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Review

P53 and Sirt1: Routes of metabolism and genome stability

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ABSTRACT

The tumor suppressor p53 is a transcription factor that regulates key processes. But, the outcomes of the p53 response go beyond its role as a nuclear transcription factor. Sirtuin (SIRT1) regulates p53 functions as transcription factor. At the same time, SIRT1 protects the genome under stress conditions. The link between p53 and SIRT1 responses is unique. Both regulate metabolism, stress signaling, cell survival, cell cycle control and genome stability. Recent studies have proposed cancer as a metabolic disease. This is due to the switch from aerobic to anaerobic metabolism during tumor development. Yet, the complex molecular circuits (in and out of the nucleus) of tumor progression remain elusive. In this review, we will focus on the interplay between p53 and SIRT1. We will discuss their roles as nodes for possible therapeutic intervention.

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1. P53, effect on metabolism and oxidative stress

Metabolic changes take place with tumor progression. Cancer cells often rewire their metabolic pathways to promote fast growing and genomic instability. The best-understood function of p53 is its central role as tumor suppressor. Emerging evidence indicates a role of p53 in monitoring/modulating cell metabolism [1]. Cell fate depends either by p53 transcription-dependent or -independent responses within mitochondria. P53 regulates many

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proteins required for metabolism and reactive oxygen species (ROS) production. Besides, p53 controls redox signaling, through the modulated expression of pro- and anti-oxidant proteins [2].

1.1. The Warburg effect and p53

Transformed cells get a series of features to proliferate fast and to escape from programmed cell death. In 1927 Otto Warburg demonstrated that tumor progression takes place together with metabolic changes [3]. Warburg observed that cancer cells shift from oxidative phosphorylation (OXPHOS) to glycolysis. This occurs even in presence of oxygen. This process is now recalled as the “Warburg effect”. Glycolysis takes part in the cytoplasm. It leads to the NADH and ATP production through conversion of glucose into pyruvate. Oxidative phosphorylation generates ATP into mitochondria. In resting conditions OXPHOS is predominant and more efficient. Even if, cells with high rates of proliferation tend to switch to glycolysis. Cancer cells make use of the pentose phosphate pathway (PPP), which originates from a bypass in the glycolysis [4]. PPP is necessary for lipid and nucleic acid synthesis and represents an important source of NADPH. NADPH is also necessary for the production of glutathione (GSH), the major intracellular antioxidant. Thus, the PPP leads to proliferate fast and to protection against oxidative stress [5].

P53 is the most important obstacle for tumor progression. The p53 homologue is present in unicellular organisms. This indicates that the tumor suppression may not be p53's original function [6]. Besides DNA damage and oncogene activation, nutrient flow changes activate p53 [7]. Recent studies show that p53 controls the metabolic switch between glycolysis and oxidative phosphorylation.

1.2. P53 and glucose metabolism

P53 inhibits glycolysis by acting at different levels. It has been demonstrated that p53 decreases glucose import by reducing the expression of GLUT1 and GLUT4 glucose transporters [8]. P53, through the inhibition of IKK, also regulates the GLUT3 expression [9]. Bensaad and co-workers demonstrated that p53 reduces glycolysis by promoting TIGAR expression [5]. TIGAR dephosphorylates fructose-2,6-bisphosphate to fructose-6-phosphate and blocks the breakdown of glucose into pyruvate. This in turn promotes the switch to the oxidative pentose phosphate pathway (ox-PPP). The latter leads to NADPH production and to a more effective protection against oxidative stress. P53-independent TIGAR accumulation is a hallmark of several tumors. Yet, the scenario is complex since p53 inhibits the glucose-6-phosphate dehydrogenase (G6PDH) expression. G6PDH takes part in the first and limiting step of the ox-PPP [4]. The mechanism by which p53 inhibits G6PDH represents a way to block ox-PPP in case of accumulation of TIGAR in cancer cells. TAp73, a member of the p53 family, induces the expression of G6PDH genes and leads to cell proliferation [10]. In mouse embryonic fibroblasts, p53 inhibits glycolysis. In these cells, P53 reduces the protein levels of the glycolytic enzyme phosphoglycerate mutase (PGM). PGM converts 3-phosphoglycerate into 2-phosphoglycerate [11]. However, p53 promotes glycolysis in muscle by inducing the expression of PGM M isoform [12] and of hexokinase II (HK2) [13]. The latter converts glucose into glucose-6-phosphate in the first step of glycolysis. This indicates that the effects of p53 on glycolysis are remarkable and tissue-specific.

1.3. P53 modulates the glucose metabolism while controlling the gluconeogenesis

Gluconeogenesis produces glucose and is essential for tumor cell growth. P53 represses the gluconeogenesis by promoting the

expression of histone deacetylase sirtuin 6 (SIRT6). SIRT6 deacetylates forkhead box protein O1 (FOXO1). In turn, this represses the expression of glucose-6-phosphatase (G6PC) and of phosphoenolpyruvate carboxykinase (PCK1). Both enzymes are rate-limiting proteins for gluconeogenesis [14].

1.4. P53 and oxidative phosphorylation

While repressing glycolysis, p53 promotes oxidative phosphorylation at distinct levels. In presence of oxygen, the pyruvate derived from glycolysis is converted in Acetyl coenzyme A (Acetyl-CoA). The latter takes part in the tricarboxylic acid (TCA) cycle. In TCA cycle, ATP is generated through oxidative phosphorylation. Besides, TCA cycle provides precursors for anabolic pathways, so supporting cell growth and proliferation. P53-deficient cells produce less ATP from the TCA cycle compared to control cells [15]. In detail, p53 promotes TCA cycle by reducing the pyruvate dehydrogenase kinase 2 (PDK2) expression. PDK2 inactivates the pyruvate dehydrogenase complex (PCD). In turn this promotes the conversion of pyruvate into lactate instead of Acetyl-CoA [16].

P53 enhances gene transcription of mitochondrial components, including subunit 1 of cytochrome c oxidase (COI) [17], and cytochrome c oxidase 2 (SCO2). SCO2 in turn regulates the subunit 1 of complex IV [15]. Besides, p53 induces the expression of the mitochondrial apoptosis-inducing factor (AIF) [18]. AIF acts as NADH/NADPH oxidase. AIF is also essential for the proper functioning of complex I.

P53 reduces the expression of the TCA cycle-associated malic enzymes ME1 and ME2. These enzymes are important for NADPH production, lipogenesis and glutamine metabolism. Thus, P53 regulates both the progression of biosynthetic pathways and the antioxidant response [19]. Besides, p53 enhances OXPHOS by promoting the transcription of glutaminase 2 (GLS2) [20,21]. GLS2 stimulates the production of glutamate and α -ketoglutarate. The latter is a key component of the TCA cycle involved in ATP production and the antioxidant response.

1.5. P53 lipid metabolism and mitochondrial homeostasis

Besides alterations in glycolysis and oxidative phosphorylation, cancer cells show a deregulated lipid metabolism. In particular, cancer cells synthesize fatty acids. The fatty acids are the main reserve of lipids. Lipids are necessary for membrane formation and signaling transduction [22]. Breast, colon and prostate cancer cells [23–25] have high levels of fatty acids synthases (FASN). This observation supports the role of FASN in tumorigenesis. In line with this, FASN inhibition counteracts cellular transformation (reviewed in [26]). FASN deficiency counteracts cancer growth in cells with activated PI3K signaling. Yet, blocking FASN in K-Ras-driven cancer cells has no effect on proliferation [27].

P53 attenuates the fatty acids synthesis, repressing the expression of the transcriptional regulator SREBP-1 (sterol regulatory element-binding protein 1c). The latter promotes the expression of triglyceride synthesis and lipogenic enzymes [28]. Thus, p53 inhibits the expression of FASN and (ATP citrate lyase) ACLY genes. Thereby, p53 may repress tumor proliferation while inhibiting the fatty acids synthesis. The fatty acid oxidation leads to the formation of Acetyl-CoA, which takes part in the TCA cycle, producing ATP, NADPH and FADPH. As mentioned above, TCA cycle is active in resting conditions. While, NADPH is necessary for the cellular protection against oxidative stress. Upon glucose deprivation, p53 induces the expression of Lpin1. This in turn stimulates the fatty acids oxidation [29]. Lpin1 is a nuclear transcriptional co-activator. Following glucose starvation Lpin1 induces the expression of genes involved in fatty acids oxidation. But, Lpin1 inhibits the fatty acid oxidation at high glucose.

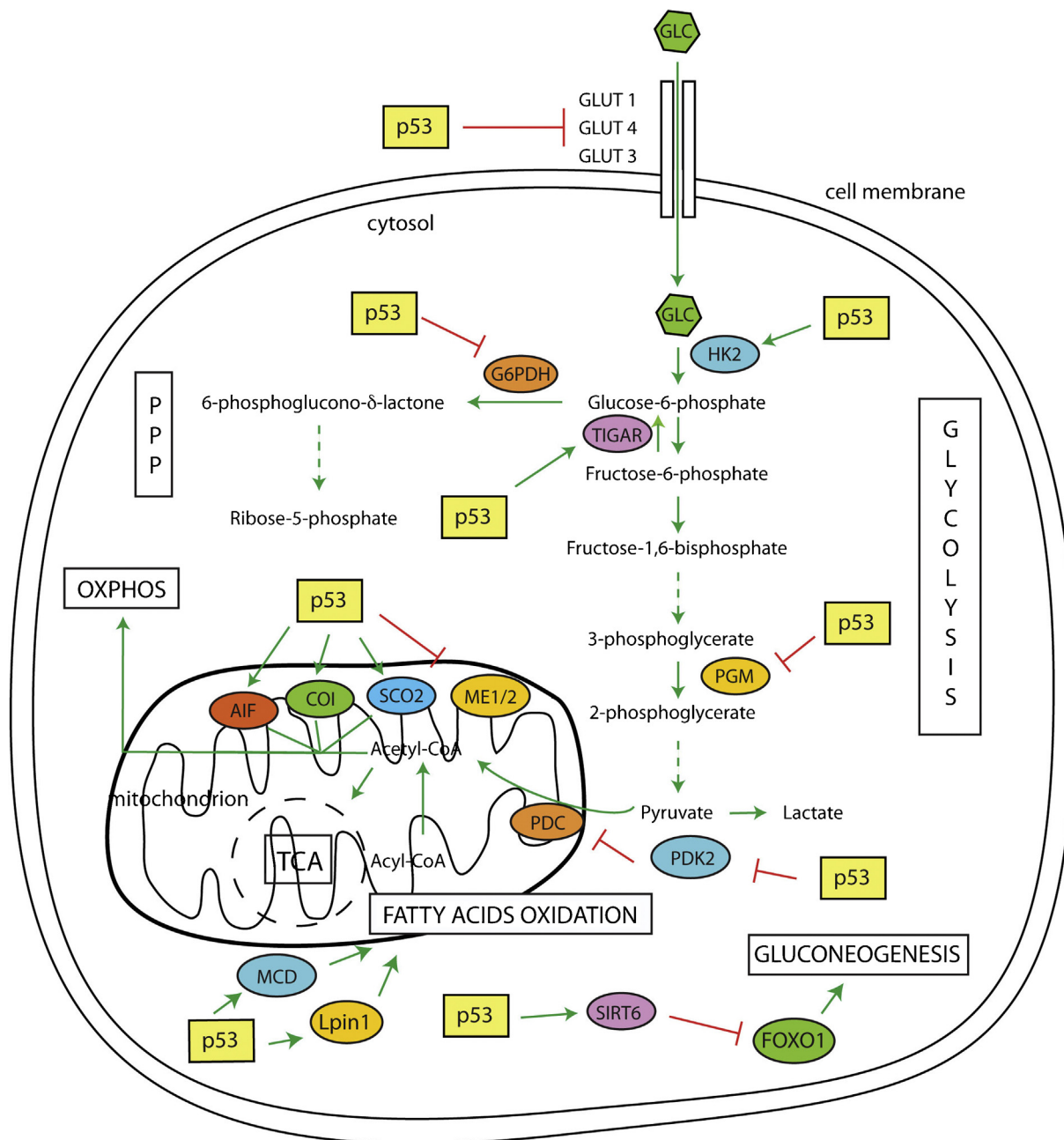


Fig. 1. p53 inhibits glycolysis by regulating several components of this process. P53 inhibits glucose transporter (GLUT 1–4–3) and the glycolytic enzyme PGM. Moreover, p53 inhibits glycolysis by promoting TIGAR expression. At the same time, p53 inhibits the ox-PPP by acting on G6PDH. The p53 role is tissue-specific. In muscle p53 enhances glycolysis by promoting the transcription of HK2. Through the expression of SIRT6, p53 reduces the gluconeogenesis. p53 stimulates the oxidative phosphorylation by inducing the expression of several important components of this metabolic process (i.e. AIF, COI and SCO2 and malic enzymes ME1/2). Moreover, p53 promotes the OXPHOS by reducing the expression of PDK2. In turn, this promotes the production of Acetyl-CoA instead of lactate. Lastly, in response of nutrient starvation, p53 promotes the expression of Lpin1 and MCD, stimulating the conversion of Acyl-CoA to Acetyl-CoA. In this way p53 stimulates the oxidative phosphorylation instead of glycolysis.

In mice, P53 controls the hepatic fatty acid oxidation in response to fasting [30]. P53 induces the transcription of malonyl-CoA decarboxylase (MCD). MCD stimulates the malonyl-CoA turnover and increases carnitine palmitoyl transferase activity. This leads to mitochondrial fatty acid uptake (Fig. 1).

In brief, P53 enhances the oxidative respiration in cells by promoting the fatty acid oxidation. In this manner, p53 may counteract the Warburg effect.

Mitochondrial DNA (mtDNA) contains genes of enzymatic complexes involved in OXPHOS. P53 protects mitochondrial DNA from mutations, promoting the transcription of the ribonucleotide reductase p53R2. Besides, p53 preserves mtDNA integrity and regulates the mtDNA copy number [31]. Thereby, p53 promotes

the oxidative phosphorylation while ensuring mitochondrial DNA protection.

Yet, it remains an open question whether (and to what extent) the metabolic status may contribute to genomic maintenance. Recent evidence suggests that genomic stability requires cooperation of p53 and SIRT1.

2. Essential effects of SIRT1 on metabolism and genome protection

Sirtuins are a family of class III deacetylases (NAD⁺-dependent). These enzymes control many cellular pathways, including metabolism, stress and genome stability.

Table 1
Sirt substrates.

Substrates	Cellular function	References
H4	Histones	PMID: 17694090
H3		PMID: 19411844
H1		PMID: 15469825
SUV39H1	Histone-modifying enzymes	PMID: 21504832
PCAF		PMID: 19188449
p300		PMID: 15632193
TIP60		PMID: 22586264
p53	Transcription factors	PMID: 11672523
E2F1		PMID: 16892051
NFkB		PMID: 15152190
P73		PMID: 16998810
FOXO 1	Regulators of metabolism	PMID: 25009184
FOXO 3a		PMID: 14976264
Myc		PMID: 21807113
HIF-1 α /HIF2- α		PMID: 24423936
ATM	Cell signaling components	PMID: 23852118
AMPK		PMID: 19276888
AKT		PMID: 24436432
Ku70	DNA repair modulators	PMID: 23247197
WRN		PMID: 18203716
Rad51		PMID: 20097625
NBS1		PMID: 17612497
APE1	Regulators of metabolism	PMID: 19934257
BRCA1		PMID: 18851829
PGC-1a		PMID: 15744310
CLOCK		PMID: 24442997
PER2	Regulators of metabolism	PMID: 18662546
PPAR γ		PMID: 15175761

The basic function of Sirtuins links chromatin dynamics/gene expression to environmental stimuli. At the same time, Sirtuins ensure genome protection [32]. Genome integrity relies on chromatin structure and DNA repair mechanisms. Chromatin and DNA repair depend by deacetylation of histones (and of other chromatin-associated factors) [33,34]. Sirtuins were discovered in yeast (Silent Information Regulator, Sir2). They were genes necessary for the repression of silent-mating type loci [35]. The mammalian family of Sirtuins comprises of seven proteins, SIRT1–SIRT7. These enzymes are ubiquitously expressed. SIRT1 is the best-studied gene and the largest in sequence. NAD⁺, allosteric modulators, nucleo-cytoplasm shuttling, transcription regulators activate SIRT1 [36]. The mammalian Sirtuins are present in distinct subcellular compartments. Some Sirtuins are present into mitochondria. This implies a role of Sirtuins for metabolism and for mitochondria homeostasis [37].

2.1. Metabolism and signaling

Metabolism and signaling pathways are interconnected [38]. Cancer cells exploit the signalling-dependent regulation of metabolism to fuel macromolecular biosynthesis. This supports their fast growth [39–41]. Nutrient-sensing molecules are the AMP-activated kinases (AMPK) and the mammalian target of rapamycin complex 1 (mTORC1). These enzymes are key regulators of the metabolic status of the cells. Besides, metabolites generate posttranslational modifications (PTMs) [42].

Cytosolic and nuclear Acetyl-CoA levels modulate PTMs, gene expression, signaling cascades and metabolism [38]. Two opposite enzymes as acetyltransferases and deacetylases regulate acetylation. The latter is a PTM induced by the metabolite Acetyl-CoA [43,44]. Intracellular metabolic conditions control the activity of these two classes of enzymes. SIRT1 deacetylase depends on NAD⁺ as a cofactor. Besides NAD⁺, NAD⁺ biosynthetic enzymes (as Nicotinamide phosphoribosyltransferase – Nampt) promote SIRT1 deacetylase activity.

Proteomic studies indicated that acetylation (and Acetyl-CoA production) regulates several signaling events. Emerging concepts

suggest that acetylation is like a “sensor” of Acetyl-CoA availability within cells. ATP-citrate lyase (ACL) and Acetyl-CoA synthetase 1 (ACECS1) are essential enzymes for Acetyl-CoA production. ACECS1 is deacetylated (and activated) by SIRT1 under nutrient-limited conditions [45]. Acetylation of ACECS1 may serve as a regulatory/inhibitory modification in response to metabolic changes. Many enzymes involved in metabolism are also acetylated [46,47]. An acetyl-mimic mutant of pyruvate kinase (PKM2) promotes tumor xenografts growth [48].

Besides, Acetyl-CoA production enhances histone acetylation and so gene transcription [49]. Nutrient availability, metabolic conditions and posttranslational modifications of the enzymes control Acetyl-CoA production. Phosphorylation of ACL by AKT and by PKA increases ACL activity [50–52]. Cancer cells have the phosphoinositide 3-kinase (PI3K)-AKT pathway activated. Acetyl-CoA production is persistent, providing a continuous signal to promote growth [38]. PTMs of deacetylases are linked to Acetyl-CoA production. SIRT1 modifications exert either stimulatory or inhibitory effects on SIRT1 activity [53]. Different kinases/modifiers and diverse multi-site regulatory mechanisms control SIRT1 activity [54]. In response to oxidative stress, c-Jun N-terminal kinase (JNK) phosphorylates SIRT1 at three sites [55]. These modifications increase SIRT1 activity. In contrast, mTOR phosphorylates SIRT1 at a single site (S47) in response to oxidative stress. This modification inhibits SIRT1 activity. AMPK targets human SIRT1 at T344. This modification reduces SIRT1 capability to deacetylate p53 [56,57]. Other kinases as CK2, DYRK1 and DYRK3 phosphorylate SIRT1 in different sites. These modifications in turn stimulate SIRT1 activity [58–60]. In contrast, CyclinB/Cdk1 (a cell cycle dependent kinase) phosphorylates SIRT1 at T530 and S540. Both modifications inhibit SIRT1 activity [61].

The first discovered non-histone substrate of SIRT1 is p53. P53 plays a central role in SIRT1-mediated senescence and in tumor progression [62]. SIRT1 represses p53-dependent transactivation in tumors or in mouse embryonic fibroblasts [63]. Yet, p53 binding to SIRT1 promoter represses SIRT1 transcription [62]. Thus, p53 provides a feedback circuit either to regulate SIRT1 expression and the p53 response. Low nutrient conditions increase NAD⁺/NADH ratio, promoting SIRT1 activity. PARP1 activity leads to NAD⁺ depletion, limiting SIRT1 activity [64]. Moreover, SIRT1 induces gene silencing through H3K9 deacetylation of target gene promoters (Fig. 2).

SIRT1 reduces the p53-dependent apoptosis induced by stress [65,66]. SIRT1-deficient mice show p53 hyperacetylation following DNA damage. They also show an increased ionizing radiation-induced apoptosis in thymocytes [66]. Other studies report a modest effect of SIRT1 on the p53-mediated responses [67,68]. These opposite results imply the existence of other mechanisms by which SIRT1 exerts its effect on p53. Convincing evidence indicates that SIRT1 regulates the p53 subcellular localization. Likely, SIRT1 prevents p53 nuclear translocation. This in turn promotes cytosolic accumulation of p53 and its passage to mitochondria. In brief, SIRT1 blocks p53 transcription-dependent apoptosis. At the same time SIRT1 increases p53-mediated (transcription-independent) apoptosis [62].

SIRT1 was first considered as a potential tumor promoter, repressing p53. Yet, recent results indicated that Sirt1 acts as tumor suppressor by facilitating mitochondria-dependent apoptotic response.

SIRT1 deacetylates different histones (H4, H3, and H1) and also many non-histone proteins. SIRT1 substrates take part in diverse cellular responses [69,70]. SIRT1 substrates can be 1) histone-modifying enzymes such as SUV39H1, PCAF, p300 and TIP60; 2) transcription factors regulating cell cycle progression/survival under various stress conditions (p53, nuclear factor (NF)- κ B, p73, forkhead transcription factors FOXO1, FOXO3a, Myc,

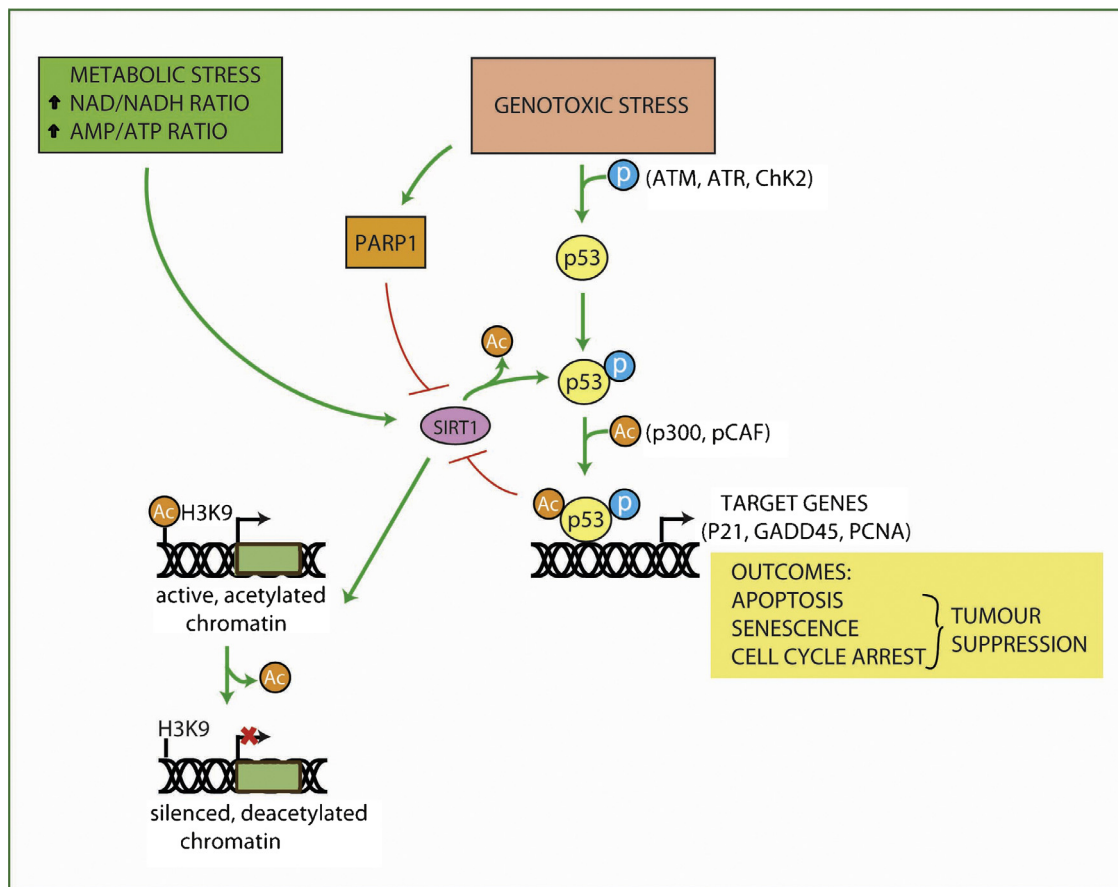


Fig. 2. Following genotoxic stresses, p53 is phosphorylated at S15 by ATM, ATR, Chk2 kinases. Besides, p53 is modified at K382 by p300 and PCAF acetyltransferases. These posttranslational modifications stimulate p53 transcription of specific target genes (p21, GADD45, PCNA). In turn this promotes cell cycle arrest, apoptosis or senescence. P53 binding to SIRT1 promoter represses SIRT1 transcription. By this mechanism, p53 provides a feedback circuit to regulate SIRT1 expression and at the same time, to modulate p53-transcription dependent response. Low nutrient conditions activate SIRT1. While, PARP1 activity leads to NAD⁺ depletion, limiting SIRT1 activity [64]. Moreover, SIRT1 induces gene silencing through H3K9 deacetylation of target gene promoters.

hypoxia-inducible transcription factors (HIF)-1 α and HIF2- α); 3) cell signaling components (modifiers, enzymes) AKT; 4) DNA repair modulators such as Ku70, WRN, NBS1, APE1; 5) regulators of metabolism, circadian clock including PGC-1 α , PER2 [71,72] (see Table 1).

Mouse models support the maintenance of genomic stability as the fundamental role of SIRT1 [32]. Yet, SIRT1 modulates the regulatory signaling circuits of cell homeostasis. SIRT1 may deal with oxidative stress, aging, metabolism, and genome protection.

To date, the identification of Sirtuin-regulated signaling targets remains incomplete. Reversal of the acetylation affects transcription factors [66] and their nuclear localization. Yet, removal of acetylation may induce protein breakdown [73].

Acetylation of the mitogen-activated protein kinase kinase-1 (MEK1) enhances its kinase activity. Treatment with Sirtuin inhibitors or siRNA silencing of SIRT1 or SIRT2, enhances MEK1 acetylation. This modification causes the consequent phosphorylation of extracellular signal-regulated kinase (ERK). An acetyl-mimic mutant of MEK1 promotes inappropriate growth properties. This indicates that acetylation of MEK1 may exert an oncogenic potential [74]. It is of interest to point out that SIRT2 is a new AKT adaptor required for optimal AKT activity. Constitutive SIRT2 binding to AKT is dependent on phosphorylation at T101 by AMP-activated kinase. Pharmacological inhibition or genetic down-regulation of SIRT2 inhibits AKT activation in stimulated cells. Of note, overexpression of SIRT2 enhances AKT-mediated pathway activation. In cells with constitutive PI3K activation, AKT interacts with a nuclear Sirtuin, (SIRT1). But,

inhibition of PI3K induces SIRT1 dissociation and increased association with SIRT2. This supports the use of SIRT1 and SIRT2 inhibitors in the treatment of tumor cells with an increased PI3K activity [75].

Reversible acetylation controls the subcellular localization of many other signaling factors/components. Besides, it regulates the silencing of gene expression. SIRT1 promotes nuclear retention of High-mobility group (HMG) B1. SIRT1 modulates damage signaling initiated by HMGB1 secretion upon stress [76]. SIRT1 reduces the expression of *survivin*, through H3K9 deacetylation on its promoter [77].

SIRT1 may promote and/or suppress tumorigenesis [32,78,79]. On one hand, SIRT1-deficiency may help tumor progression, promoting genomic instability. Yet, tumor cells tend to need of Sirtuins to proliferate, to repair with low fidelity and to evolve [78]. The bifurcated role of SIRT1 in tumorigenesis is due to its peculiar role in genome protection [78].

2.2. Genomic stability

SIRT1 acts on the genome through various mechanisms and at different levels. SIRT1 regulates chromatin modifications, facilitating DNA repair. Besides, SIRT1 connects energy and metabolic flows to chromatin dynamics and gene expression.

SIRT1 facilitates both constitutive heterochromatin (CH) and facultative heterochromatin (FH) formation. SIRT1 enhances methyl-transferases activity. This promotes the methylation of CpG islands (reviewed in [79]).

SIRT1 induces epigenetic silencing of target genes [80,81]. SIRT1 modifies histone (H4K16Ac, H3K9Ac, H1K26Ac) and chromatin factors (as the histone methyl-transferase SUV39H1). Loss of SIRT1 prevents both the spreading of heterochromatin marks (H3K79me3) and localization of heterochromatin protein 1 (HP1) [82]. The interplay between SIRT1 and SUV39H1 is mediated by the E3 ubiquitin ligase MDM2. SIRT1 inhibits SUV39H1 polyubiquitination by MDM2 and so increases SUV39H1 [83]. High levels of SUV39H1 *in vivo* enhance its turnover in pericentromeric heterochromatin regions. This ensures genome integrity. SIRT1 may generate aberrant methylation of the CpG islands in promoters following DNA damage. This promotes heritable gene silencing [84]. SIRT1-mediated gene silencing may affect both tumor promoting and tumor suppressor genes. SIRT1 inhibition reactivates silenced tumor suppressor genes in cancer cell. This occurs without loss of promoter hypermethylation [85].

2.3. DNA repair

SIRT1 takes part in DNA signaling and repair at different levels. For the repair of singlestrand breaks (SSBs), SIRT1 controls the nucleotide excision repair (NER) pathway. SIRT1 interacts with XPA (xeroderma pigmentosum complementation group A) [86]. SIRT1 enhances XPC (xeroderma pigmentosum complementation group C) expression. SIRT1 prevents AKT-mediated nuclear localization of XPC transcriptional repressors. Inhibition of SIRT1 affects XPC transcription, impairing NER function [87]. Several DNA repair factors are also substrates of SIRT1, among them X-ray repair cross-complementing gene 4 protein (XRCC4p) [88]; Ku70 [89]; Werner's Syndrome protein (WRN) [90]. SIRT1 binds to and modifies Nijmegen breakage syndrome protein (NBS1). NBS1 is a regulatory component of the MRE11-Rad51-NBS (MRN) nuclear complex [91,92]. MRN complex works as a "sensor" in the early stages of double strand break (DSB) signaling. MRN promotes the formation of γ -H2AX foci upon γ -irradiation [93]. SIRT1 recruitment to DSBs depends on ATM-mediated signaling (*i.e.* γ -H2AX phosphorylation) [94]. SIRT1 interacts with (and modifies) two members of the MYST acetyltransferase family (hMOF and TIP60). Both enzymes are necessary for cell growth, DNA repair and apoptosis [95–97]. SIRT1 inhibits their activity by promoting their ubiquitin-mediated degradation. Following DNA breaks, SIRT1 binding is reduced and hMOF and TIP60 take part in the damage response [97–99]. SIRT1 is also connected to the non-homologous end joining (NHEJ) repair pathway, through the protein Ku70. Deacetylation of Ku70 by SIRT1 prevents Ku70 translocation. At the same time, SIRT1 promotes Ku70-dependent DNA repair [100–102].

3. SIRT1-p53: nodes connecting metabolism and genome integrity

Mouse models support a role of SIRT1 for genome protection [66,93,103,104]. SIRT1 regulates p53 acetylation. SIRT1-deficient thymocytes exhibit p53 hyperacetylation [66]. Double knockout mice show that genomic integrity needs cooperation between p53 and SIRT1 [93].

In mice, evidence shows that p53 tumor suppressor function relies on p53 ability to modulate metabolism [105]. Besides, the p53 family members p63 and p73 are emerging as critical components in the regulation of metabolism [106,107]. This implies that the metabolic functions of p63/p73 may also contribute to tumor suppression. Yet, these effects remain elusive in particular with tumors expressing mutant forms of p53 [108].

SIRT1 modulates both p53 transcription-dependent and p53-independent apoptosis. The latter is initiated through cytochrome c release from the mitochondria. Emerging evidence indicates that SIRT1 prevents p53 nuclear translocation. SIRT1 redirects p53 from

the cytosol to the mitochondria in response to increased ROS. Likely, the biological effect of p53 enrichment into mitochondria induces transcription-independent apoptosis. In this way, oxidative stress modulates cell fate through SIRT1-mediated p53 deacetylation (reviewed in [62]).

DNA Damage stress Response (DDR) relies on cell cycle checkpoints for repairing DNA lesions. Failure to balancing of DDR response promotes ageing and cancer. How are cellular metabolism and DDR interconnected? Besides, the roles of p53 and SIRT1 remain still undefined.

The chemotherapeutic drug cisplatin, causes oxidative stress and various types of DNA alterations. Stechow and co-workers perform metabolic profiling by mass spectrometry (MS) of embryonic stem (ES) cells. ES cells are treated for different time periods with cisplatin. MS and transcriptomics analyses of cisplatin-treated ES-cells show that cisplatin alters the metabolic pathways. Yet, several metabolic enzymes induced by cisplatin are also p53 target genes. These results show that metabolic pathways are interconnected with DNA damage response. It is of interest that p53 plays a central role for both processes [109].

Emerging evidence indicates that metabolic changes have a direct effect on chromatin and DNA repair. Several chromatin-modifying enzymes, involved in DNA repair, are regulated by metabolic cofactors. Thus, alterations of energy and metabolic flows have profound consequences on genome integrity.

Chromatin plays an essential role in DNA repair pathways (non-homologous end-joining (NHEJ) or homologous recombination (HR)). Many histone modifications are necessary to assembly signaling-platforms for repair mechanisms. Histone modifications (including phosphorylation, acetylation, methylation, ubiquitylation) regulate DSB repair [110–114]. Enzymes, involved in histone modifications, need metabolites as cofactors or substrates for their activity. Metabolic cofactors/substrates including Acetyl-CoA (involved in Acetyl-CoA-dependent histone acetylation) and NAD⁺ modulate histone modifications. NAD⁺ is essential for NAD⁺-dependent deacetylation or NAD⁺-dependent polyADP-ribosylation of chromatin. Besides, S-adenosyl-L-methionine (SAM) and FAD/ α -ketoglutarate induce methylation and demethylation of histones and/or DNA. Metabolic modifications may contribute to DNA double-strand (DSBs) repair defects [115]. At what extent do the metabolic changes interfere with chromatin-directed repair processes? It remains an open question. These studies represent an exciting area of investigation.

4. Conclusions and perspectives

Cancer is a complex disease driven by epigenetic changes, genetic modifications in oncogenes and tumor suppressors. Yet, alterations in metabolism have profound effects on the cell growth/survival. Cell homeostasis requires fine-tuning of energy and metabolic flows with genome stability. P53 and SIRT1 are nodes regulating metabolism, DNA repair and senescence.

Metabolic p53 responses are important for maintaining cell homeostasis and for preventing tumor development. Metabolic and other stress signals activate p53 [116]. Recently, other authors reviewed the cytosolic functions of p53 [117]. P53 regulates metabolism and induces senescence. This represents a paradigm for targeting of metabolic alterations associated with cancer [118].

Recent evidence indicates a dual effect of SIRT1 on cancer. SIRT1 enhances cell survival, allowing indefinite cell division. At the same time, SIRT1 promotes genome stability under stress conditions [79].

DNA repair needs dynamic chromatin remodeling, re-assembly of nucleosome, histone variant exchanges, signaling response. Metabolite-associated changes at chromatin may promote malignant transformation through deregulation of DNA repair [115]. How do metabolic changes interfere with chromatin-directed

repair processes? It remains elusive. The in-depth understanding of metabolite effects on DNA repair will help the development of combined targeted therapies to eradicate cancer.

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