IJIRR

International Journal of Information Research and Review
Vol. 06, Issue, 05, pp.6306-6313, May, 2019

REVIEW ARTICLE

ROLE OF SIRT1 IN CANCER BIOLOGY REVIEW ARTICLE

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ARTICLE INFO

Article History:
Received 19th February, 2019
Received in revised form
29th March, 2019
Accepted 30th April, 2019
Published online 30th May, 2019

Keywords:
SIRT1, Sirtuin, Cancer,
Lysine acetylation.

ABSTRACT

SIRT1, an NAD^+-dependent deacetylase, has been explained in the literature as a important factor in the regulation of cellular stress responses. Its expression has been shown to be altered in cancer cells, and it targets both histone and non-histone proteins for deacetylation and thereby alters metabolic programs in response to diverse physiological stress. Interestingly, many of the metabolic pathways that are influenced by SIRT1 are also altered in tumor development. Not only does SIRT1 have the potential to regulate oncogenic factors, it also orchestrates many aspects of metabolism and lipid regulation and recent reports are beginning to connect these areas. SIRT1 influences pathways that provide an alternative means of deriving energy (such as fatty acid oxidation and gluconeogenesis) when a cell encounters nutritive stress, and can therefore lead to altered lipid metabolism in various pathophysiological contexts. This review helps to show the various connections between SIRT1 and major pathways in cellular metabolism and the consequence of SIRT1 deregulation on carcinogenesis and lipid metabolism.

INTRODUCTION

Mammalian sirtuins deacetylases has seven family members (SIRT1-7) that have been shown to be critical regulators of cell signaling pathways. Deacetylases are enzymes that remove acetyl groups from the ε-amino group of lysine residues of histone and non-histone proteins and thereby alter protein function. Deacetylation reactions can take place in the nucleus and cytoplasm, and affect multiple cellular processes (Haberland, 2009). Because some members of the various classes of histone deacetylases (HDACs) have been shown to be overexpressed in diverse cancers, current views suggest that perturbed acetylation patterns on proteins may contribute to cellular transformation and tumor progression (Krusche, 2005 and Weichert, 2011). The most well studied sirtuin family member, SIRT1, has been shown to alter cellular metabolism and responses to stress and thereby influence programs that direct transcription, apoptosis, autophagy DNA damage repair and senescence (Powell, 2011; Brooks, 2009; Liu, 2009). Influencing diverse physiological processes, it is not surprising that the role of SIRT1 in cellular growth control is complex and its enzymatic activity exerts important cell-type specific effects. This complexity, likewise, extends to studies involving human tumors.

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For example, SIRT1 expression was found to be significantly associated with shorter overall and relapse-free survival of gastric carcinoma (Cha, 2009), distant metastatic relapse and shorter survival in breast carcinoma (Lee, 2011) and overall survival and event-free survival in soft tissue sarcoma (Kim, 2013). On the other hand, immune-histo-chemical analysis of a tissue microarray demonstrated that 23 of 82 carcinomas showed lower SIRT1 expression, and 18 of 82 showed higher expression relative to normal colonic mucosa, indicating the complexity of SIRT1 in tumorigenesis (Kabra, 2009). Additionally, SIRT1 mRNA has been shown to be down regulated in gastric cancer (Yang, 2013). Other studies have shown that nuclear SIRT1 expression was detected in about 28% of pancreatic ductal adenocarcinoma (PDAC), and expression was found to be significantly higher in poorly differentiated carcinomas. Moreover, strong SIRT1 expression was a significant predictor of poor survival both in univariate and multivariate analyses, further suggesting that imbalances in protein acetylation may influence cancer progression (Stenzinger, 2012). Overexpression of SIRT1 has been detected in diverse primary solid tumors and hematopoietic malignancies of the breast, colon, prostate, liver and also some types of leukemia (Lee, 2011; Chen, 2011), while loss of SIRT1 in $Sirt1^{-/-}$ mice is associated with smaller prostates that exhibited a morphologic phenotype similar to that commonly observed within PIN lesions (Powell, 2009). Due to the fact that SIRT1 activity regulates the function of signaling

pathways associated with cell growth and motility (Holloway, 2010; Zhang, 2009 and Saxena, 2015), it's over expression could have grave consequences for tumor progression. Conversely, the inhibition of SIRT1/2 was shown to be effective in inhibiting cell proliferation, while inducing apoptosis in cancer cells. These effects have been linked to SIRT1 regulation of several well-established tumorigenic pathways, like Wnt-β catenin and Akt/PI3K (Simmons, 2014; Pruitt, 2006 and Ikenoue, 2008). In this review, we have highlighted reports on SIRT1-mediated regulation of processes involved in lipid metabolism and homeostasis and discuss the implications for tumor biology.

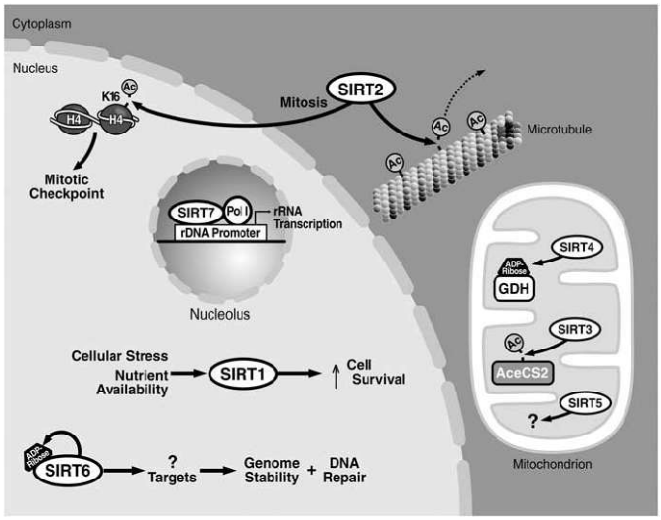

Figure 1 Cellular localization, enzymatic activities and targets of the mammalian sirtuins. SIRT1 responds to changes in nutrient availability and cellular stress to promote cell survival by deacetylating histone and non-histone targets in the nucleus. SIRT2 is mainly localized in the cytoplasm and deacetylates a-tubulin, but during mitosis, it shuttles to the nucleus and deacetylates histone H4-K16 to promote chromatin condensation. SIRT2 may function as part of a mitotic checkpoint to ensure that cells do not pass through mitosis if a stress signal or DNA damage is present. SIRT3, 4 and 5 localize to the mitochondria. SIRT3 deacetylates and activates acetyl-CoA synthetase 2 (AceCS2) to enhance acetyl-coA production. SIRT4 ADP-ribosylates and represses glutamate dehydrogenase (GDH) to suppress insulin signaling. No targets or enzymaticac tivity have been identified for SIRT5. SIRT6 promotes DNA repair and guards against genomic instability in the nucleus. Its targets have not been identified. SIRT7 localizes to the nucleolus where it interacts with RNA pol-I to promote transcription of rRNA genes. SIRT1, sirtuins

Sirtuin enzymatic activities: deacetylation and mono-ADP-ribosylation: The conserved catalytic domain shared by the sirtuins functions as a mono-ADP-ribosyltransferase and as a b-nicotinamide adenine dinucleotide (NADþ)-dependent lysine deacetylase (Frye, 1999 and Landry, 2000). The deacetylase domain in the sirtuins is different from that of class I and II HDACs, which are Znþdependent enzymes (North, 2004). Sirtuins use one NADþ molecule and generate acetyl-ADP-ribose and nicotinamide during the deacetylation reaction. While SIRT1, 2, 3 and 5 have significant deacetylase activity towards a histone H4 peptide, SIRT4, 6 and 7 have low to undetectable deacetylase activity in vitro on tested substrates. SIRT1 deacetylates histones and other nuclear targets, including p53, Ku70 and FOXO (Forkhead box, class O) in vivo. Of the sirtuins, only SIRT2 deacetylates tubulin, also a target of the class II deacetylase HDAC6 (Hubbert, 2002). Mono-ADP-ribosylation, during which ADP-ribose from NADþ is transferred to an acetylated target protein, is conserved from bacteria to humans and is carried out by several families of proteins. Mono-ADP-ribosylated cellular proteins include histones, high mobility group (HMG) family members, actin, a- and b-tubulin and glutamate dehydrogenase (Hassa, 2006). SIRT1 preferably transfers mono-ADP-ribose to histone H1 SIRT6 is more efficient with bovine serum albumin (BSA), and SIRT2 can also ADP-ribosylate BSA in vitro. SIRT6 robustly mono-ADP ribosylates itself through an intramolecular reaction. In vivo, SIRT4 ADP-ribosylates GDH, which inhibits its activity (Haigis, 2006). A conserved histidine residue in the catalytic core of the sirtuins is important for their deacetylase and mono-ADP-ribosyl transferase activities (Frye, 1999). Deacetylation and ADP-ribosylation may be linked and dependent on each other. ADP-ribose generated in the deacetylation reaction is added to a substrate following its deacetylation. Alternatively, some sirtuins might have only mono-ADP-ribosyl transferase activity.

Regulation of Peroxisome Proliferator-Activated Receptor (PPAR) and PPARγ Coactivator 1α (PGC-1α) Mediated Transcription: Cancer cells require critical transcription programs to up-regulate the numerous pathways needed to sustain pathogenic cell growth. This program is implemented by key transcription factors that can transform cells into metabolically abnormal states that lead to and often sustain tumor growth. One such transcription program is driven by PPAR-γ, which is a major factor in adipogenesis, the mechanism by which preadipocytes differentiate into mature adipocytes. Without PPAR-γ, precursor cells are unable to manifest the characteristic features of adipocytes (S.R., 2005). PPAR-γ is a critical transcription factor capable of promoting the adipogenic program when over-expressed in mouse fibroblasts, producing fat cells with similar functions to mature adipocytes (Tontonoz, 1994). Knockout studies further demonstrated the importance of PPAR-γ and linked its involvement with both brown and white fat depots (Barak, 1999) and CCAAT-enhancer-binding protein-α (C/EBP-α), which was also shown to have critical functions in adipogenesis (Freytag, 1994). Gain of function studies revealed that C/EBP-α also initiated adipogenesis, however, unlike PPAR-γ, C/EBP was only required for the formation of white adipose tissue and not brown adipose tissue (Freytag, 1994). Notably, PPAR-γ can initiate adipogenesis in C/EBP-deficient mouse fibroblasts but C/EBP could not initiate adipogenesis without PPAR-γ. Therefore, PPAR-γ is thought to be the dominant player and is also a SIRT1 target. Interestingly, Tian *et al.*, demonstrated that PPAR-γ is deacetylated in a trichostatin-A-senstive and NAD-dependent manner and acetylation-defective PPAR-γ mutants are associated with decreased lipid synthesis in breast cancer cells (Tian, 2005). PPAR-γ interacts with PGC-1α, which during development regulates brown adipose tissue (BAT) development by acting in conjunction with transcription factors like nuclear respiratory factor 1 (Nrf1). Together Nrf1 and PPAR-γ collaborate to control thermogenesis and mitochondrial biogenesis (Lin, 2005 and Uldry, 2006). PGC-1α induces pyruvate dehydrogenase kinase4 (PDK4), which inactivates pyruvate dehydrogenase by phosphorylation and prevents pyruvate entry into the citric acid cycle. PDK4 is localized in the mitochondria and uses its kinase activity to inhibit the pyruvate dehydrogenase complex by slowing the conversion of pyruvate to acetyl-CoA, which allows more conservation of glucose. In addition to being a target gene of the thyroid hormone receptor as discussed earlier, PDK4 is also transcriptionally regulated by other factors such as FOXO1, estrogen-related receptor-α (ERRα), and PPARγ that partner with PGC-1α (Pilegaard, 2004). Thus, factors that control the fate of acetyl-CoA will also have an impact on lipid metabolism and how malignant cells experiencing limited

glucose respond to this nutritive stress. Interestingly, SIRT1-dependent fat mobilization is mediated through interactions with PPAR-γ cofactors, NCoR and SMRT, which alter the expression of genes associated with adipogenesis including PPAR-γ itself (Picard, 2004). Also, SIRT1 potentiates the activity of PPAR-α and PGC-1α, leading to increased lipolysis and fat loss in mature adipocytes (Picard, 2004). This is important because activity of PGC-1α is critical to the activation of the SIRT1-dependent gluconeogenic pathway that is associated with the action of both FOXO1 and hepatocyte nuclear factor 4 α (HNF4-α) (Sugden, 2008). The expression of SIRT1 protein is also associated with protection from hepatic steatosis (Pfluger, 2008). In contrast, hepatic-specific knock-down of SIRT1 is concomitant with fatty liver and increased inflammation (Purushotham, 2009 and Xu, 2010). Both SIRT1 and Wnt signaling have been shown to attenuate adipogenesis, however, only recently was SIRT1/2 shown to regulate Wnt signaling at multiple levels within a cancer context (Holloway, 2010; Saxena, 2015; Simmons, 2014). For example, SIRT1/2 loss of function was shown to lead to a reduction in Dishevelled (Dvl) protein levels across multiple cancer cell lines (Holloway, 2009). In addition to regulating Dvl protein stability, SIRT1/2 was also shown form a complex with Dvl and Tiam1 and promote Rac activation in multiple cancer cell lines (Saxena, 2015). While SIRT1/2-mediation regulation of the Dvl/Tiam1 binding was shown to be important for Rac1 activation (Saxena, 2015), a separate study demonstrated that SIRT1 also serves as a positive regulator of the Frizzled-7 gene which has been shown to contribute to constitutive Wnt pathway activation (Simmons, 2014). Collectively, these studies demonstrate that SIRT1 contributes at multiple levels to the regulation of transcriptional activity of proteins involved in the generation and distribution of fat cells, which is important in influencing lipid homeostasis.

Regulation of sirtuins by NADþ/NADH ratios and inhibition by nicotinamide: Since NADþ is a critical cofactor for sirtuin enzymatic activity, changes in levels of NADþ and NADH, or their ratio, induced by diet and metabolic status, may regulate the biological activity of sirtuins in vivo as discussed below. CD38, which localizes to the inner nuclear membrane, hydrolyses NADþ to nicotinamide (Aksoy, 2006). In CD38_/_ mice, NADþ levels are increased 10- to 20-fold, and the SIRT1 substrate p53 is lessacetylated (Aksoy, 2006). Nicotinamide phosphoribosyl transferase (Nampt), which is induced after some forms of stress, convertsm nicotinamide to nicotinamide mononucleotide, which then reacts with ATP to regenerate NADþ. Overexpression of Nampt increases NADþ levels and induces SIRT1 activity, with changes in gene expression paralleling those in cells overexpressing SIRT1. Nampt decreases as primary cells age and undergo replicative senescence, which lowers NADþ levels and SIRT1 activity (van der Veer, 2007). Inhibition of Nampt activity induces premature senescence in early-passage primary cells, while overexpression of Nampt delays senescence and increases survival after oxidative stress in late-passage primary cells (van der Veer, 2007). These effects of Nampt are dependent on SIRT1, as overexpression of a catalytically inactive SIRT1 blocks lifespan extension and accelerates senescence (van der Veer, 2007). Another cellular enzyme that uses NADþ is poly (ADPribose) polymerase (PARP), a nuclear protein involved in DNA repair that cleaves NADþ into nicotinamide and ADP-ribose. Poly (ADP-ribose) is added to histones and other nuclear proteins including p53. Activation of PARP after DNA damage quickly depletes cells of NADþ with a concomitant increase in nicotinamide levels, which may suppress the activity of the sirtuins (Zhang, 2003). Future experiments aimed at elucidatingthe consequences of and the interplay among mono-ADP ribosylation, poly-ADP ribosylation and deacetylation of the same target protein, like histones and p53, will reveal how sirtuins influence cell survival after DNA damage. Nicotinamide promotes cell survival and longevity by protecting cells against stress, injury and inflammatory responses (Li, 2003). As a precursor to NADþ, nicotinamide inhibits sirtuins by blocking the regeneration of NADþ through interception of an ADP-ribosylenzyme-acetyl peptide intermediate. Nicotinamide extends the replicative lifespan of primary human fibroblasts, and inhibits SIRT1 with an IC50 of o50 mM and PARP-1 with an IC50B100 mM. Since nicotinamide is found in mammalian cells at 50–150 mM, nicotinamide is a physiological inhibitor of both sirtuins and PARP (Yang, 2006).

Regulation of SIRT1 expression in primary cells and its overexpression in cancer: SIRT1 is overexpressed in a number of cancers. This overexpression occurs in part at the transcriptional level following the loss of repressors of the SIRT1promoter. Two p53 binding sites in the SIRT1 promoter normally repress SIRT1 expression. However, in the absence of nutrients, Foxo3a translocates to the nucleus, interacts with p53, inhibits its suppressive activity and leads to increased SIRT1 expression (Nemoto, 2004). P53 mice show increased basal expression of SIRT1 in selective tissues, including adipose tissue, but SIRT1 levels were not further elevated upon nutrient withdrawal (Nemoto, 2004) SIRT1 levels may be higher in tumors that have lost p53. As discussed below, SIRT1 deacetylates both p53 and FOXO proteins, which feedback to regulate SIRT1 expression. Another tumor suppressor that regulates SIRT1 is E2F1, which binds the SIRT1 promoter and regulates basal expression and induction after DNA damage. E2F1-Rb complexes bind target promoters and recruit HDAC-containing complexes to repress transcription of genes that control cell-cycle progression. E2F1 is acetylated by p300/CBP-associated factor (PCAF), which enhances its DNA-binding, transactivation activity, and stability, and transforms E2F1 into an activator of transcription. SIRT1 also deacetylates E2F1 and may regulate apoptosis induction in response to DNA damage through this factor (Wang, 2006). The fine balance and regulation of acetylases and deacetylases may determine the cellular response to DNA damage: DNA repair for low levels of DNA damage and apoptosis for extensive DNA damage. Loss of E2F1 may have a dual effect on SIRT expression: increased basal expression and impaired induction after DNA damage. Such dysregulation of SIRT1 expression might tip the cellular response to DNA damage to favor apoptosis induction instead of DNA repair (Figure 3). SIRT1 is also regulated by the tumor suppressor gene hypermethylated in cancer 1 (HIC1). SIRT1 mRNA and protein levels are increased in HIC1_/_ mouse embryonic fibroblasts (MEFs). Similar to the intimate feedback loop with E2F1, SIRT1 interacts with HIC1 and represses its own expression. SIRT1 also deacetylates HIC1 and promotes HIC1 sumoylation at the same lysine acetylated by the histone acetyltransferases (HATs) CBP/p300 (Stankovic-Valentin, 2007). HIC1 functions as a transcriptional repressor when deacetylated and sumoylated (Stankovic-Valentin, 2007). HIC1 promoter hypermethylation occurs during tumorigenesis and aging, leading to the upregulation of SIRT1. The normal downregulation of SIRT1 protein seen during aging might be lost in cells without HIC1,

making them resistant to replicative senescence after oxidative stress, and vulnerable to transformation if mutations are propagated. HICþ/_ mice are tumor prone and show a p53- and SIRT1- dependent block in apoptosis induction in response to DNA damage. Loss of HIC1 and concomitant increase in SIRT1 prolongs lifespan, but facilitates tumor development as less apoptosis is induced in response to DNA damage. SIRT1 expression is also regulated at the posttranscriptional level by HuR (Abdelmohsen, 2007). HuR is a ubiquitously expressed mRNA-binding protein that binds the 30UTR of SIRT1 to stabilize the SIRT1 transcript. HuR decreases dramatically as cells age and reach senescence and this leads to a destabilization of SIRT1 mRNA (Abdelmohsen, 2007). High levels of SIRT1 and HuR contribute to the enhanced survival of rapidly proliferating cells after oxidative damage, as opposed to senescent cells that are more sensitive to oxidative damage. After oxidative damage, HuR is phosphorylated by Chk2, which promotes dissociation of HuR from SIRT1 mRNA, leading to lower levels of SIRT1 and an enhanced sensitivity to apoptosis induction. Thus, the extent of DNA damage is relayed to SIRT1, in part, by activation of Chk2. High levels of DNA damage and increased activation of Chk2 decrease expression of SIRT1, tipping the balance towards acetylation of p53 and other factors that induce apoptosis.

Deacetylation of SIRT1 targets in response to cellular stress promotes survival: Modification on p53 after DNA damage is controversial. In response to DNA damage, SIRT1_/_ MEFs show hyperacetylation of p53 at multiple lysines, not just the SIRT1 target K379, but this is not accompanied by a further increase in expression of p53 target genes such as p21, Bax or mdm2, nor by an increase in apoptosis. A SIRT1- specific inhibitor, EX-527, increases p53 acetylation without any consequence on cell survival after DNA damage, unlike TSA, which inhibits HDAC1 and results in decreased survival following DNA damage (Solomon, 2006). Thus, more than just SIRT1-mediated deacetylation of p53 may be required to promote survival after DNA damage. MEFs from mice engineered to express p53 with seven C terminal lysines mutated to arginines (p537KR), to mimicuna cetylated p53, respond to DNA damage similarly to MEFs from wild-type mice, but show enhanced stability of p537KR that allows for enhanced induction of target genes in thymocytes after DNA damage. Immortalized p537KR MEFs undergo senescence earlier, suggesting that regulation of p53 acetylation may fine-tune p53 activity over the lifespan of an organism. ES cells from mice engineered to express p53 with six C terminal lysines mutated to arginines (p536KR) show less transactivation of targets after DNA damage than ES cells that are p53þ/_. MEFs from these mice show no difference in p53 stability or target transactivation after DNA damage (Feng, 2005). Thymocytes from p536KR mice are slightly more resistant to apoptosis after irradiation (IR), with impaired upregulation of PUMA and DR5, but equivalent induction of mdm2, Bax and Pidd, and no alteration in p53 stability. Since these C terminal lysines are also modified by ubiquitination, neddylation, methylation and sumoylation, these studies suggest a role for acetylation in conjunction with other post-translational modifications in controlling p53 stability, localization and activity. A specific role for SIRT1 deacetylation of p53 in thymocytes and other tissues should be examined through tissue-specific alterations in SIRT1 levels. Additionally, conditional double-knockout mice lacking both SIRT1 and HDAC1 will address whether these deacetylases are redundant intargeting of p53 or if both are needed in response to certain types of stress and signaling pathways. FOXO transcription factors, including FOXO1, FOXO3a, FOXO4 and FOXO6, respond to DNA damage and oxidative stress and regulate expression of cell-cycle, DNA repair and apoptosis genes (Furukawa-Hibi, 2005). The importance of FOXO proteins in cancer is underscored as the FOXO proteins are important regulators of cell growth and are found as novel fusion proteins after chromosomal translocations in several types of cancer. The FOXOs are regulated by post-translational modifications including phosphorylation and acetylation. After oxidative stress, FOXO proteins are phosphorylated and relocalize to the nucleus, where they associate with HATs to form active transcriptional complexes, but the FOXOs themselves are acetylated on several lysine residues by multiple HATs, which inhibits their transactivation activity. SIRT1 deacetylation of FOXO suppresses transactivation of proapoptoticprotei ns Bim and Fas ligand by FOXO, while promoting expression of p27kip and GADD45a to induce cell-cycle arrest (Brunet, 2004 and Kobayashi, 2005). While overexpression of SIRT1 inhibits apoptosis induced by FOXO3a after cellular stress and SIRT1_/_ MEFs are more sensitive to oxidative damage, the ability of FOXO3a to induce cell-cycle arrest is enhanced by overexpression of SIRT1 and diminished in SIRT1_/_ cells (Brunet, 2003). SIRT1 and FOXO1 are recruited to the manganese superoxide dismutase promoter, and the deacetylase activity of SIRT1 is required for transactivation of this antioxidant gene, indicating that SIRT1 also promotes survival by inducing the repair of oxidative damage. Thus, SIRT1 appears to promote cell-cycle arrest and DNA repair downstream of FOXO proteins, promoting survival rather than apoptosis. The ability of SIRT1 to promote survival after oxidative stress agrees with the model that SIRT1 promotes a longer lifespan, as increased resistance to oxidative stress correlates with longevity. While the FOXO homolog in Caenorhabditis elegans plays a key role in lifespan regulation, demonstration of a similar role in mammalian lifespan will require development of conditional transgenic mouse models.

As FOXO and p53 share many transcriptional targets, the consequences of stress signals in cells containing wild-type FOXO and p53, versus in tumor cells containing a mutation in either or both p53 or FOXO, are predicted to vary. The ability of SIRT1 to promote cellcycle arrest and DNA repair after DNA damage might require both p53 and FOXO deacetylation. The fact that p53 and FOXO interact following oxidative stress, highlight the possibility that SIRT1 mediates survival following cellular stress through both p53 and FOXO (Brunet, 2004). In primary cells with wild-type p53 and FOXO proteins, SIRT1 will promote cell-cycle arrest versus apoptosis after DNA damage. However, in tumor cells lacking wild-type p53 or FOXO, SIRT1 may have a different effect, and careful studies with various mutants of p53, FOXO and SIRT1 are needed to determine the interplay among these factors. CBP/p300 acetylation of FOXO proteins shifts the response towards apoptosis. Again, overexpression of SIRT1 in primary cells may influence the downstream signaling pathways initiated after DNA damage and determining whether cells with DNA damage proliferate without arresting for repair, potentially leading to tumorogenesis. Tumor cells might require high levels of SIRT1 to protect against apoptosis, therefore allowing for the continued proliferation of tumor cells with genomic instability. Another SIRT1 target that promotes survival in cells that have suffered DNA damage is Ku70. Ku70 is SIRT1 localizes to the nucleus where it

deacetylates various targets and regulates the cellular response to stress. SIRT1 promotes cellular survival by initiating cell-cycle arrest and DNA repair through deacetylation of p53, FOXO and Ku70. While SIRT1 clearly deacetylates p53, the consequence of this mainly localized to the nucleus where it is involved in DNA damage repair, but a small fraction is localized in the cytoplasm where Ku70 regulates apoptosis through sequestration of the proapoptoticprotei n Bax (Sawada, 2003). DNA damage promotes Ku70 acetylation on multiple lysines in its C terminus, disrupting the association with Bax, which on release transits to the mitochondria and initiates apoptosis. SIRT1, along with a classI/II HDAC, maintains Ku70 in a deacetylated state. SIRT1, while mainly localized in the nucleus, can shuttle to the cytoplasm, but the site of SIRT1-mediated deacetylation of Ku70 is not yet clear. Only nuclear SIRT1 appears to be important for cell survival in response to DNA damage, as mutants that are constitutively cytoplasmic do not protect against oxidative stress. Future experiments will determine if acetylation of Ku70 regulates its DNA repair functions in the nucleus. For SIRT1 to promote cell survival in cells with DNA damage, the increased acetylation of Ku70 after DNA damage must be promptly reversed by deacetylation of Ku70. The factors that fine-tune Ku70 acetylation and deacetylation are not known. High levels of SIRT1 in primary cells may tip the balance towards survival after DNA damage. As cells age and SIRT1 levels are diminished, DNA damage should result in increased levels of apoptosis. In pre-malignant cells overexpressing SIRT1, Ku70 may not be properly activated in response to DNA damage that is too extensive to be repaired, allowing for the accumulation of mutations without the induction of apoptosis. Treatment of cancers with a combination of HDAC and sirtuin inhibitors might promote apoptosis in combination with standard chemotherapy agents that damage DNA. The balance between acetylation and deacetylation of specific factors is regulated at an additional level, since SIRT1 itself deacetylates several HATs and regulates their enzymatic activities (Kalkhoven, 2002). SIRT1 directly interacts with PCAF and p300 to promote their deacetylation and enzymatic inactivation. The importance of HATs in cancer is highlighted by their frequent mutation, deletion and translocation in several types of cancer. Recruitment of SIRT1 to its targets brings it in close proximity to HATs and allows SIRT1-mediated deacetylation of p300, CBP and PCAF. The balance of HAT and HDAC/SIRT1 levels and their dysregulation in cancer alter the expression, stability and localization of target proteins.

The critical role of SIRT1 during development may be coopted for tumor cell survival: SIRT1 clearly plays an important role in development: knockout mice show multiple defects, and most die before or just after birth [57]. SIRT1 and p53 double-knockout mice have the same phenotype as SIRT1_/_ mice indicating that p53 hyperacetylation is not responsible for the developmental defects downstream of SIRT1 (Kamel, 2005) Generation of conditional mice lacking both SIRT1 and FOXO will reveal the contribution of FOXO proteins to SIRT1's role in development. SIRT1 normally limits proliferation and possibly tumor development as small interfering RNA (siRNA)-mediated SIRT1 depletion in primary human fibroblasts enhances their proliferation (Abdelmohsen, 2007). In the context of cells containing wild-type p53 and intact cell-cycle checkpoints, SIRT1 limits tumor formation by inducing cellular senescence. However, loss of p53 and other tumor suppressor genes increases SIRT1 expression and can lead to transformation and formation of tumor cells that are addicted to SIRT1 overexpression. Various tumor cell lines cease growth and undergo apoptosis after knockdown of SIRT1 expression via siRNA (Abdelmohsen, 2007 and Ford, 2005). Therefore, SIRT1 appears to be a key survival factor for some tumor cells. SIRT1 is overexpressed in acute myeloid leukemia (AML) blasts from patients as well as AML cell lines. The overexpression found in multiple types of nonmelanoma skin cancers, including early stages, suggests that SIRT1 may be playing a critical role in promoting proliferation in skin cancer. The ability of cancer cells to undergo senescence correlates with their response to treatment. Interestingly, SIRT1 mRNA and protein levels are higher in drug-resistant cancer cell lines than in the original cell lines and in patient tumors after chemotherapy than before therapy (Chu, 2005) siRNA mediated knockdown of SIRT1 expression partially reverses the drug-resistant phenotype, while SIRT1 overexpression or activation of SIRT1 with resveratrol increases expression of the multidrug resistance protein, MDR1 (Sawada, 2003). Differences in the expression level of SIRT1 in primary versus transformed cells needs to be expanded to other cancer types, to identify cancers which might benefit from treatment with SIRT1-specific inhibitors. SIRT1-specific inhibitors may be useful chemotherapeutics to target tumors whose survival depends on SIRT1. Overexpression of SIRT1 in tumors is likely to affect both histone and non-histone acetylated targets. An example of a tumor dependent on SIRT1-mediated deacetylation of a non-histone target is B-cell lymphoma; SIRT1 deacetylates and deactivates the critical oncogene B-cell lymphoma 6 protein (BCL6). BCL6, a protooncogene, functions as a transcriptional repressor and recruits HDACs and other corepressors to unique promoters. BCL6 is specifically expressed in mature B cells and is required for the formation of germinal centers through repression of genes involved in differentiation and apoptosis. Chromosomal translocations involving BCL6 are found in non-Hodgkin's lymphoma and BCL6 is constitutively expressed in some B-cell lymphomas. BCL6 is regulated by several post-translational modifications, including phosphorylation, which targets BCL6 for proteasome-mediated degradation, and acetylation by p300, which inactivates BCL6 repression of targets through disruption of the interaction with HDACs. Like nuclear factor-kB (NF-kB), p53 and Ku70, BCL6 is deacetylated by both HDACs and SIRT1. BCL6 repressor activity is controlled by competing HATs and HDACs/SIRT1, and acetylation impairs the oncogeneic properties and transforming capabilities of BCL6. Cambinol, a SIRT1 inhibitor, inactivates BCL6 in Burkitt's lymphoma cells by promoting its acetylation, and leads to apoptosis induction. In mouse xenograft models, cambinol alone was effective specifically against tumors expressing BCL6.

DNA damage does not promote BCL6 acetylation, but inhibition of SIRT1 with cambinol sensitizes cells to DNA-damage-induced apoptosis independently of p53. Cambinol also induced p53, FOXO3a and Ku70 acetylation, indicating that multiple targets of SIRT1 may control the response to DNA damage. Tumor cells addicted to SIRT1 may be sensitized to apoptosis induction by combined use of SIRT1 and HDAC inhibitors to sensitize them to DNA damaging chemotherapeutic agents. In addition to its effects on specific non-histone targets, SIRT1 may promote cancer development by deacetylating histones. SIRT1 preferentially deacetylates H3-K9, H3-K14 and H4-K16 in vitro and in vivo. Importantly, loss of H4-K16 acetylation is a hallmark of human tumors, and while this could be due to a loss of HAT association or

function, it could also reflect overexpression of SIRT1 in tumors. Over expression of SIRT1, other deacetylases, and/or chromatin remodeling factors may silence key tumor suppressor genes as an early event in the transformation process (Jones, 2007). Loss of these tumor suppressor genes can relieve constraints on replicative senescence and allow tumor cells to proliferate without normal checkpoints in place. Epigenetic changes at the level of histone acetylation are mitotically inherited, allowing for improper silencing to be passed on during cell division. Long-term silencing of genes in embryonic stem cells is controlled by polycomb group proteins. PcG proteins function as large complexes that regulate growth, development and differentiation by acting on chromatin to alter gene expression, and PcGs are overexpressed in several cancers. The recent 'cancer stem cell' hypothesis implicates genes controlling self-renewal in pluripotent stem cells with the aberrant survival of tumor cells that have regained the ability to self-renew. In stem cells, SIRT1 directly associates with Suz12, a member of PcG complexes and like PcG proteins, SIRT1 is overexpressed in breast and colon cancers. In potential glioblastoma stem cells expressing the marker CD133, SIRT1 was overexpressed B5-fold compared to CD133- negative cells from tumor samples (Li, 2006) indicating a potential role for SIRT1 in driving the self renewal and resistance to apoptosis characteristic for these cancer stem cells.

Regulation of Forkhead Box Protein O1 (FOXO1) in Cancer: Lipid metabolism is a balancing act of synthesis and breakdown of fat stores for utilization by diverse tissues. Lipolysis is a complicated and multi-step process. Hydrolysis of triglycerides to glycerols and free-fatty acids is accomplished by a series of tri-, di-, and monoacylglyceride lipases (Zechner, 2009). Lipolysis is regulated postranslationally, and the rates of lipolysis are proportional to the cellular levels of adipose triacylglycerol lipase (ATGL), a rate limiting lipolytic enzyme. Both ATGL and hormone-sensitive lipase (HSL) are important enzymes involved in intracellular breakdown of triacylglycerols. ATGL is capable of initiatiating lipolysis and HSL follows and acts on diacylglycerol where both participate in a cooperative fashion for the efficient lipolysis of white adipose tissue. ATGL has been reported to be downstream of SIRT1, and reports show that SIRT1 knockdown decreases basal and isoproterenol-stimulated lipolysis in cultured adipocytes. This effect was attributed in part to the transcriptional suppression of (ATGL) and it was concluded that SIRT1 controls ATGL transcription primarily by deacetylating and activating FOXO1, as ATGL is a FOXO target gene (Chakrabarti, 2011). To appreciate the relationship between SIRT1, ATGL and FOXO1 it is of great utility to understand the importance of FOXO transfactors to cancer biology as a whole. The FOXO family of transcription factors involvement in carcinogenesis is varied depending upon the family member and the tissues involved. For example, FOXO1 has been reported to function as a key regulator of multidrug resistance 1 (*MDR1*) gene transcription. Elevated gene expression of *MDR1* (P-glycoprotein) is a major cause of chemoresistance in many cancer cells and FOXO1 has been shown to be a transcriptional activator of MDR1 in adriamycin-resistant breast cancer cells (Han, 2008). Importantly, studies have shown that decreased FOXO acetylation leads to increased nuclear retention of FOXO1 and enhanced expression of FOXO1 target genes (Frescas, 2005) Nuclear FOXO1 is associated with cisplatin and tamoxifen-resistance in gastric and breast cancer cells respectively (Choi, 2013 and Park, 2001). Additionally, overexpression of SIRT1 with FOXO1 potentiated the transcription of multiresistance protein 2 (MRP2), and the basal activity and expression of SIRT1 was increased in tamoxifen-resistant breast cancer cells. SIRT1 inhibition was reported to reduce both the nuclear FOXO1 levels and MRP2 expression while enhancing cytotoxic effects of paclitaxel and doxorubicin in tamoxifen-resistant breast cancer cells. Interaction of FOXO1 (a direct activator of ATGL) and SIRT1 (an activator of FOXO1) led to activation of FOXO1 which is linked with increased tumorigenicity of cancer cells via acylglycerol kinase (Wang, 2004) FOXO1, whose activity is increased by deacetylation of SIRT1 (Yang, 2005 and Daitoku, 2004) also regulates thyroid hormone-induced transcription of key hepatic gluconeogenic genes (Singh, 2013). Interestingly, SIRT1 has been reported to regulate thyroid hormone-induced genes, interact directly with the T3 receptor (TR-β), and contribute to T3-induced regulation of hepatic genes such as CPT1a, PDK4 and SREBP1c (Thakran, 2013). Because of the complexity of SIRT1 loss in animal models and the global involvement of thyroid hormone in regulating metabolism, identifying genes co-regulated by SIRT1 and T3 may prove beneficial. This is important because lipid metabolism is influenced by thyroid hormones such as T3 and a link between SIRT1 and T3-mediated gene expression that influences lipolysis could help reveal cell-type specific contributions of SIRT1. One of the genes regulated by thyroid hormone and SIRT1, carnitine palmitoyltransferase I (CPT1), is a mitochondrial enzyme responsible for the formation of acyl carnitines by catalyzing the transfer of the acyl group of a long-chain fatty acyl-CoA from coenzyme A to L-carnitine. This modification allows for subsequent movement of the acyl carnitine from the cytosol into the intermembrane space of mitochondria. The mitochondrial oxidation of long-chain fatty acids is initiated by the sequential action multiple enzymes including CPT1 and its deficiency results in a decreased rate of fatty acid β-oxidation. Thus, its altered expression resulting from aberrant regulation of SIRT1 could impact fatty acid metabolism. Collectively, these reports establish a connection between SIRT1 regulation of FOXO1, a transcription factor that in turn can influence cell growth and lipid mobilization in cancer cells.

Conclusions

Activation of SIRT1 in cells leads to the initiation and suppression of a myriad of processes. SIRT1 as a histone deacetylase is associated with epigenetic mechanisms of gene regulation; however it also has many non-histone/chromatin targets as well. The role of SIRT1 as a regulator of lipid metabolism integrates several metabolic research focus areas, including obesity, diabetes, hepatic steatosis, and cancer. In some cancers, SIRT1 expression is often increased in tumors as compared to benign adjacent tissue. SIRT1 acts upon several transcription factors by activating (FOXO1, PGC-1α) or suppressing (SREBP1c) their activity and producing an overall decrease in the level of lipogenesis in cells. Other factors, including mTOR and autophagy related proteins, are likely involved in lipid homeostasis and further research will be needed to validate the contribution to the SIRT1-dependent mechanisms described herein. However, based on the selected factors described, the overall implications of the research cited suggest that further investigations of SIRT1 may be of interest for clarifying investigate deeper, the roles of SIRT1 in various factors affecting cancer biology.

REFERENCES

Abdelmohsen, K., *et al*., Phosphorylation of HuR by Chk2 regulates SIRT1 expression. *Mol Cell,* 2007. 25(4): p. 543-57.

Aksoy, P., *et al*., Regulation of intracellular levels of NAD: a novel role for CD38. *Biochem Biophys Res Commun*, 2006. 345(4): p. 1386-92.

Aksoy, P., *et al*., Regulation of SIRT 1 mediated NAD dependent deacetylation: a novel role for the multifunctional enzyme CD38. *Biochem Biophys Res Commun,* 2006. 349(1): p. 353-9.

Barak Y., N.M.C., Ong E.S., Jones Y.Z., Ruiz-Lozano P., Chien K.R., Koder A., Evans R.M., PPAR-γ is required for placental, cardiac, and adipose tissue development. . *Mol. Cell.,* 1999. 4: p. 585-595.

Brooks C.L., G.W., How does SIRT1 affect metabolism, senescence and cancer? *Nat. Rev. Cancer.,* 2009. 9: p. 123-128.

Brunet, A., *et al*., Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science, 2004. 303(5666): p. 2011-5.

Cha E.J., N.S.J., Kwon K.S., Kim C.Y., Park B.H., Park H.S., Lee H., Chung M.J., Kang M.J., Lee D.G., *et al*., Expression of DBC1 and SIRT1 is associated with poor prognosis of gastric carcinoma. *Clin. Cancer Res.,* 2009. 15: p. 4453-4459.

Chakrabarti, P., *et al*., SIRT1 controls lipolysis in adipocytes via FOXO1-mediated expression of ATGL. J Lipid Res, 2011. 52(9): p. 1693-701.

Chen J., Z.B., Wong N., Lo A.W., To K.F., Chan A.W., Ng M.H., Ho C.Y., Cheng S.H., Lai P.B., *et al*., Sirtuin 1 is upregulated in a subset of hepatocellular carcinomas where it is essential for telomere maintenance and tumor cell growth. *Cancer Res.,* 2011. 71: p. 4138-4149.

Choi H.K., C.K.B., Phuong N.T., Han C.Y., Han H.K., Hien T.T., Choi H.S., Kang K.W. , SIRT1-mediated FOXO1 deacetylation is essential for multidrug resistance-associated protein 2 expression in tamoxifen-resistant breast cancer cells. . *Mol. Pharm.,* 2013. 10: p. 2517-2527.

Chu, F., *et al*., Control of multidrug resistance gene mdr1 and cancer resistance to chemotherapy by the longevity gene sirt1. Cancer Res, 2005. 65(22): p. 10183-7.

Daitoku H., H.M., Matsuzaki H., Aratani S., Ohshima T., Miyagishi M., Nakajima T., Fukamizu A., Silent information regulator 2 potentiates FOXO1-mediated transcription through its deacetylase activity. *Proc. Natl. Acad. Sci. USA.,* 2004. 101: p. 10042-10047.

Feng, L., *et al*., Functional analysis of the roles of posttranslational modifications at the p53 C terminus in regulating p53 stability and activity. *Mol Cell Biol,* 2005. 25(13): p. 5389-95.

Ford, J., M. Jiang, and J. Milner, Cancer-specific functions of SIRT1 enable human epithelial cancer cell growth and survival. *Cancer Res,* 2005. 65(22): p. 10457-63.

Frescas, D., L. Valenti, and D. Accili, Nuclear trapping of the forkhead transcription factor FoxO1 via Sirt-dependent deacetylation promotes expression of glucogenetic genes. *J Biol Chem,* 2005. 280(21): p. 20589-95.

Freytag, S.O., D.L. Paielli, and J.D. Gilbert, Ectopic expression of the CCAAT/enhancer-binding protein alpha promotes the adipogenic program in a variety of mouse fibroblastic cells. *Genes Dev*, 1994. 8(14): p. 1654-63.

Frye, R.A., Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity. *Biochem Biophys Res Commun,* 1999. 260(1): p. 273-9.

Furukawa-Hibi, Y., *et al*., FOXO transcription factors in cell-cycle regulation and the response to oxidative stress. *Antioxid Redox Signal*, 2005. 7(5-6): p. 752-60.

Haberland, M., R.L. Montgomery, and E.N. Olson, The many roles of histone deacetylases in development and physiology: implications for disease and therapy. *Nat Rev Genet,* 2009. 10(1): p. 32-42.

Haigis, M.C., *et al*., SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic beta cells. *Cell,* 2006. 126(5): p. 941-54.

Han, C.Y., *et al*., Role of FoxO1 activation in MDR1 expression in adriamycin-resistant breast cancer cells. *Carcinogenesis,* 2008. 29(9): p. 1837-44.

Hassa, P.O., *et al*., Nuclear ADP-ribosylation reactions in mammalian cells: where are we today and where are we going? *Microbiol Mol Biol Rev,* 2006. 70(3): p. 789-829.

Holloway K.R., C.T.N., Saxena M., Metoyer C.F., Kandler E.F., Rivera C.A., Pruitt K. SIRT1 regulates Dishevelled proteins and promotes transient and constitutive Wnt signaling. . *Proc. Natl. Acad. Sci. USA.* , 2010. 107: p. 9216-9221.

Holloway, K.R., *et al*., SIRT1 positively regulates breast cancer associated human aromatase (CYP19A1) expression. *Mol Endocrinol,* 2013. 27(3): p. 480-90.

Hubbert, C., *et al*., HDAC6 is a microtubule-associated deacetylase. Nature, 2002. 417(6887): p. 455-8.

Ikenoue, T., *et al*., PTEN acetylation modulates its interaction with PDZ domain. *Cancer Res,* 2008. 68(17): p. 6908-12.

Jones, P.A. and S.B. Baylin, The epigenomics of cancer. *Cell,* 2007. 128(4): p. 683-92.

Kabra N., L.Z., Chen L., Li B., Zhang X., Wang C., Yeatman T., Coppola D., Chen J., SIRT1 is an inhibitor of proliferation and tumor formation in colon cancer. *J. Biol. Chem.,* 2009. 284: p. 18210-18217.

Kalkhoven, E., *et al*., The PHD type zinc finger is an integral part of the CBP acetyltransferase domain. *Mol Cell Biol,* 2002. 22(7): p. 1961-70.

Kamel, C., *et al*., SirT1 fails to affect p53-mediated biological functions. *Aging Cell,* 2006. 5(1): p. 81-8.

Kim J.R., M.Y.J., Kwon K.S., Bae J.S., Wagle S., Yu T.K., Kim K.M., Park H.S., Lee J.H., Moon W.S., *et al*., Expression of SIRT1 and DBC1 is associated with poor prognosis of soft tissue sarcomas. PLoS One., 2013(8:e74738. doi: 10.1371/journal.pone.0074738.).

Kobayashi, Y., *et al*., SIRT1 is critical regulator of FOXO-mediated transcription in response to oxidative stress. *Int J Mol Med,* 2005. 16(2): p. 237-43.

Krusche, C.A., *et al*., Histone deacetylase-1 and -3 protein expression in human breast cancer: a tissue microarray analysis. *Breast Cancer Res Treat,* 2005. 90(1): p. 15-23.

Landry, J., *et al*., The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases. *Proc Natl Acad Sci U S A,* 2000. 97(11): p. 5807-11.

Lee H., K.K.R., Noh S.J., Park H.S., Kwon K.S., Park B.H., Jung S.H., Youn H.J., Lee B.K., Chung M.J., *et al.* , Expression of DBC1 and SIRT1 is associated with poor prognosis for breast carcinoma. *Hum. Pathol.,* 2011. 42: p. 204-2013.

Li, F., Z.Z. Chong, and K. Maiese, Cell Life versus cell longevity: the mysteries surrounding the NAD+ precursor nicotinamide. *Curr Med Chem,* 2006. 13(8): p. 883-95.

Lin J., H.C., Spiegelman B.M Metabolic control through the PGC-1 family of transcription coactivators. *Cell Metab.,* 2005. 1: p. 361-370.

Liu, T., P.Y. Liu, and G.M. Marshall, The critical role of the class III histone deacetylase SIRT1 in cancer. Cancer Res, 2009. 69(5): p. 1702-5.

Nemoto, S., M.M. Fergusson, and T. Finkel, Nutrient availability regulates SIRT1 through a forkhead-dependent pathway. *Science,* 2004. 306(5704): p. 2105-8.

North, B.J. and E. Verdin, Sirtuins: Sir2-related NAD-dependent protein deacetylases. *Genome Biol,* 2004. 5(5): p. 224.

Park, J., *et al*., The forkhead transcription factor FOXO1 mediates cisplatin resistance in gastric cancer cells by activating phosphoinositide 3-kinase/Akt pathway. *Gastric Cancer,* 2014. 17(3): p. 423-30.

Pfluger, P.T., *et al*., Sirt1 protects against high-fat diet-induced metabolic damage. *Proc Natl Acad Sci U S A,* 2008. 105(28): p. 9793-8.

Picard, F., *et al*., Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. Nature, 2004. 429(6993): p. 771-6.

Pilegaard, H. and P.D. Neufer, Transcriptional regulation of pyruvate dehydrogenase kinase 4 in skeletal muscle during and after exercise. *Proc Nutr Soc,* 2004. 63(2): p. 221-6.

Powell, M.J., *et al*., Disruption of a Sirt1-dependent autophagy checkpoint in the prostate results in prostatic intraepithelial neoplasia lesion formation. *Cancer Res,* 2011. 71(3): p. 964-75.

Pruitt K., Z.R.L., Ohm J.E., McGarvey K.M., Kang S.H., Watkins D.N., Herman J.G., Baylin S.B, Inhibition of SIRT1 reactivates silenced cancer genes without loss of promoter DNA hypermethylation. *PLoS Genet.,* 2006. 40: p. 2004-2007.

Purushotham, A., *et al*., Hepatocyte-specific deletion of SIRT1 alters fatty acid metabolism and results in hepatic steatosis and inflammation. Cell Metab, 2009. 9(4): p. 327-38.

S.R., F., Regulation of PPAR-γ activity during adipogenesis. . *Int. J. Obes.* , 2005. 29: p. S13-S16.

Sawada, M., *et al*., Ku70 suppresses the apoptotic translocation of Bax to mitochondria. *Nat Cell Biol,* 2003. 5(4): p. 320-9.

Saxena, M., *et al*., The sirtuins promote Dishevelled-1 scaffolding of TIAM1, Rac activation and cell migration. Oncogene, 2015. 34(2): p. 188-98.

Simmons G.E., J., Pandey S., Nedeljkovic-Kurepa A., Saxena M., Wang A., Pruitt K., Frizzled 7 expression is positively regulated by SIRT1 and β-catenin in breast cancer cells. . PLoS One., 2014. 9: p. 102-105.

Singh, B.K., *et al*., FoxO1 deacetylation regulates thyroid hormone-induced transcription of key hepatic gluconeogenic genes. *J Biol Chem,* 2013. 288(42): p. 30365-72.

Solomon, J.M., *et al*., Inhibition of SIRT1 catalytic activity increases p53 acetylation but does not alter cell survival following DNA damage. *Mol Cell Biol,* 2006. 26(1): p. 28-38.

Stankovic-Valentin, N., *et al*., An acetylation/deacetylation-SUMOylation switch through a phylogenetically conserved psiKXEP motif in the tumor suppressor HIC1 regulates transcriptional repression activity. *Mol Cell Biol,* 2007. 27(7): p. 2661-75.

Stenzinger A., E.V., Klauschen F., Sinn B., Lorenz K., Warth A., Goeppert B., Ehemann V., Muckenhuber A., Kamphues C., *et al*., High SIRT1 expression is a negative prognosticator in pancreatic ductal adenocarcinoma. *BMC. Cancer.,* 2013. 13: p. 450-454.

Sugden M.C., C.P.W., Holness M.J., PPAR control: It's SIRTainly as easy as PGC. . *J. Endocrinol.,* 2010. 204: p. 93-104.

Thakran, S., *et al*., Role of sirtuin 1 in the regulation of hepatic gene expression by thyroid hormone. *J Biol Chem,* 2013. 288(2): p. 807-18.

Tian L., W.C., Hagen F.K., Gormley M., Addya S., Soccio R., Casimiro M.C., Zhou J., Powell M.J., Xu P., *et al.* , Acetylation-defective mutant of PPAR-γ is associated with decreased lipid synthesis in breast cancer cells. *Oncotarget.,* 2014. 5: p. 7303-7315.

Tontonoz P., H.E., Spiegelman B.M., Stimulation of adipogenesis in fibroblasts by PPARγ2, a lipid-activated transcription factor. *Cell.,* 1994. 79: p. 1147-1156.

Uldry, M., *et al*., Complementary action of the PGC-1 coactivators in mitochondrial biogenesis and brown fat differentiation. Cell Metab, 2006. 3(5): p. 333-41.

van der Veer, E., *et al*., Extension of human cell lifespan by nicotinamide phosphoribosyltransferase. *J Biol Chem,* 2007. 282(15): p. 10841-5.

Wang, C., *et al*., Interactions between E2F1 and SirT1 regulate apoptotic response to DNA damage. *Nat Cell Biol*, 2006. 8(9): p. 1025-31.

Wang, X., *et al*., Acylglycerol kinase promotes cell proliferation and tumorigenicity in breast cancer via suppression of the FOXO1 transcription factor. Mol Cancer, 2014. 13: p. 106.

Weichert W., R.A., Niesporek S., Noske A., Buckendahl A.C., Dietel M., Gekeler V., Boehm M., Beckers T., Denkert C, Class I histone deacetylase expression has independent prognostic impact in human colorectal cancer: specific role of class I histone deacetylases in vitro and in vivo. *Clin. Cancer Res.,* 2008. 14: p. 8.

Xu F., G.Z., Zhang J., Rivera C.A., Yin J., Weng J., Lack of SIRT1 (Mammalian Sirtuin 1) activity leads to liver steatosis in the SIRT1+/− mice: A role of lipid mobilization and inflammation. Ye J. Endocrinology., 2010. 151: p. 2504-2514.

Yang Q., W.B., Gao W., Huang S., Liu Z., Li W., Jia J., SIRT1 is downregulated in gastric cancer and leads to G1-phase arrest via NF-κB/Cyclin D1 signaling. . *Mol. Cancer Res.,* 2013. 11: p. 1497–1507.

Yang Y., H.H., Haller E.M., Nicosia S.V., Bai W. , Suppression of FOXO1 activity by FHL2 through SIRT1-mediated deacetylation. *EMBO J.,* 2005. 24: p. 1021-1032.

Yang, T. and A.A. Sauve, NAD metabolism and sirtuins: metabolic regulation of protein deacetylation in stress and toxicity. *Aaps j,* 2006. 8(4): p. E632-43.

Zechner, R., *et al*., Adipose triglyceride lipase and the lipolytic catabolism of cellular fat stores. *J Lipid Res,* 2009. 50(1): p. 3-21.

Zhang, J., Are poly(ADP-ribosyl)ation by PARP-1 and deacetylation by Sir2 linked? *Bioessays,* 2003. 25(8): p. 808-14.

Zhang, Y., *et al*., Deacetylation of cortactin by SIRT1 promotes cell migration. *Oncogene,* 2009. 28(3): p. 445-60.

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