



Sirtuins in Cancer: a Balancing Act between Genome Stability and Metabolism

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Minireview

Sirtuins in Cancer: a Balancing Act between Genome Stability and Metabolism

Seung Min Jeong^{1,2,*}, and Marcia C. Haigis^{3,*}

Genomic instability and altered metabolism are key features of most cancers. Recent studies suggest that metabolic reprogramming is part of a systematic response to cellular DNA damage. Thus, defining the molecules that fine-tune metabolism in response to DNA damage will enhance our understanding of molecular mechanisms of tumorigenesis and have profound implications for the development of strategies for cancer therapy. Sirtuins have been established as critical regulators in cellular homeostasis and physiology. Here, we review the emerging data revealing a pivotal function of sirtuins in genome maintenance and cell metabolism, and highlight current advances about the phenotypic consequences of defects in these critical regulators in tumorigenesis. While many questions should be addressed about the regulation and context-dependent functions of sirtuins, it appears clear that sirtuins may provide a promising, exciting new avenue for cancer therapy.

INTRODUCTION

Genomic instability is associated with most cancers and can be a marker of malignant transformation (Abbas and Dutta, 2009; Deng, 2006; Negrini et al., 2010). During tumorigenesis, genomic instability appears to facilitate the acquisition of tumorigenic mutations to support tumor cell survival and proliferation. Genomic instability can occur by environmental agents or normal cellular processes. For example, ionizing radiation (IR) and ultra-violet (UV), which can produce DNA lesions such as pyrimidine dimers, single-strand DNA breaks (SSBs) and double-strand (DSBs), are well known genotoxic agents. Spontaneous DNA alterations can occur during normal DNA replication. Additionally, reactive oxygen species (ROS) produced by cellular metabolism can also induce DNA lesions.

To maintain genomic integrity, eukaryotic cells have developed a tightly coordinated DNA damage response (DDR) pathway. Upon DNA damage, ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and RAD3-related protein (ATR) are activated and induce phosphorylation of downstream mediator proteins to trigger cell cycle arrest and DNA repair (Abraham, 2001; Ciccio and Elledge, 2010; Su, 2006). Indeed, dysregulations of DDR are commonly associated with tumorigenesis and are observed in many tumors (Ciccio and Elledge, 2010; Negrini et al., 2010).

Tumors exhibit aberrant cellular metabolism characterized by elevated aerobic glycolysis, glutaminolysis and lipid metabolism. The Warburg effect, which describes that tumor cells preferentially use glucose for aerobic glycolysis in the presence of ample oxygen (Warburg, 1956), has emerged as a central metabolic hallmark of many cancers and indicates that alterations in metabolism contribute to the malignant phenotype (Tennant et al., 2010; Vander Heiden et al., 2009). In addition to glucose, many cancer cells exhibit enhanced glutamine metabolism and cannot survive in the absence of glutamine (Wise and Thompson, 2010). Recent studies have shown that a number of well-established oncogenic cues, including Myc, Ras or mTORC pathways play critical roles in inducing glutaminolysis (Csibi et al., 2013; Dang, 2010; Wang et al., 2010). Also, there is increasing evidence that tumor cells show alterations in lipid metabolism (Santos and Schulze, 2012). Changes in lipid metabolism contribute to membrane synthesis, energy homeostasis and cellular signaling. This metabolic reprogramming allows tumor cells to fulfill their bioenergetic and biosynthetic needs for rapid proliferation, and also provide additional metabolic advantages for their survival and growth under limited nutrient conditions (Gatenby and Gillies, 2004; Tong et al., 2009; Wise and Thompson, 2010).

Genomic instability and altered metabolism are hallmarks of many cancers. Thus, defining the connection between DDR and metabolic processes is an area of intense interest. Recent studies have shown that DNA damage also induces metabolic changes in cells (Cosentino et al., 2011), and many metabolic proteins, involved in glycolysis and glutaminolysis, are important component of cell cycle regulation and DNA repair (Ciccio and Elledge, 2010; Lapenna and Giordano, 2009). However, the molecular events and specific factors that are involved in regulating genomic stability and cell metabolism are not well elucidated.

Sirtuins are the homologs of the yeast Sir2 gene, which has been known to promote replicative life span and mediate gene silencing in yeast (Guarente and Kenyon, 2000; Haigis

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and Sinclair, 2010). Sirtuins function as nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylases, mono ADP-ribosyltransferases, lipoamidase (SIRT4), and deacylases (Du et al., 2011; Haigis and Sinclair, 2010; Mathias et al., 2014). Based on their enzymatic activities, sirtuins have been involved in a wide range of biological processes such as stress response, differentiation, proliferation, metabolism and aging. Due to their pivotal roles as regulators of cellular homeostasis in response to the cellular environment, mounting studies have investigated the roles of sirtuins in cancer (Haigis and Sinclair, 2010). This review provides an update on the functions of sirtuins in genome stability and metabolism, and further focusing on the implication of sirtuins in the interplay between stress response and metabolism.

SIRTIINS IN GENOMIC STABILITY

DNA damage initiates a tightly coordinated signaling response to maintain genomic integrity, and defects in the DDR often lead to increased incorporation of mutations into newly synthesized DNA, the accumulation of chromosomal instability and tumor development (Abbas and Dutta, 2009; Negrini et al., 2010). The DDR is primarily initiated by activation of related kinases ATM, ATR, and DNA-dependent protein kinase (DNA-PK) and by members of the poly (ADP-ribose) polymerase (PARP) family (Ciccia and Elledge, 2010). Following the recognition of DNA lesions, these sensor proteins induce phosphorylation of CHK1, CHK2 and γ -H2AX to trigger cell cycle arrest and to initiate assembly of DNA damage repair machinery (Abraham, 2001; Ciccia and Elledge, 2010). Accumulating evidence indicates that sirtuins have evolved to coordinate both stress response and cellular adaptation against genotoxic stress.

In the nucleus and cytoplasm

Mammals have seven sirtuins (SIRT1-7), three of which (SIRT1, 6 and 7) are mainly localized in the nucleus. SIRT1 is one of the best-characterized sirtuins. SIRT1 can remove the acetyl group from the lysine residues in histones and non-histone proteins (Finkel et al., 2009). In the past decade, numerous targets of SIRT1 have been identified, suggesting that SIRT1 plays a central role in a large variety of cellular processes. The involvement of SIRT1 in genomic stability has been supported by several lines of evidence. In response to DNA damage, SIRT1 is recruited to DNA DSBs in an ATM kinase-dependent manner (Oberdoerffer et al., 2008; Wang et al., 2008). This recruitment is important for γ -H2AX foci formation and accumulation of the DDR-related proteins such as Rad51, NBS1 and BRCA1 at the breaks. Thus, *Sirt1*-deficient mouse embryonic fibroblasts (MEFs) exhibited a marked reduction of recruitment of these proteins after DNA damage (Oberdoerffer et al., 2008). In mouse embryos, absence of SIRT1 results in a large amount of chromosome abnormalities, and SIRT1 heterozygous deletion accelerates tumorigenesis in p53^{+/−} mice (Wang et al., 2008).

At the same time, SIRT1 is implicated in DNA repair pathways. When DNA DSBs occur, SIRT1 promotes homologous recombination (HR) DNA repair by deacetylating WRN, a member of the RecQ DNA helicase family with functions in maintenance of genomic stability (Li et al., 2008). Another studies have reported that SIRT1 interacts with telomere *in vivo* and SIRT1 overexpressed mice display increased HR DNA repair throughout the entire genome (Palacios et al., 2010). Moreover, SIRT1 is also involved in non-homologous end joining (NHEJ) DNA repair. Deacetylation of Ku70 by SIRT1 enhances Ku70-dependent DNA repair and inhibits mitochondrial

apoptosis after genotoxic stimuli (Jeong et al., 2007; Sawada et al., 2003;). Also, SIRT1-mediated deacetylation of Krüppel associated box (KRAB)-associated protein 1 (KAP1) enhances the interaction between KAP1 and p53-binding protein 1 (53BP1) and NHEJ repair pathway (Lin et al., 2015). Finally, SIRT1 can regulate nucleotide excision repair (NER) by deacetylating and activating xeroderma pigmentosum A and C proteins (XPA and XPC) upon UV damage. Deacetylated XPA and XPC recognize DNA SSBs and recruit other NER factors at the breaks for DNA repair (Fan and Luo, 2010; Ming et al., 2010). Taken together, these studies support an essential role for SIRT1 as a tumor suppressor by improving genome stability.

SIRT6 functions as NAD⁺-dependent deacetylase and ADP-ribosyltransferase (Liszt et al., 2005; Michishita et al., 2008). Interestingly, SIRT6 knockout (KO) mice exhibit striking premature aging phenotypes such as lymphopenia, reduced subcutaneous fat, lordokyphosis and severe metabolic defects (Mostoslavsky et al., 2006). Because SIRT6 associates with telomere and deacetylates histone H3K9, which enhances the association of WRN protein at these regions and maintains proper telomeric chromatin (Michishita et al., 2008), defects of telomere functions in SIRT6 KO mice likely accounts for the premature aging phenotypes. SIRT6 KO mice also exhibited hypersensitivity to DNA damage and genomic instability, implying that SIRT6 has an important role in the DDR (Lombard et al., 2008; Mostoslavsky et al., 2006). Indeed, like SIRT1, SIRT6 is involved in several DNA repair pathways such as base excision repair (BER), HR and NHEJ. After DNA damage, SIRT6 has been reported to bind to DNA DSBs and enhance HR DNA repair through C-terminal binding protein (CtBP) interacting protein (CtIP) deacetylation (Kaidi et al., 2010). SIRT6 enhances NHEJ DNA repair by stabilizing DNA-PK, which senses DNA DSBs and promotes DNA repair (McCord et al., 2009). Recent studies also showed that upon oxidative DNA damage, SIRT6 associates with PARP1 and stimulates its activity through ADP-ribosylation, promoting NHEJ and HR DNA repair (Mao et al., 2011). Thus, these results suggest that SIRT6 might function as a tumor suppressor by inhibiting genetic instability.

SIRT7 is localized to the nucleolus as well as the nucleus and has histone deacetylase activity (Morris, 2013). SIRT7 regulates ribosomal DNA transcription in part by activating RNA polymerase 1 (Ford et al., 2006). Interestingly, recent studies suggested that SIRT7 has tumor promoting activities. Barber et al. (2012) showed that SIRT7 plays a critical role in maintaining oncogenic transformation by repressing transcription of genes involved in anchorage-independent- and contact inhibited-cell growth. In support of this notion, SIRT7 expression is highly increased in human hepatocellular carcinoma and SIRT7 loss results in the suppression of tumor cell growth (Kim et al., 2013). In addition, many other studies have suggested a critical role of SIRT7 in genotoxic stress resistance and cell survival. SIRT7 overexpression protects tumor cells against doxorubicin-induced cell death (Kiran et al., 2015) and conversely, SIRT7 KO MEFs are resistant to oxidative DNA damage (Vakhrusheva et al., 2008a). SIRT7 is also known to directly deacetylate and hyperactivate the p53 tumor suppressor *in vitro* and *in vivo*, and *Sirt7*-deficient primary cardiomyocytes show a significantly diminished resistance to genotoxic stress (Vakhrusheva et al., 2008b). Interestingly, Mao et al. showed that, like SIRT6, SIRT7 overexpression enhances NHEJ and HR DNA repair after paraquat treatment (Mao et al., 2011), raising the possibility that SIRT7 may play a oncogenic role by protecting tumor cells against genotoxic stresses.

Table 1. Mouse models of sirtuins

Sirtuin	Mouse models	Phenotypes	Role in tumorigenesis
SIRT1	Tg	Reduced incidence of spontaneous carcinomas and sarcomas	Suppression
	SIRT1 ^{Tg} p53 ^{+/-}	Reduced overall tumor incidence in p53 ^{+/-} background	Suppression
	SIRT1 ^{Tg} APC ^{min/+}	Inhibition of intestinal tumors	Suppression
	SIRT1 ^{+/-} p53 ^{+/-}	Mammary tumors	Suppression
	KO	Inhibition of chronic myelogenous leukemia development	Promotion
	SIRT1 ^{Tg} PTEN ^{+/-}	Increased thyroid and prostate carcinomas	Promotion
SIRT2	KO	Mammary tumors (female), and liver and intestinal tumors (male)	Suppression
SIRT3	KO	Spontaneous mammary gland tumors	Suppression
SIRT4	KO	Spontaneous lung tumors and hyperinsulinemia	Suppression
SIRT5	KO	Defect in urea cycle and hyperammonemia	Unknown
SIRT6	KO	Premature aging phenotypes and short life span (~ 3 weeks)	Unknown
	SIRT6 ^{fl/fl} APC ^{min/+}	Increased intestinal tumors	Suppression
SIRT7	KO	Premature aging phenotypes and short life span (~ 1 year)	Unknown

SIRT2 is primarily localized in cytoplasm and functions as a cell cycle regulator (Dryden et al., 2003). SIRT2 regulates acetylation levels of H4K16 during mitosis, enabling chromatin compaction (Vaquero et al., 2006). SIRT2 overexpression induces a prolonged cell cycle, while downregulation inhibits cell cycle progression and induces cell cycle arrest (Dryden et al., 2003; North and Verdin, 2007). As an important cell cycle regulator, SIRT2 is required for genome maintenance by modulating the anaphase-promoting complex/cyclosome activity through deacetylation of CDH1 and CDC20 (Kim et al., 2011). SIRT2 loss causes accumulation of mitotic regulators such as the Aurora kinases that drive mitotic defects, resulting in centrosome amplification, aneuploidy and cell death. Also, SIRT2 KO mice (Table 1) develop mammary tumors and/or hepatocellular carcinomas (HCC) (Kim et al., 2011). Consistent with this idea, a recent study directly illustrates the importance of SIRT2 in cell cycle and genome stability. Serrano et al. showed that SIRT2 loss results in significant defects in cell cycle regulation and genome stability associated with defective monomethylation of H4K20 (Serrano et al., 2013). These studies imply that SIRT2 plays an important role in genome integrity by controlling cell cycle progression and DNA replication.

In the mitochondria

SIRT3, SIRT4 and SIRT5 are located in the mitochondria and have been implicated in mitochondria functions. SIRT3 is a major mitochondrial deacetylase that targets many enzymes involved in metabolism (Verdin et al., 2010). Beyond metabolic targets, SIRT3 has been shown to regulate the production of reactive oxygen species (ROS) from mitochondria by multiple mechanisms. For example, SIRT3 deacetylates and activates isocitrate dehydrogenase 2 (IDH2) and manganese superoxide dismutase (MnSOD) (Qiu et al., 2010; Tao et al., 2010), which maintain cellular ROS homeostasis. SIRT3 also deacetylates numerous components of the electron transport chain, suggesting that SIRT3 could directly suppress ROS production (Bell and Guarente, 2011). In this regard, SIRT3 loss increases cellular ROS levels, contributing to genomic and mitochondrial DNA instability, and SIRT3 KO mice develop estrogen receptor and progesterone receptor-positive mammary tumors (Kim et al., 2010a). Importantly, SIRT3 can bind and deacetylate Ku70 in response to DNA damage (Sundaresan et al., 2008), suggesting that SIRT3 might be involved in Ku70-dependent DNA repair.

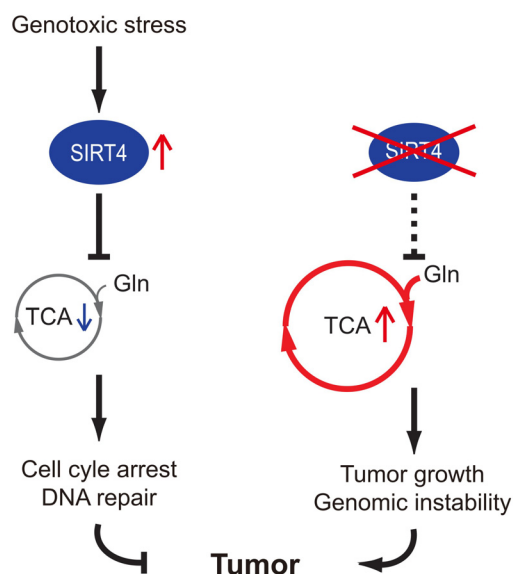


Fig. 1. The regulation of metabolic response to DNA damage by SIRT4. DNA damage-induced SIRT4 represses the metabolism of glutamine (Gln) into TCA cycle, which contributes to the control of cell cycle progression and the maintenance of genomic integrity. Loss of SIRT4 leads to both increased glutaminolysis and DNA damage-induced genomic instability, resulting in tumorigenesis.

As discussed above, DNA damage elicits signaling pathways that initiate cell cycle arrest and DNA repair. However, the cellular metabolic response to DNA damage is not well elucidated. Recently, we found that SIRT4 functions as a unique “metabolic block” upon genotoxic stress (Jeong et al., 2013). SIRT4 is the most highly induced sirtuins in response to DNA damage stimuli and represses glutamine consumption without affecting glucose uptake, resulting in a decrease in the incorporation of glutamine into the tricarboxylic acid (TCA) cycle intermediates. This metabolic response contributes to cell cycle arrest of damaged cells and promotes the repair of damaged DNA. Indeed, loss of

SIRT4 impaired DNA damage-induced cell cycle arrest and resulted in accumulation of DNA damage, and SIRT4 KO MEFs possessed more aneuploidy and exhibited an increased genomic instability (Fig. 1). Additionally, SIRT4 expression is decreased in many human tumors and, importantly, two independently derived SIRT4 KO mice spontaneously develop several types of tumors, most frequently lung tumors (Jeong et al., 2013). These findings identify SIRT4 as a tumor suppressor connecting two hallmarks of cancer: genomic instability and dysregulation of cell metabolism, suggesting that targeting of this link may be clinically beneficial.

SIRT5 is one of the least-studied mitochondrial sirtuins. It has been reported that SIRT5 enhances the urea cycle to detoxify ammonia by deacetylating carbamoyl phosphate synthetase 1 (CPS1), and *Sirt5*-deficient mice display high ammonia levels in blood under fasting or high protein diet (Nakagawa et al., 2009). However, except for its role in the urea cycle, SIRT5 KO mice did not exhibit any phenotypes and the physiological significance of SIRT5 in genomic maintenance is largely unknown.

SIRTIINS IN CELL METABOLISM

Reprogramming of cellular energy metabolism is a pivotal hallmark of cancer (Hanahan and Weinberg, 2011). Tumor cells often display elevated glycolysis and glutaminolysis to support their continued growth and survival. Enhanced glycolysis contributes to the bioenergetic needs of cancer cells and thus facilitates rapid cell proliferation (Tong et al., 2009). In addition, cancer cells also use critical intermediates derived from TCA cycle for the biosynthesis of nucleic acids, fatty acids and NADPH to support their growth. Thus, replenishment of the mitochondrial carbon pool by increased glutamine metabolism is essential for the maintenance of mitochondrial integrity and its biosynthetic roles in cancer cells (DeBerardinis et al., 2007; Wise and Thompson, 2010). On the other hand, many cancer cells show alterations in lipid metabolism, which contributes to the synthesis of membranes and signaling molecules, and energy homeostasis in cancer cells (Currie et al., 2013; Santos and Schulze, 2012).

In addition to their roles in sustaining genomic stability, sirtuins are recognized as crucial regulators of cell metabolism. Sirtuins target many enzymes involved in central metabolism (Verdin et al., 2010) and the activities of sirtuins are controlled by cellular metabolic status through sensing changes of intracellular NAD⁺ levels (Haigis and Guarente, 2006). Indeed, many studies have shown that sirtuins regulate glucose, glutamine and lipid metabolism (Guarente, 2013; Houtkooper et al., 2012; Martinez-Pastor and Mostoslavsky, 2012), implying that sirtuins may be implicated in tumor cell metabolism.

In the nucleus and cytoplasm

SIRT1 deacetylates a growing number of substrates that are involved in a wide variety of glucose metabolism. Peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α), a master transcriptional co-activator of a number of genes, is a well-known target of SIRT1. In the liver, activated SIRT1 during fasting increases the deacetylation of PGC-1 α , promoting the induction of gluconeogenic genes (Rodgers et al., 2005). In this regard, SIRT1 reinforces gluconeogenesis by activating a forkhead box protein O1 (FOXO1) transcription factor and peroxisome proliferators-activated receptor γ (PPAR γ) through deacetylation (Frescas et al., 2005; Houtkooper et al., 2012). Additionally, SIRT1 inhibits glycolysis by repressing the expression of glycolytic genes through deacetylation of hypoxia-inducible

factor 1 α (HIF-1 α), and by directly inhibiting glycolytic enzyme phosphoglycerate mutase 1 (PGAM1) through deacetylation (Hallows et al., 2012; Lim et al., 2010). SIRT1 is also involved in glucose metabolism by positively regulating insulin secretion from pancreatic β cells through uncoupling protein (UCP) 2 (Bordone et al., 2006; Moynihan et al., 2005).

On the other hand, SIRT1 plays an important role in lipid metabolism. During fasting, deacetylated PGC-1 α by SIRT1 activates PPAR α , which promotes fatty-acid oxidation (FAO) by increasing the expression of related genes in muscle (Gerhart-Hines et al., 2007). The sterol regulatory element-binding protein (SREBP) family has essential roles in lipid homeostasis. It has been shown that SIRT1 deacetylates SREBP-1c to stimulate fat oxidation under fasting condition (Ponugoti et al., 2010). Moreover, SIRT1 can interact with liver X receptor (LXR) proteins, an upstream regulator of SREBP-1c, and activates it (Li et al., 2007). SIRT1 also induces fat metabolism and reduces fat storage in white adipose tissue by inhibiting PPAR γ (Picard et al., 2004), facilitating fat catabolism. Thus, it appears that the expression and activity of SIRT1 are induced in several tissues during fasting or low nutrient conditions, which coordinates metabolic shift toward increased lipid metabolism for the organism's need for energy.

AMP-activated protein kinase (AMPK), a central energy sensor, has a key role in the maintaining cellular energy homeostasis. SIRT1 is also tightly related to AMPK activity, since SIRT1 activates the AMPK activator LKB1 through deacetylation (Lan et al., 2008) and AMPK increases NAMPT, a key NAD synthetic enzyme. (Canto et al., 2009). It has been shown that AMPK is involved in DDR. For example, in response to DNA damage, ATM phosphorylates and activates LKB1, activating AMPK (Fu et al., 2008; Sapkota et al., 2002). Activated AMPK stimulated mitochondrial biogenesis, and regulates DDR by interacting with p53 (Alexander and Walker, 2011). In line with these, Liu *et al.* showed that SIRT1 regulates DNA replication and DDR by sensing glucose deprivation and DNA damage through topoisomerase II binding protein1 (TopBP1) (Liu et al., 2014). These suggested that SIRT1 may play important roles in regulating energy metabolism in response to cellular stresses.

In addition to its essential roles in genomic stability, SIRT6 also functions as a critical regulator of glucose homeostasis. SIRT6 modulates glucose metabolism by maintaining deacetylation of H3K9 in promoters of glycolytic genes and functioning as a co-repressor of HIF-1 α (Zhong et al., 2010). Thus, SIRT6 loss shift cellular metabolism toward increased glycolysis, a metabolic reprogramming similar to the Warburg effect. In mice, SIRT6 loss enhances the expression of GLUT1, the glucose transporter, leading to increased glucose uptake, and SIRT6 KO mice die early caused by a severe hypoglycemia (Mostoslavsky et al., 2006). In this regard, one recent study proved that SIRT6 functions as a tumor suppressor by repressing aerobic glycolysis, and showed that conditional SIRT6 KO mice exhibited increased tumorigenesis (Sebastian et al., 2012). Moreover, SIRT6 expression was decreased in human cancers such as pancreatic cancer and colon carcinoma (Sebastian et al., 2012), indicating that SIRT6 functions as a tumor suppressor acting to suppress aerobic glycolysis. With regard to glucose homeostasis, SIRT6 is involved in gluconeogenesis. SIRT6-mediated deacetylation of general control nonrepressed protein 5 (GCN5) induces the acetylation of PGC-1 α acetylation and suppresses hepatic glucose production (Dominy et al., 2012).

Other data suggest that SIRT6 also regulates fat utilization. Mice with a liver-specific deletion of SIRT6 exhibit a fatty liver

and hepatocytes from these mice show decreased FAO (Kim et al., 2010b), while SIRT6 overexpression protects mice against high-fat diet (HFD) induced fat accumulation (Kanfi et al., 2010).

Compared to its premature aging phenotypes, including a reduction of life span, heart hypertrophy, loss of subcutaneous fat and degenerative cardiac hypertrophy (Vakhrusheva et al., 2008b), the metabolic functions of SIRT7 are emerging. Interestingly, it was reported that SIRT7 functions as a negative regulator of HIF signaling. SIRT7 knockdown results in increased transcriptional activities of HIF-1 and HIF-2 in several cancer cell lines (Hubbi et al., 2013), implying that SIRT7 might be involved in cancer metabolism. Recent studies point to a link between SIRT7 and lipid metabolism. SIRT7 KO mice exhibit chronic hepatosteatosis (Shin et al., 2013) and liver-specific deletion of SIRT7 also develop hepatic microvesicular steatosis (Ryu et al., 2014). Opposite to these results, another report showed that SIRT7-deficient mice are resistant to HFD-induced hepatic steatosis and obesity (Yoshizawa et al., 2014). Thus, future studies should be undertaken to uncover the functions and molecular mechanisms of SIRT7 in metabolism and tumorigenesis.

In response to cellular stress and calorie restriction, SIRT2 deacetylates FOXO1 and FOXO3a (Jing et al., 2007; Wang et al., 2007) that modulates glucose and lipid metabolism, suggesting that SIRT2 is implicated in metabolic homeostasis. Indeed, it has been showed that SIRT2 promotes gluconeogenesis by deacetylating the rate-limiting enzyme phosphoenolpyruvate carboxykinase (PEPCK), thereby modulating cellular response to glucose (Jiang et al., 2011). In addition, transcriptional repression of SIRT2 by HIF-1 α leads to compromised PGC1 α deacetylation, which results in reduction of β -oxidation and thus the development of obesity (Krishnan et al., 2012). At the same time, SIRT2 destabilizes HIF-1 α through deacetylation and regulates tumor metabolism under hypoxic conditions (Seo et al., 2015).

In the mitochondria

Because of their localization, mitochondrial sirtuins have been expected to play key roles as sensors and regulators of energy status in this organelle. SIRT3 has been shown to bind and regulate multiple enzymes for metabolic homeostasis. For example, during low nutrient conditions, SIRT3 plays an essential role for maintenance of energy homeostasis by deacetylating mitochondrial proteins (Hebert et al., 2013). SIRT3 targets several components of the TCA cycle and electron transport chain including NADH dehydrogenase (ubiquinone) 1 Alpha sub-complex 9 (NDUF9) (Ahn et al., 2008), IDH2 (Someya et al., 2010) and ATP synthase (Anderson and Hirschey, 2012). Moreover, SIRT3 can promote mitochondrial FAO by deacetylating long-chain acyl coenzyme A dehydrogenase (LCAD) (Hallows et al., 2011; Hirschey et al., 2010) to stimulate alternative energy production pathways during fasting. In addition, SIRT3 also enhances ketone body production by activating 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2) through deacetylation (Shimazu et al., 2010).

Recently, we and others demonstrated that SIRT3 loss shifts cellular metabolism toward enhanced glycolysis, a common metabolic switch in many cancer cells (Vander Heiden et al., 2009). SIRT3 mediates this metabolic reprogramming through HIF-1 α , a key transcription factor that induces a lot of glycolytic genes (Bell et al., 2011; Finley et al., 2011). SIRT3 loss increases ROS, leading to HIF-1 α stabilization. As a consequence, SIRT3 KO MEFs exhibit both enhanced glycolysis and increased glucose-dependent cell proliferation (Finley et al.,

2011). SIRT3 is also involved in tumor suppression by regulating iron homeostasis. SIRT3 loss contributes to tumor growth by increasing cellular iron metabolism, which is essential for DNA synthesis, oxygen transport and respiration (Jeong et al., 2015).

Previously, it has been shown that SIRT4 regulates glutamine metabolism in the pancreas by inhibiting mitochondrial glutamate dehydrogenase (GDH) which converts glutamate to the TCA cycle intermediates α -ketoglutarate and ammonia (Ahuja et al., 2007; Haigis et al., 2006). Recently, we and others reported that SIRT4 exerts tumor suppressive activities by repressing mitochondrial glutamine metabolism, in part through modification and repression of GDH (Csibi et al., 2013; Jeong et al., 2013). SIRT4 loss enhances glutamine anaplerosis and glutamine-dependent cell proliferation, while SIRT4 overexpression inhibits glutamine metabolism and sensitizes tumor cells to glucose depletion. In this regard, the tumor suppressive role of SIRT4 was further evaluated in the context of Myc-induced B cell lymphomagenesis (Jeong et al., 2014). SIRT4 overexpression inhibits glutamine utilization and proliferation of human Burkitt lymphoma cells. Moreover, SIRT4 loss in a mouse Burkitt lymphoma model, E μ -Myc transgenic mouse, accelerates lymphomagenesis and mortality. Importantly, SIRT4 is involved in cellular ammonia production. Ammonia is produced as a byproduct of glutamine catabolism in the mitochondria and it has been reported that in glioblastoma cells, most of the ammonia (> 90%) in the media was derived from this glutamine anaplerosis (Yang et al., 2009). Thus, SIRT4-mediated reduction of glutamine consumption was accompanied by a reduction in ammonia production, and SIRT4 KO cells produce more ammonia (Jeong et al., 2013; 2014). Because ammonia derived from glutaminolysis has been known as a regulator of autophagy (Eng et al., 2010), it will be interesting whether SIRT4 affects autophagic flux in cancer cells.

SIRT4 was known to have NAD⁺-dependent mono-ADP-ribosyltransferase activity without recognized deacetylase activity (Haigis et al., 2006). Interestingly, our recent study proved that SIRT4 can coordinate cellular lipid metabolism by repressing malonyl CoA decarboxylase (MCD) through deacetylation (Laurent et al., 2013). In mice, SIRT4 represses FAO and promotes lipid anabolism under nutrient-replete conditions, and thus SIRT4 KO mice exhibit deregulated lipid metabolism, increased exercise tolerance and protection against diet-induced obesity (Laurent et al., 2013). The fact that SIRT4 appears to have important roles in FAO suggests that SIRT4 may regulate tumor cell growth by limiting fat utilization.

As previously mentioned, an early study showed that SIRT5 regulates ammonia metabolism through the deacetylation of CPS1. Importantly, it has been reported that SIRT5 also possesses NAD⁺-dependent demalonylase and desuccinylase activities (Du et al., 2011). Further evidence is the finding that SIRT5 binds to glutaminase, the first enzyme for mitochondrial glutamine metabolism, and inhibits it through desuccinylation (Polletta et al., 2015). Given the existence of plenty of succinylation sites on proteins, involved in the TCA cycle, amino acid degradation and lipid metabolism (Park et al., 2013), SIRT5 is likely to possess other metabolic roles. Thus, future studies will need to dissect the role of SIRT5 in cancer metabolism in influencing acetylation and/or succinylation of target proteins.

DOUBLE-EDGED ROLES OF SIRTUINS IN CANCER

Sirtuins have merged as key regulators of genomic stability and metabolic homeostasis, contributing to stress resistance

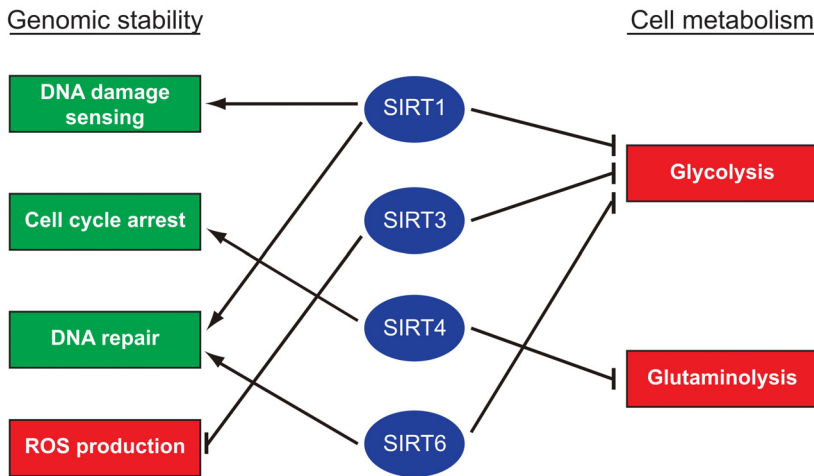


Fig. 2. Sirtuins regulate genomic stability and metabolism. The roles of sirtuins in the DDR and cell metabolism are summarized. Oncogenic and tumor suppressive pathways are displayed in red and green, respectively.

and tumor suppression. However, as we discussed about the oncogenic functions of SIRT7, there is plenty of evidence suggesting that several sirtuins may promote tumor growth and survival. Several studies have demonstrated that the expression of SIRT1 is upregulated in various human cancers (Bradbury et al., 2005; Huffman et al., 2007; Lim, 2006; Wang et al., 2008). In line with these, SIRT1 overexpression promotes the incidence of thyroid and prostate carcinomas in PTEN-deficiency mice (Herranz et al., 2013). Also, in another study, SIRT1 deletion suppresses BCR-ABL transformation of bone marrow cells and development of a CML-like myeloid disease (Yuan et al., 2012). Increased SIRT2 expression was also observed in certain types of cancer including acute myeloid leukemia (Dan et al., 2012), pancreatic cancer and neuroblastoma (Liu et al., 2013), and its expression is positively correlated with high-grade human HCC and prostate cancers (Chen et al., 2013; Hou et al., 2012). In addition, it was reported that SIRT3 expression is increased in several oral squamous cell carcinoma (OSCC) samples and downregulation of SIRT3 inhibits survival and proliferation of OSCC cells (Alhazzazi et al., 2011). Consistent with these findings, SIRT3 can promote the proliferation of bladder carcinoma cells by abrogating p53-induced growth arrest and senescence (Li et al., 2010), and protect cancer cells against DNA damage-induced cell death through Ku70 deacetylation (Sundaresan et al., 2008). Finally, SIRT6 can function as an oncogene by promoting cancer-induced inflammation, angiogenesis and metastasis in pancreatic cancer cells (Bauer et al., 2012), and contributing cancer cell survival against chemotherapeutic agents through the inhibition of FOXO3a activity (Khongkow et al., 2013).

It has been known that many genes, which have tumor suppressive activities, can function as oncogenes depend on genetic context, tumor type and stage. Because sirtuins function as key regulators of cellular homeostasis, they may serve as barriers to inhibit tumor initiation. However, on the other hand, tumor cells take advantage of sirtuins to contribute to their growth and survival by enhancing stress resistance and modulating cell metabolism. Thus, further studies are needed for delineating the roles of sirtuins in cancer.

CONCLUSION

There has been a tremendous amount of advances in our un-

derstanding of the role of sirtuins in cancer. Growing evidence supports that sirtuins are clearly involved in regulating genome integrity and metabolic processes (Fig. 2), and link these two hallmarks of cancer. However, the roles of sirtuins in tumorigenesis are complex and may function as both tumor suppressor and oncogene. Thus, further work will be needed to pinpoint the exact molecular mechanisms that enabling the role of each sirtuin in cancer. Also, it remains to be determined whether sirtuins plays an important role in tumor invasion and metastasis. Last, the delineation of the interaction between sirtuins during tumorigenesis will allow for a deeper understanding of how they coordinately regulate genomic fidelity and metabolism of cancer.

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