputs into spatial and temporal components often determines the biological response. This becomes even more evident in the case of metabolic sensing. Specifically, to maintain homeostasis cells also need to couple the intracellular metabolic status, extracellular signals and nutrient availability, in addition to assessing them independently. This requires a complex interplay between various molecular mechanisms in cells. With the evolution of multicellularity, signal generation, sensing and integration had to be orchestrated across tissues, still maintaining heterogeneity among various tissues. Apart from the spatial control of metabolic sensing, time-dependent responses become critical since (a) metabolic inputs are not constant and (b) the metabolic demand varies, for example, during development and aging[1, 2] and under various physiological states such as sleep and wake cycles[3, 4].

Genetic screens in various organisms followed by biochemical and phenotypic characterizations have led to the discovery of key factors that mediate metabolic sensing. AMPK (AMP activated kinase)[5] sirtuins (NAD-dependent deacylases)[6, 7] and TOR (Target of Rapamycin that responds to amino acids and ATP)[8] form the 'trinity' of metabolic sensors. These factors are known to govern almost all aspects of cellular and organismal physiology, including maintenance of metabolic homeostasis.

In this review, we have specifically highlighted the importance of the NAD-dependent deacylases, sirtuins, in mediating metabolic sensing/signaling. We have aimed at providing insights into their roles in orchestrating spatial and temporal control by their ability to regulate intracellular and extracellular signals. For intracellular signaling, we have focussed on the importance of bidirectional control of cellular physiology emanating from nucleus and the mitochondria. For extracellular signals, we have reviewed the key role of sirtuins in regulating the evolutionarily conserved nutrient sensing endocrine pathway, the Insulin/IGF signaling (IIS).

2 Nuclear–Mitochondrial Cross-Talk

Although mitochondria have been well established to function as semi-autonomous organelles, nuclear transcription is key to not only contribute to the ETC (electron transport chain) complexes but also to regulate mitochondrial biogenesis and encode all the metabolic enzymes, which localize to the mitochondria. The readers are encouraged to refer to extensive reviews by Richard Scarpulla and others which describe the

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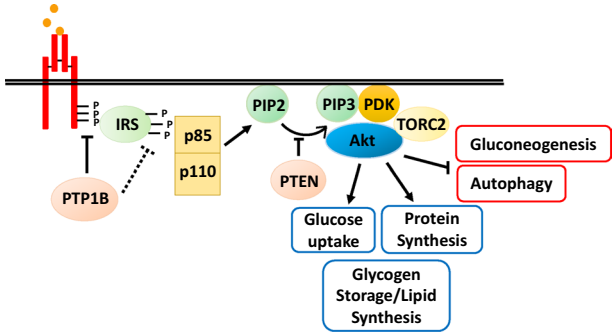

Figure 1: Canonical Insulin Signaling Pathway.

transcriptional mechanisms that govern mitochondrial functions[9–11].

Until recently, mitochondria were regarded as organelles that would respond to extrinsic cues (from within and outside cells) and modulate its functions to generate ATP. However, emerging literature has clearly indicated that mitochondria elicit and control several signaling mechanisms that impinge on various aspects of cellular physiology. Termed as Retrograde Signaling, mitochondrial signals in the form of ATP, ROS, Calcium and NAD/NADH are now recognized for acting as mediators of intracellular signals[12, 13].

Calorie restriction: It is loosely defined as a dietary regimen in which diet or calorie intake is reduced to different extents. Typically it involves a restriction of 30% or more of the macronutrients without affecting the micronutrients.

3 Insulin/IGF Signaling (IIS)

IIS is an evolutionarily conserved mechanism across metazoans and involves an intricate signal transduction pathway, described and reviewed elsewhere[14,] but depicted in Fig. 1. IIS is critical to maintain organism-wide nutrient and metabolic homeostasis. For example, in the case of insulin signaling, this entails secretion of insulin (or related peptides) from insulin secreting cells, which bind to cognate receptors (receptor tyrosine kinases) present on almost all cells across tissues[15]. Nutrient uptake, specifically glucose, is dependent on the action of insulin and at a cellular level, insulin signaling is essential to maintain physiology[16]. Control of insulin signaling can be elicited at various levels from production/secretion of the ligands (insulin) to receptor binding/activity and all the way up to transcription of downstream genes[15]. Reduced signaling, termed insulin resistance, is known to cause metabolic diseases such as obesity and diabetes[16]. Genetic perturbations in IIS from worms to mice have shown that they are also involved in organismal aging[17–22].

4 Sirtuins

Sirtuins (Sir2 like proteins) are evolutionarily conserved NAD^+-dependent protein deacylases. Among the metabolic sensors, sirtuins seem to be most ancient—evolutionarily being present in Archaea and present in all species studied thus far. Sir2 was first identified in yeast as a histone deacetylase, which was part of **S**ilent **I**nformation **R**egulator (SIR) complex and shown to play a role in heterochromatinization and repression of rDNA, telomeres and mating type loci[23–25]. They have been shown to play important role in regulating aging and in mediating the beneficial effects of calorie restriction (CR) across model organisms, from yeast to mice[26–31]. Based on homology and previous reports, it emerges that mammals uniquely have seven Sir2 paralogs, compared to five each in yeast, flies and worms[32, 33]. Mammalian sirtuins (SIRT1-SIRT7) are located in different cellular compartments: SIRT1, SIRT6 and SIRT7 are located in nucleus, SIRT2 in cytoplasm, and SIRT3, SIRT4 and SIRT5 are localized in mitochondria (Table 1, Fig. 2). Owing to their dependence on NAD^+ for their activity, wherein cleavage of NAD^+ is coupled to deacylation of substrate protein, they act as metabolic sensors. Apart from deacetylation, sirtuins also possess multiple catalytic activities such as demalonylation, desuccinylation, deglutarylation (SIRT5), ADP-ribosylation (SIRT4, SIRT6) and demyristoylation (SIRT6)[34] (Table 1). Below, we have discussed the importance of each of these sirtuins, specifically in metazoans, in mediating spatial and temporal control of metabolic signaling.

4.1 Sirtuins and Spatio-Temporal Control of Organismal Physiology

The contents of this review illustrate the well-established cellular functions of sirtuins being

Table 1: List of mammalian sirtuins, their localization and established activities.

Sirtuin	Localization	Activity	References
SIRT1	Nucleus	Deacetylation, decrotonylation?	Imai et al. Nature [2000], Bao et al. eLife [2014]
SIRT2	Cytoplasm	Deacetylation	North et al. Mol Cell [2003]
SIRT3	Mitochondria	Deacetylation, decrotonylation?	Onyango et al. PNAS [2002], Bao et al. eLife, [2014]
SIRT4	Mitochondria	ADP-ribosylation, deacetylation, delipoylation	Haigis et al. Cell [2006], Laurent et al. Mol Cell [2013], Mathias et al. Cell [2014]
SIRT5	Mitochondria	Deacetylation, demalonylation, desuccinylation, deglutarylation	Nakagawa et al. Cell [2009], Du et al. Science [2011], Tan et al. Cell Metab [2014]
SIRT6	Nucleus	ADP-ribosylation, deacetylation, demyristoylation, depalmitoylation?	Liszt et al. JBC [2005], Michishita et al. Nature [2008], Jiang et al. Nature [2013]
SIRT7	Nucleolus	Deacetylation, desuccinylation	Barber et al. Nature [2012], Li et al. Nat Comm [2016]

elicited from different organelles or tissues in mediating homeostasis. It is also motivated by the observations, which together indicate that given the diverse developmental and metabolic fates of different tissues in metazoans, sirtuins may play a central role in synchronizing metabolic sensing at an organismal level both in space and time (Fig. 2).

4.2 SIRT1

SIRT1 acts as a master regulator of transcription by deacetylating a plethora of factors including transcription factors, co-activators/-repressors, chromating modifiers and histones themselves[35]. SIRT1 has now been implicated in diverse cellular and organismal phenotypes ranging from differentiation to mood disorders[36–39]. Since it is nearly impossible to highlight every mechanism that is affected by SIRT1, we have concentrated on its functions in mediating inter-organellar and inter-tissue communication brought about by IIS. Studies in cell culture and gain- and loss of function perturbations in various model systems from worms, flies, mice and human cells have shown that SIRT1 in the nucleus plays a pivotal role in controlling mitochondrial functions and insulin signaling at a cellular level[40, 41].

4.3 Nuclear Control of Mitochondria Through SIRT1

Cell line-based studies and genetic perturbations of SIRT1/Sir2 in specific tissues such as liver/fat body, muscles and adipocytes have illustrated its importance in modulating mitochondrial functions, across species[27, 42, 43].

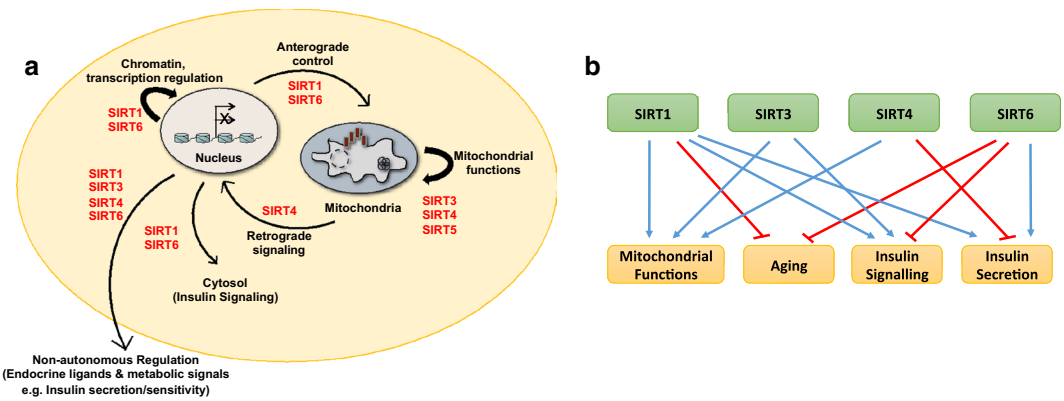

Figure 2: a Schematic indicating Sirtuin mediated spatial control of cellular functions and their role in dictating extracellular ligands/signaling. b Brief overview of phenotypes associated with Sirtuin functions vis-à-vis their role in nuclear-mitochondrial and insulin signaling.

SIRT1-dependent deacetylation of all the key factors, such as ERRa (Estrogen-related Receptor alpha), NRF1 (Nuclear Respiratory Factor 1), PPARa (Peroxisome Proliferator Activated Receptor Alpha) and PGC1a (Peroxisome proliferator activated receptor gamma coactivator 1-alpha), is necessary to activate transcription of genes involved in fatty acid oxidation, TCA cycle, ketogenesis and mitochondrial biogenesis Fig. 2, [43, 44]. Specifically, SIRT1 deacetylates and activates PPARa in liver to increase in the expression of fatty acid oxidation genes like CPT1, LCAD and CD36, and loss of SIRT1 in liver leads to hepatic steatosis even under normal fed conditions[43, 45]. Further highlighting its role in regulating fat metabolism including beta-oxidation in the mitochondria, adenoviral overexpression of SIRT1 in the livers of *db/db* mice (mice homozygous for a point mutation in Leptin Receptor causing decreased leptin signaling and are used as a model system for diabetes and obesity[46]) has been shown to decrease hepatic steatosis[47]. In muscles, fasting has been shown to increase NAD^+ levels via AMPK, which activates SIRT1. Together AMPK and SIRT1 activate PGC1a (via phosphorylation and deacetylation, respectively) leading to elevated transcription of nuclear encoded mitochondrial ETC components like cytochrome-*c*, COX-IV and mitochondrial biogenic genes like TFAM[44, 48]. Similarly, knockdown or overexpression of SIRT1 in flies has been associated with decreased or increased mitochondrial output, respectively, in both fat body and muscles[26, 27].

Hepatic steatosis: A pathological condition arising due to perturbed fat homeostasis in the liver. It is characterized by accumulation of lipid droplets, inability to breakdown and mobilize fat. Clinicallly it is one of the major causes of non-alcoholic liver failure, which is associated with hyper-inflammation.

Insulin resistance: A pathological condition in which the cells are unable to respond to insulin and thus cannot absorb glucose from blood. This is typically characterized by a hyperglycemic state and reduced signaling flux through Akt. To tackle this situation, beta cells of pancreas produce more insulin to maintain the blood glucose. If this condition persists, it ultimately may lead to type 2 diabetes mellitus.

4.4 SIRT1 is Essential for Maintaining Insulin/IGF Signaling Within Cells

It is important to note that SIRT1 is critical in maintaining intracellular insulin signaling and it impinges on this pathway at all levels either transcriptionally or by regulating the activities of the components. Again, studies in cell lines, worms, flies and mice have shown that SIRT1 is essential for enabling cells to respond to insulin or in other words increasing insulin sensitivity and its loss has been shown to cause insulin resistance[27, 49–51].

SIRT1 has been shown to activate IRS-1 and IRS-2, which are immediately downstream of insulin receptor. SIRT1 activates IRS-1 indirectly, via NF-κB and JNK[52]. In the case of IRS-2, SIRT1 plays a direct role in its activation. The activatory tyrosine phosphorylation on IRS-2 is enhanced upon deacetylation by SIRT1[53]. The next component in IIS, namely phosphoinositide 3-kinase (PI3 K) that converts PIP2 to PIP3, is controlled by SIRT1. Specifically under calorie-restricted conditions, SIRT1 has been shown to downregulate transcription of regulatory subunits of PI3 K, namely p55a and p50a, by deacetylating and inhibiting STAT3, as shown in skeletal muscles[54]. PTEN (phosphatase and tensin homolog) is a lipid phosphatase that converts PIP3 into PIP2, counteracting the activity of PI3 K and acting as a negative regulator of IIS. SIRT1 deacetylates and inhibits PTEN, thus activating insulin signaling[55]. SIRT1 represses the transcription of *Ptpn* and hence seems to relieve the repressive action of PTP1b on insulin signaling[56].

Subsequent to conversion of PIP2 to PIP3, concerted action of two kinases, i.e,. PDK (3-phosphoinositide dependent protein kinase-1) and Akt is a key to transduce the membrane-anchored insulin signal to the interior of the cell. SIRT1 activates both PDK1 and Akt via deacetylation and seems to enhance the flux of insulin signaling[57]. Interestingly, under conditions of oxidative stress, SIRT1 prevents Akt activation by deacetylating and activating PTEN[58].

In addition to mechanistic underpinnings of SIRT1-mediated control, its importance in regulating glucose homeostasis has been evidenced by genetic alterations both in the entire organism, and in specific tissues such as muscle and liver/fat body in flies and mice[27, 49–51]. Importantly, overexpression of Sir2.1/dSir2 has been found to be sufficient to improve insulin sensitivity in worms and flies, suggesting its evolutionarily conserved role in regulating insulin signaling and sensitivity[26, 29, 59]. Despite this, the mechanistic basis for Sir2.1/dSir2 regulating insulin signaling and sensitivity is poorly understood.

4.5 Role of SIRT1 in Regulating Insulin Secretion

Apart from the above-described role in regulating insulin signaling at a cellular level, SIRT1 acts to modulate this signaling 'top–down' by controlling the expression and secretion of insulin and insulin-like molecules. In mammals, SIRT1 has been shown to regulate insulin secretion via its ability to control transcription of various genes including the repression of UCP2 (uncoupling protein 2)[60]. Gain of function studies in the beta islets have clearly demonstrated that SIRT1 increases insulin secretion[61]. Interestingly, the expression of SIRT1 itself has been shown to be modulated during glucose stimulated insulin secretion (GSIS) in mice. Specifically, SIRT1 expression seems to oscillate during GSIS and a reduction of SIRT1 protein that is mediated by a microRNA,

microRNA: It is a small, 22 nucleotide non-coding RNA that is involved in post-transcriptional regulation of mRNA. MicroRNAs are known to both inhibit translation and degrade mRNAs and hence act as key regulators of gene expression.

miR-9, has been implicated in the 'fall-phase' of insulin secretion from the beta islets[62].

Studies in Drosophila and mice have also indicated a central role for SIRT1 in controlling the expression of dILPs/insulin non-autonomously. Fat body-specific overexpression of SIRT1 decreases dILP2 and dILP5 transcription while knockdown of SIRT1 in fat body increases dILP2 and dILP5 transcription. Interestingly, no such effect was seen by perturbing SIRT1 in muscles[27]. Similar results have been seen in liver-specific SIRT1 knockout or overexpression studies in mice, where SIRT1 expression/function in hepatocytes has been negatively correlated with serum insulin levels[43, 47].

Together, these findings show that whereas SIRT1 in the islets is required for GSIS, SIRT1 from the fat body or liver inhibits circulating serum insulin. This clearly indicates that multiple control mechanisms, which are spatially separated, regulate insulin secretion. Moreover, these also highlight the importance of liver and fat body as central organs that remotely modulate insulin signaling, across evolution. This raises the possibility of differential metabolic sensing, via sirtuins, in each of these tissues mediating non-overlapping but concerted effect on the evolutionarily conserved endocrine system that is critical for survival of organisms.

4.6 Control of Endocrine Ligands/ Signaling by SIRT1

Pointing towards a general theme in the SIRT1-dependent control of spatial endocrine signals, emerging studies published in the recent past have shown that presence or absence of SIRT1 affects growth hormone (GH), fibroblast growth factors (FGFs) and insulin-like growth factor (IGF) signaling. Specifically, SIRT1 has been shown to deacetylate cAMP response element binding protein (CREB) and Glycogen synthase kinase 3 beta (GSK3β) and in turn negatively regulate GH transcription from anterior pituitary gland[63]. It also negatively regulates IGF1 transcription in liver by deacetylating and inhibiting STAT5[64]. On the other hand, SIRT1 positively regulates FGF21 transcription and signaling, and promotes fasting response in liver[65]. Given the intricate interplay between various endocrine pathways, it will be interesting to address if SIRT1 mediates tissue-specific origin or control of organismal physiology, by altering the ratios of various ligand-dependent signaling mechanisms.

5 SIRT3

5.1 Regulation of Mitochondrial Functions

SIRT3 has now been well characterized as the major deacetylase present in mitochondria and multiple proteomic studies have identified several proteins involved in almost every aspect of mitochondrial physiology as its substrates Fig. 2, [66, 67]. Highlighting its importance in the core function of mitochondria that is oxidative phosphorylation, SIRT3 has been shown to deacetylate electron transport chain and ATP synthase components. Specifically, SIRT3-dependent deacetylation of NDUFA9[68] and ATP synthase F1 complex proteins[69] have been associated with increased mitochondrial respiration and ATP production. Indicating the central role of SIRT3 in maintaining the flux through TCA cycle, fatty acid oxidation and urea cycle, it is now known to deacetylate several enzymes such as isocitrate dehydrogenase (IDH2)[70], succinate dehydrogenase (SDH)[71], long chain acyl CoA dehydrogenase (LCAD)[72] and ornithine transcarbamoylase OTC[73]. SIRT3-dependent deacetylation of ROS scavengers MnSOD and Catalase reduces ROS[74, 75] pointing towards its role in oxidative stress response.

5.2 SIRT3 and Spatial Control of Metabolic Signaling

Although little is known about the role of SIRT3 in mediating intracellular signaling, its ability to regulate ROS seems to hint at this possibility. This is because, ROS is now well regarded as a key factor in mediating both stress responses and intracellular signaling[76, 77]. Whether ROS homeostasis mediated by SIRT3 impinges in encoding spatial cues via signaling remains to be seen (except for one report, see below).

While several reports have highlighted bidirectional cross-talk between mitochondria and insulin signaling, the importance of mitochondrial sirtuins in mediating any such pathways is less understood. However, SIRT3 has been shown to impinge on insulin signaling via ROS and hence determine insulin sensitivity in muscles[78].

6 SIRT4

SIRT4 is one of the most evolutionarily conserved mitochondrial sirtuins whose localisation, unlike the other mitochondrial sirtuins, seems to be restricted to this organelle[79]. Although this molecule is least studied and its

catalytic activity is still ambiguous, recent studies have provided insights into its role in regulating metabolism and organismal physiology.

6.1 Organelle-Specific Control Elicited by SIRT4

SIRT4 has been shown to repress glutamate dehydrogenase (GDH) activity by ADP-ribosylation, which has been associated in the control of insulin secretion from beta islets[80]. Although, SIRT4-mediated GDH repression has now shown to negatively impinge on the ability of cancer cells to utilize glutamine[81], a broader significance of GDH regulation in normal physiology is still limited.

Providing a breakthrough to the field, Nasrin et al. in 2010 showed that SIRT4 knockout mice have increased fatty acid oxidation in WAT, muscles and liver and that they were protected from high fat diet induced obesity. Further studies have clearly established that SIRT4 is a negative regulator of beta-oxidation[82–84]. It is still unclear if the ability of SIRT4 to regulate fatty acid oxidation is mediated locally within the mitochondria.

7 SIRT4 Plays a Crucial Role in Mitochondrial Retrograde Signaling

Paradoxically, despite paucity of reports on the functions of SIRT4 within the mitochondria, its presence or absence has been seen to affect nuclear transcription and hence encode a spatial control over cellular physiology. It is now clear that the ability of SIRT4 to negatively regulate fatty acid oxidation genes from the nucleus is the reason for these mice to show a lean phenotype and be protected from high fat diet induced obesity. Tracing the causal mechanism for increased beta oxidation in the absence of SIRT4, Ho et al. showed that reduced cellular ATP (or energy deficiency) was critical in eliciting a mitochondrial signal that controlled nuclear transcription of genes involved in fat metabolism and mitochondrial biogenesis[82]. Concurrently, Laurent et al. showed that loss of SIRT4 causes increased NAD levels in cytosol, which activated SIRT1[83]. Together, SIRT4 has now been shown to act via the AMPK-SIRT1-PPARa-PGC1a axis to regulate transcription from the nucleus Fig. 2[82–84].

8 SIRT6

8.1 Cell Autonomous Mechanisms Downstream to SIRT6

Besides SIRT1, SIRT6 is the second most widely studied sirtuin in the field. Unlike SIRT1, SIRT6 is mostly chromatin bound and has been shown to mediate most of its effects on cellular physiology via transcription. SIRT6 has now shown to possess ADP-ribosylase, deacetylase and demyristoylase activities (see below). It has emerged as a key factor in regulating glucose homeostasis by controlling transcription of glycolytic genes downstream to HIF1a (Hypoxia-inducible factor 1-alpha)[85]. In addition to its roles in mediating DNA damage and inflammatory responses, SIRT6 is required for maintaining telomeric chromatin and length[86].

With regards to cellular signaling, SIRT6 has been shown to negatively regulate insulin signaling in a cell autonomous manner. Specifically, SIRT6 loss of function studies have clearly demonstrated that increased insulin signaling and hypoglycemia results in one of the most obvious or primary phenotypes that causes lethality[85, 87]. However, little is known about the mechanistic underpinnings of how SIRT6 affects insulin signaling intracellularly, except for the negative regulation of AKT transcription via c-jun[88].

8.2 Organismal Level Control of Signaling by SIRT6

Although several studies have shown that SIRT6 knockouts have whole body phenotypes ranging from lymphopenia, loss of subcutaneous fat, lordokyphosis, and severe metabolic defects, little is known about the tissue specific contributions towards this[89]. With regards to its ability to control inter-tissue communication, SIRT6 has been recently shown to control insulin secretion by regulating FoxO1. Forkhead box O1 (FoxO1) and Forkhead box O3 (FoxO3) are transcription factors involved in the regulation of cell cycle, apoptosis, metabolism and aging, and they are evolutionarily conserved from yeast to mammals[90]. Specifically, SIRT6 deacetylates FoxO1 leading to its exclusion from the nucleus and derepression of *pdx1* and *glut2* genes. Pdx1 mediates the transcription of insulin and beta cell maintenance, whereas Glut2 function is necessary for the glucose entry into the pancreatic beta cells to release insulin[91, 92]. Loss of SIRT6 in pancreatic beta cells leads to impaired GSIS and glucose intolerance. These pancreatic cells also show defects in mitochondrial structure and oxidative phosphorylation[93]. Interestingly, SIRT6 absence has been associated with severe loss in circulating IGF-1 levels, which has been shown to have both overlapping and non-overlapping effects with insulin on organismal physiology[89]. Interestingly, gain of function transgenic overexpression

of SIRT6 that manifests in a longevity phenotype has been largely attributed to an overall decrease in insulin/IGF signaling at an organismal level[94]. Again, the mechanistic and physiological understanding of how SIRT6 conrols IIS is still not available.

8.3 Is SIRT6 Acting as a Key Regulator of Cellular Secretion?

A recent report described a novel activity for SIRT6, namely, demyristoylation (ref). TNFa (tumor necrosis factor-alpha) is a direct target of SIRT6 which gets secreted in response to demyristoylation providing an important non-autonomous proinflammatory cue to the cells. Although, TNFa is currently the only identified target of SIRT6, considering that myristoylation is a predominant modification which mediates the membrane tethering of secreted factors, it is not difficult to imagine the existence of other targets[95]. Efforts to identify proteins that show altered secretion, specifically brought about by the de-fatty acylase activity of SIRT6 revealed, unexpectedly, ribosomal proteins. Specifically, using a catalytic mutant of SIRT6 that retains only its defatty-acylase activity showed it possibly exerts its action via exosomes[96]. It will be interesting to see the tissue-specific control of such cellular outputs or if and how these would mediate an organism-wide phenotype.

9 Temporal Control of Signaling or Sensing by sirtuins

Although sirtuins in general, but more specifically SIRT1 and SIRT6, have been clearly associated with aging and age-related diseases, whether they control intracellular and extracellular signaling in a temporal manner, is still unclear. In fact, it is likely that a significant amount of biology remains to be discovered or detailed in this context. This is relevant because, SIRT1 and SIRT6 expressions have been well documented to alter during development, growth and aging across all organisms studied thus far. Even in the context of intracellular signaling, the protein turn-over of sirtuins is still poorly characterized and it will be exciting to see if and how both short-term and long-term signaling and epigenetic memory is maintained by these two sirtuins. Since all sirtuins are known to be dependent upon NAD, it will be exciting to ask whether tissue- and organelle-specific alterations in NAD concentrations, across the lifespan of an organism, can elicit varied sirtuin-mediated responses. Given the paucity of information in this context, in this section we have reviewed literature that hints at the existence of such temporal controls in a physiological setting.

9.1 SIRT1

SIRT1 and its homologs in lower organisms like yeast (Sir2), *C. elegans* (Sir 2.1) and *D. melanogaster* (dSir2/SIRT1), have been shown to increase lifespan and mediate the beneficial effects of calorie restriction on organismal physiology[29, 30, 97, 98]. Multiple pathways such as rDNA and telomere maintenance, insulin signaling, stress resistance, mitochondrial functions, repression of transposable elements and genomic stability have been implicated as mediators for the role of Sir2/SIRT1 in regulating lifespan and healthspan[99, 100]. SIRT1 has been shown to maintain heterochromatin by regulating multiple factors like SUV39H1, MECP2 and HP1[101, 102]. A recent report in Drosophila has shown the importance of SIRT1 in suppressing the age-associated transposition of mobile elements in fat body of aged fly[103]. SIRT1 has been shown to relocalize across the genome during stress to repair the damaged DNA. This relocalization causes altered gene expression similar to that of aging brain, and overexpression of SIRT1 counters the abrogated transcription[104]. This supports the chromatin theory of aging which suggests that derepression of heterochromatinized regions caused by relocalization of chromatin factors leads to aging[105]. Multiple studies have shown that muscle functions get altered during aging and loss of mitochondrial functions and insulin resistance has been the major causes attributed to this. During aging, SIRT1 levels decrease in muscles, causing decreased expression of nuclear-encoded mitochondrial complex components, but not mitochondrial-encoded mitochondrial components. This leads to nuclear–mitochondrial asynchrony and loss of muscle functions, which can be rescued by pharmacological activation of SIRT1[106]. Apart from autonomous regulation, non-autonomous regulation of skeletal muscle by SIRT1 in brain has also been shown. In brain-specific SIRT1-overexpressing mice, there is increased lifespan and it is partially mediated via Nk2 homeobox-1 (Nkx2-1) and orexin type 2 receptor (Ox2r)-dependent regulation of sleep–wake cycles and skeletal muscle functions[107].

9.2 SIRT6

Loss of function studies of SIRT6 in mice have shown accelerated aging phenotype. The mice, which develop normally up till 3 weeks of age

Exosomes: They are extracellular vesicles released from cells by fusion of multivesicular bodies (MVBs) with the plasma membrane. They contain membrane proteins and cytosolic components, including microRNAs.

show acute degenerative phenotype and succumb to death by postnatal day 24[89]. Gain of function studies have shown the role of SIRT6 to improve overall healthspan of the organism including protection against age-related decline in glucose tolerance. The livers of these mice are more proliferative and the adipose tissue shows reduced inflammation which is predominantly attributed to reduction in age-associated macrophage activation[108].

SIRT6 has been shown to be a positive regulator of longevity with transgenic male mice overexpressing SIRT6 showing a mean lifespan extension by 16%. These mice show better glucose tolerance, attenuated IGF-1 signaling via increased expression of IGFBPs and altered phosphorylation levels of major Insulin/IGF pathway components including IGF-R, Akt and FOXO[94].

SIRT6 also functions in maintaining genome integrity via silencing of retrotransposons. The silencing of these mobile elements becomes less efficient with age and their activation leads to development of age-related disorders, like cancer and neurodegeneration[109, 110]. SIRT6 mono-ADP ribosylates KAP1, a nuclear co-repressor protein, to maintain L1 elements in the silenced state[111]. Indicating its role in linking chromatin, gene expression and nuclear architecture, SIRT6 has been shown to regulate the expression of many age-associated genes such as cell cycle inhibitor cdkn2a and laminA via the NFkB subunit RelA[112].

10 Conclusion

Given the enormous heterogeneity in terms of metabolic inputs and tissue-specific functions, it makes perfect evolutionary sense to encode mechanisms that synchronize organ systems. At a cellular level, it ultimately boils down to metabolic sensing within cytoplasm, mitochondria and the nucleus. By virtue of their mostly ubiquitous expression across tissues (and across species), in addition to being localized to the key cellular compartments, and dependence on NAD^+ for their activity, sirtuins emerge as one of the key factors that play a central role in establishing and maintaining regulatory networks.

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