Review paper

Folia Neuropathologica

Sirtuins and their interactions with transcription factors and poly(ADP-ribose) polymerases

Henryk Jęśko[1], Robert P. Strosznajder[2]

[1]Department of Cellular Signalling, Mossakowski Medical Research Centre Polish Academy of Sciences, Warsaw, [2]Laboratory of Preclinical Research and Environmental Agents, Department of Neurosurgery, Mossakowski Medical Research Centre Polish Academy of Sciences, Warsaw, Poland

Folia Neuropathol 2016; 54 (3): 212-233 DOI: 10.5114/fn.2016.62531

Abstract

Sirtuins (SIRT1 to -7) are unique histone deacetylases (HDACs) whose activity depends on NAD^+, thus making them capable of sensing the cellular metabolic status. Sirtuins orchestrate the stress response and damage repair, and are able to modulate the course of ageing and neurodegenerative diseases. Despite their classification as HDACs, sirtuins deacetylate a vast number of targets in many cellular compartments, and some display additional enzymatic activities including mono(ADP-ribosyl)ation. SIRTs interact with multiple signalling proteins, transcription factors and enzymes including p53, FOXOs (forkhead box subgroup O), PPARs (peroxisome proliferator-activated receptors), NF-κB, and DNA-PK (DNA-dependent protein kinase). Sirtuins also interact extensively with the family of poly(ADP-ribose) polymerases (PARPs), a crucial and widespread class of NAD^+-consuming post-translational protein modifiers. PARPs share a significant number of roles with sirtuins: these enzymes modulate DNA repair, gene expression, and the activities of signalling pathways.

We focus on the expanding cross-talk between sirtuins, transcription factors and PARPs, which is a highly promising therapeutic target in a number of age-related neurodegenerative disorders, including the most devastating: Alzheimer's and Parkinson's diseases.

Key words: *sirtuins, poly(ADP-ribose) polymerases, FOXO, neurodegeneration, Alzheimer's disease, Parkinson's disease, oxidative stress.*

Introduction

Sirtuins belong to the broad category of histone deacetylases (HDACs), enzymes that modulate signalling proteins, enzymes and transcription factors (TFs) via removal of lysine acetylation. Acylations (including Lys acetylation) are an increasingly recognized, evolutionarily conserved category of post-translational protein modifications; the action of HDACs thus allows highly controlled spatiotemporal regulation of protein activity, interactions and localization. Crucial aspects of cellular homoeostasis depend on acylations including the prevention and mitigation of stress and the removal of the resulting damage. There are over 45 HDAC enzymes identified in eukaryotes, divided into 4 groups (classes) according to their homology to yeast HDACs [38]. Class I enzymes (HDAC1 to -3 and HDAC8) show the stron-

Communicating author

Henryk Jęśko, Department of Cellular Signalling, Mossakowski Medical Research Centre Polish Academy of Sciences, 5 Pawinskiego St., PL-02106 Warsaw, Poland, e-mail: havjes@gmail.com

gest similarity to yeast Rpd3 (reduced potassium dependency 3), while class II enzymes are related to yeast HDA1 and fall into two sub-classes according to the same structural criterion: IIa (HDAC4 to -7 and -9) and IIb (HDAC6, -10). The seven known mammalian class III enzymes are termed sirtuins (SIRT1 to -7; the name stems from a yeast homologue dubbed silent information regulator 2) (Table I). Sirtuins are the only HDACs to use NAD^+ for the reaction; these enzymes localize to various cellular compartments (Table I) [132,207,234] including cytosol (SIRT1, -2), mitochondria (SIRT3-5), and nucleus (SIRT1, -6 and -7, plus cell cycle-dependent transient re-location of SIRT2). Class IV includes only one enzyme, HDAC11.

The unique dependence on NAD^+ availability makes sirtuins excellent sensors of metabolic condition of the cell. Sirtuins transfer the acetyl group removed from a protein to the ADP-ribose moiety of NAD^+; this causes the NAD^+ molecule to break down to nicotinamide and O-acetyl-ADP-ribose (OAADPR), which are SIRT auto-inhibitory compounds. Moreover, OAADPR undergoes rather extensive metabolism and may serve as a signalling molecule capable of modulating gene silencing, ion channel opening,

Table I. Mammalian sirtuin sub-cellular localisation and activities. According to [20,234], modified

	Predicted MW	Primary subcell. localization	Activity	Key targets
SIRT1	80.41; 76.0 kDa[1] 	Nucleus	Deacetylase	p53, FOXO1, 3 & 4, PARP-1; APE1; DNA-PK; RARβ, PGC1α, PPARγ, NFκB, IGF1, histone H1, H3, H4
SIRT2	43.2; 39.5 kDa[2] 	Cytoplasm	Deacetylase	Histone H4, α-tubulin
SIRT3	28.8 kDa; 36.6 kDa[3] ; 43.6 kDa[14] 	Mitochondria	Deacetylase, ADP-ribosyltransferase	Acetyl-coA synthetase, glutamate dehydrogenase, Ku70, isocitrate dehydrogenase
SIRT4	35kDa[15] to 47.3 kDa[4] 	Mitochondria	ADP-ribosyltransferase	Glutamate dehydrogenase
SIRT5	33.8 kDa[5] 	Mitochondria, cytosol[11]	Deacetylase, demalonylase, desuccinylase[10]	Cytochrome c; carbamoyl phosphate synthetase 1; urate oxidase
SIRT6	39.1 kDa[6] 	Nucleus[12], synaptosomes[13]	Deacetylase, ADP-ribosyltransferase	Histone H3; PARP-1; DNA-PK
SIRT7	44.9 kDa[7] 	Nucleus	Deacetylase[9]	RNA Pol I complex; RNA Pol II complex; histone H3[9]; chromatin remodelling proteins[8]

[1]*Mouse; two alternative splicing variants predicted* ***in silico****; Measured MW ~120 kDa [230].*
[2]*Human; two alternative splicing variants predicted [231].*
[3]*Mouse; two alternative splicing variants predicted [232].*
[4]*Mouse [233].*
[5]*Human [234]; http://www.uniprot.org/uniprot/Q9NXA8#Q9NXA8*
[6]*Human [235].*
[7]*Human [236].*
[8]*[237].*
[9]*[238].*
[10]*[6].*
[11]*[239].*
[12]*[7].*
[13]*[240].*
[14]*[241].*
[15]*[242].*

and the function of macro-domain histone proteins [197]. Nicotinamide in turn is also used to re-synthesize NAD^+, and this aspect has additional importance for SIRT activity. However, despite the significant sequence homology between sirtuins, not all of them are deacetylases, and some display other enzymatic activities (Table I). SIRT5 has been found to remove succinyl and malonyl groups from lysines in proteins [47]. SIRT3 and SIRT6 can ADP-ribosylate proteins [113,182] in addition to their deacetylase function [53,90]. Moreover, SIRT4 displays protein mono(ADP-ribosyl)transferase activity and no detectable deacetylation capability [5,71].

Despite the somewhat misleading 'histone deacetylase' term, sirtuins also (un)modify a vast spectrum of non-histone proteins. The targets of SIRT1, which is by far the best characterized sirtuin, include histones, a broad range of stress signalling proteins, and transcription factors (TFs) (Table I). SIRT1 is mainly involved in the regulation of the stress response and macromolecular repair (through its influence on p53 [64], heat shock factor HSF1 [114], forkhead box subgroup O – FOXO proteins [25], peroxisome proliferator-activated receptor – PPAR family [159], Ku70 [85]), anti-inflammatory response (via NF-κB [136,230]), exerts a pro-survival influence (through IIS – insulin/IGF-I signalling [210]), and modulates the generation of mitochondria [66]. Long-term experimental SIRT1 activation *in vivo* is able to retard the onset of age-related metabolic stress and mortality [136]. Its roles in neuronal plasticity/learning and memory phenomena have also been demonstrated [59].

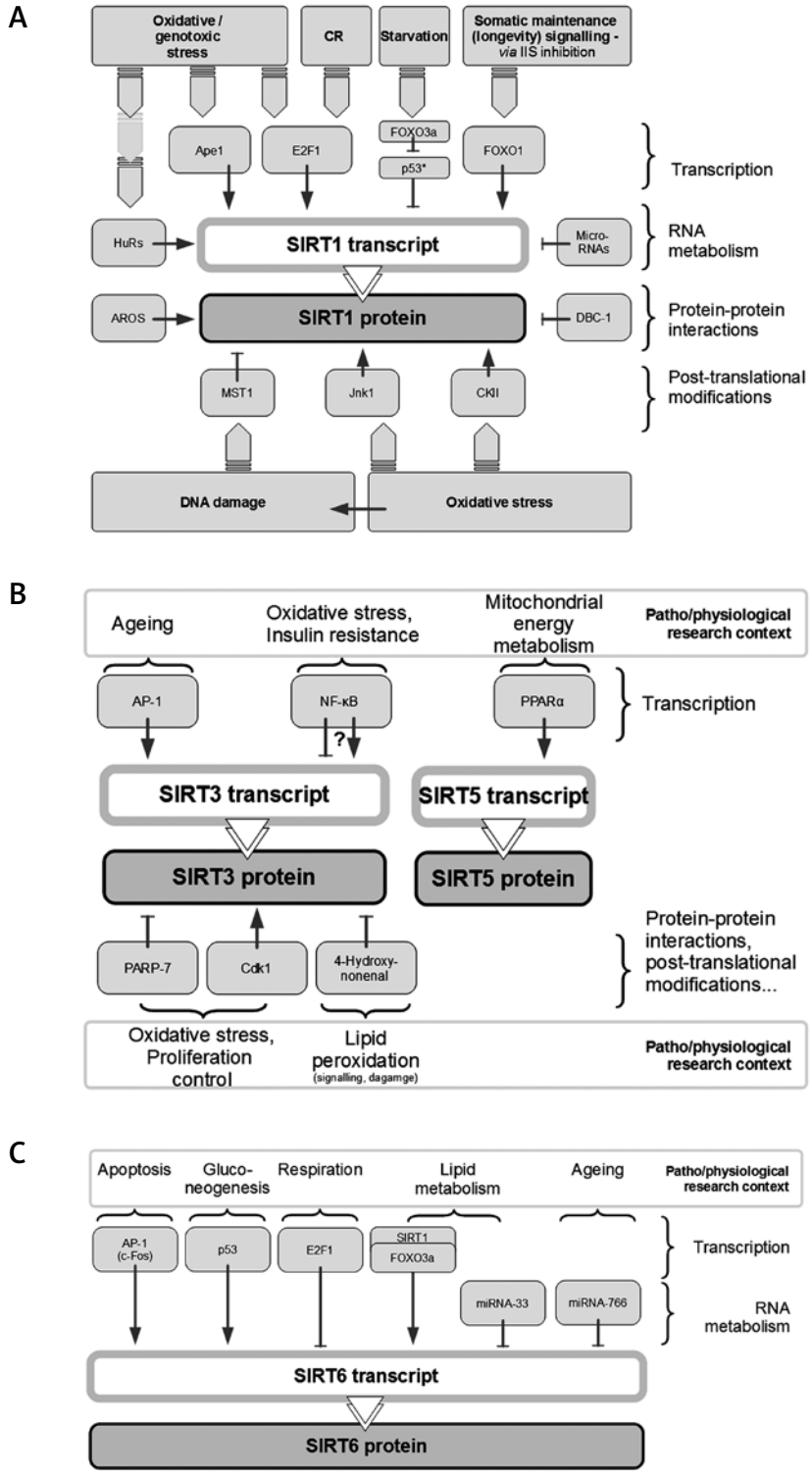
The extensive links of sirtuins with stress signalling, cellular metabolism rates and energy status parallel their cross-talk with the family of poly(ADP-ribose) polymerases (PARPs). PARP-1, the oldest known and best described member of the family, is a 113 kDa protein (in humans) involved in the regulation of chromatin structure, DNA repair, gene expression, and cell death. Its moderate activation is necessary for cellular survival under stress [60]. However, PARP-1 overactivation by glutamate-evoked NO (nitric oxide) production mediates neuronal death in a number of pathological conditions [2,43,188]. The complexity of the enzyme's engagement in the modulation of the cell survival/death equilibrium is additionally reflected by the large changes of its stress response capacity with age [189]. Moreover, the activity of PARPs can be influenced by glutamatergic, cholinergic and possibly other neurotransmission systems [3,63,142], although the significance of this dependency is not fully understood.

An array of interactions has been identified between PARPs and sirtuins, adding to the multiple already described levels of sirtuin regulation (Fig. 1), with increasingly recognized significance for the stress response, metabolic regulation and survival/death decisions.

The multiple levels of sirtuin regulation

SIRT1 to -7 are expressed in the brain and undergo regulation in response to a number of stimuli leading to high regional and developmental variation [169,209] which is modified in the course of ageing [23] and numerous diseases. The transcriptional and post-transcriptional regulation of sirtuins (Fig. 1A-C) occurs at all levels from mRNA expression to post-translational modifications and protein-protein binding.

– A reciprocal relationship links sirtuins with TFs from the FOXO family. Although the majority of findings point to the influence of sirtuin on FOXOs (described below), there are results indicating that FOXOs are able to modulate sirtuin signalling (Fig. 1A, C). The SIRT-1 gene contains several functional FOXO-responsive elements [219]. The signalling between sirtuins and FOXOs extensively cross-talks with the p53 pathway (Fig. 1A, C, Fig. 3A, B). The SIRT1 promoter contains p53-binding sites; p53 interacts there with FOXO3a, mediating the induction of SIRT1 expression by caloric restriction (CR) [144]. In the regulation of glucose metabolism, SIRT6 is important for the p53-dependent nuclear sequestration of FOXO1 [235]. p53 potentially could also impact sirtuins through its links with microRNAs, especially with the *miR-34* family [171].
– A feedback mechanism links SIRT1 with the activity of E2F1 (E2 promoter binding factor), which senses stress conditions (oxidative/stress, CR) [206]: E2F1 activates SIRT1 gene transcription, while SIRT1 exerts feedback inhibition on its TF activity. E2F1 also suppresses *Sirt6* expression, relieving the sirtuin's negative influence on glycolysis in cancer cells [217].
– Oxidative stress activates SIRT1 expression via APE1 (apurinic/apyrimidinic endonuclease-1), a DNA repair endonuclease that possesses much less understood secondary activity as a gene expression regulator [7].



AP-1 – activator protein-1, APE1 – apurinic/apyrimidinic endonuclease-1, AROS – active regulator of SIRT1, CKII – casein kinase II, CR – caloric restriction, Cdk1 – cyclin-dependent kinase 1, DBC-1 – deleted in breast cancer-1, E2F1 – E2 promoter binding factor 1, FOXO – forkhead box subgroup O, HuRs – Hu RNA-binding proteins, Jnk – Jun N-terminal kinase, MST1 – mammalian sterile 20-like kinase 1, NF-κB – nuclear factor κB, PPAR – peroxisome proliferator-activated receptor

**Only selected aspects of p53-dependent modulation are shown; p53 binds a number of sites in the SIRT1 gene, with varying influence on its RNA synthesis and splicing.*

Fig. 1. The multiple levels of sirtuin regulation. **A**) SIRT1, **B**) SIRT3, SIRT5, **C**) SIRT6.

Apart from transcriptional regulation, sirtuin expression has been described to undergo modulation by RNA-binding proteins and non-coding regulatory RNAs.

– The stress-modulated HuR proteins (Hu antigen R, the name derived from the role in the paraneoplastic neurological Hu syndrome) stabilise *Sirt1* mRNA [30] and can influence its alternative splicing [238].
– *Sirt1* mRNA is down-regulated by an antisense long non-coding RNA [214].
– A number of microRNAs also reduce *Sirt1* expression [175], notably in the context of metabolic disturbances, i.e. in the course of obesity-induced changes in fat storage, regulation of mitochondrial numbers, and oxidative energetic metabolism [57]. Persistent down-regulation of *Sirt1* is also observed in ageing. Like in obesity [57], it is caused by elevated *miRNA-34a* [106,184], a proposed brain ageing marker [108] which is capable of modulating cellular senescence [9,83]. A similar effect on senescence has been noted for other microRNAs that target *Sirt1*: *miRNA-22* [81,241] and *miRNA-217* [129]. *Sirt-1* reduction by up-regulated miRNA (*miR-181*) also occurs in the hippocampus of a mouse AD model (3×Tg) [170]. Sirtuin regulation by microRNAs might be in fact a widespread phenomenon in inflammatory and thus possibly neurodegenerative conditions: links exist between *miRNA-34a*, *-132*, *-138*, *-217*, *-373*- and *-520c*-mediated *Sirt1* reduction with NF-κB signalling (at least in the periphery) [49,115,191,220,231], and a reciprocal impact of NF-κB on *Sirt1* expression via miRNA has been noted [94]. Some of the *Sirt1*-regulating miRNAs also respond to oxidative stress, further supporting their potential involvement in neurodegenerative insults [34].

  Apart from Sirt1, also Sirt6 undergoes regulation by microRNAs. Although the results are much less numerous, they also suggest links with aging/senescence and metabolic regulation [37]. Notably, potential feedback regulation between Sirt6 and miRNA-766 modifies the former's role in aging. SIRT6 undergoes reduction by miR-766; with increasing donor age, the re-programming potential of human fibroblasts and the SIRT6 levels fall while miRNA-766 increases. The SIRT6 3'-untranslated region binds miRNA-766 and the microRNA reduces both SIRT6 expression and fibroblast re-programming potential. In turn, SIRT6 reduction could be linked to the increased acetylation of histones observed during ageing in the gene coding for miR-766 [180]. Besides direct suppression, microRNAs can also impact sirtuins indirectly via down-regulation of NAD+ biosynthesis [36], or by affecting IIS components [89], and can mediate IIS' modulation of sirtuins [176].

Beyond the translational level SIRT1 protein binds AROS (active regulator of SIRT1), a protein capable of differentiating its impact upon sirtuin activity depending on the cell status. In response to genotoxic insults in cancer cells AROS supports the inhibitory influence of SIRT1 on p53 [99], while in normal cells the interaction is weak and incapable of modifying SIRT1 activity [102]. SIRT1 also interacts with DBC-1 (deleted in breast cancer-1), which inhibits its enzymatic activity and anti-apoptotic influence, also in a manner dependent on cell phenotype (normal vs. transformed) [10].

SIRT1 protein also undergoes a number of covalent modifications.

– Its nuclear translocation and activation in conditions of oxidative stress is mediated by JNK1 (Jun N-terminal kinase 1)-catalysed phosphorylation [143]. Inhibition of DNA damage-induced, p53-dependent apoptosis by SIRT1 occurs after its phosphorylation by CKII (casein kinase II) [93]. The pro-survival SIRT1 activation also takes place in response to its phosphorylation by DYRK1 and DYRK3 (dual specificity tyrosine phosphorylation regulated kinases) [68]. However, DNA damage may also lead to SIRT1 inhibition, which is done by MST1 (mammalian sterile 20-like kinase 1) [232].
– Lysine SUMOylation (small ubiquitin-like modifier) is an activating event important for SIRT1 activity towards p53; de-SUMOylation of SIRT1 overrides its anti-apoptotic activity in stress conditions [227].
– Activating S-glutathionylation of SIRT1 by the redox-modulated enzyme glutaredoxin 2 may be critical to the sirtuin's role in vascular development [24].

Besides these specific mechanisms of regulation, the activity of sirtuins has also been shown to be post-translationally de-stabilized and inhibited by products of oxidative damage to lipids such as 4-hydroxynonenal [27,56].

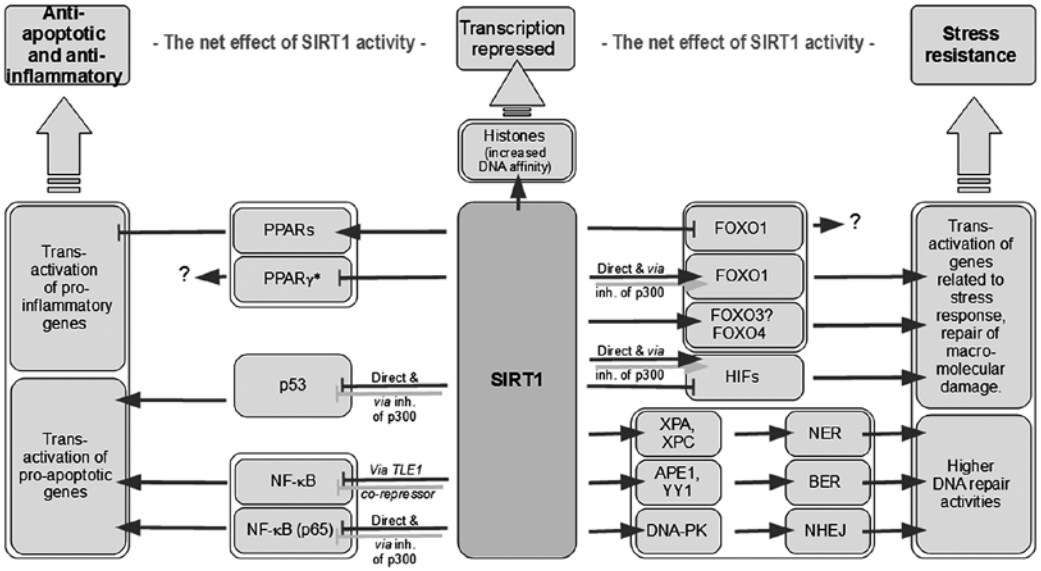
A number of further protein-protein interactions and post-translational sirtuin modifications are described below. They form part of the multiple feedback regulatory loops connecting sirtuins with their signalling targets.

Transcriptional and post-transcriptional regulators as sirtuin targets

Sirtuins post-translationally regulate vast numbers of proteins including histones, TFs and co-activators, and enzymes (Table I, Fig. 2). Deacetylation restores the affinity of inactivated core histones to DNA, thus allowing general gene silencing [82] (Fig. 2). This mechanisms may constitute one of the ways sirtuins reduce overall metabolic rates [145] and improve neuron survival. However, binding to specific promoters (e.g. via interactions with sequence-specific proteins there) allows sirtuins to modify histones and affect chromatin structure also in a localized manner [21].

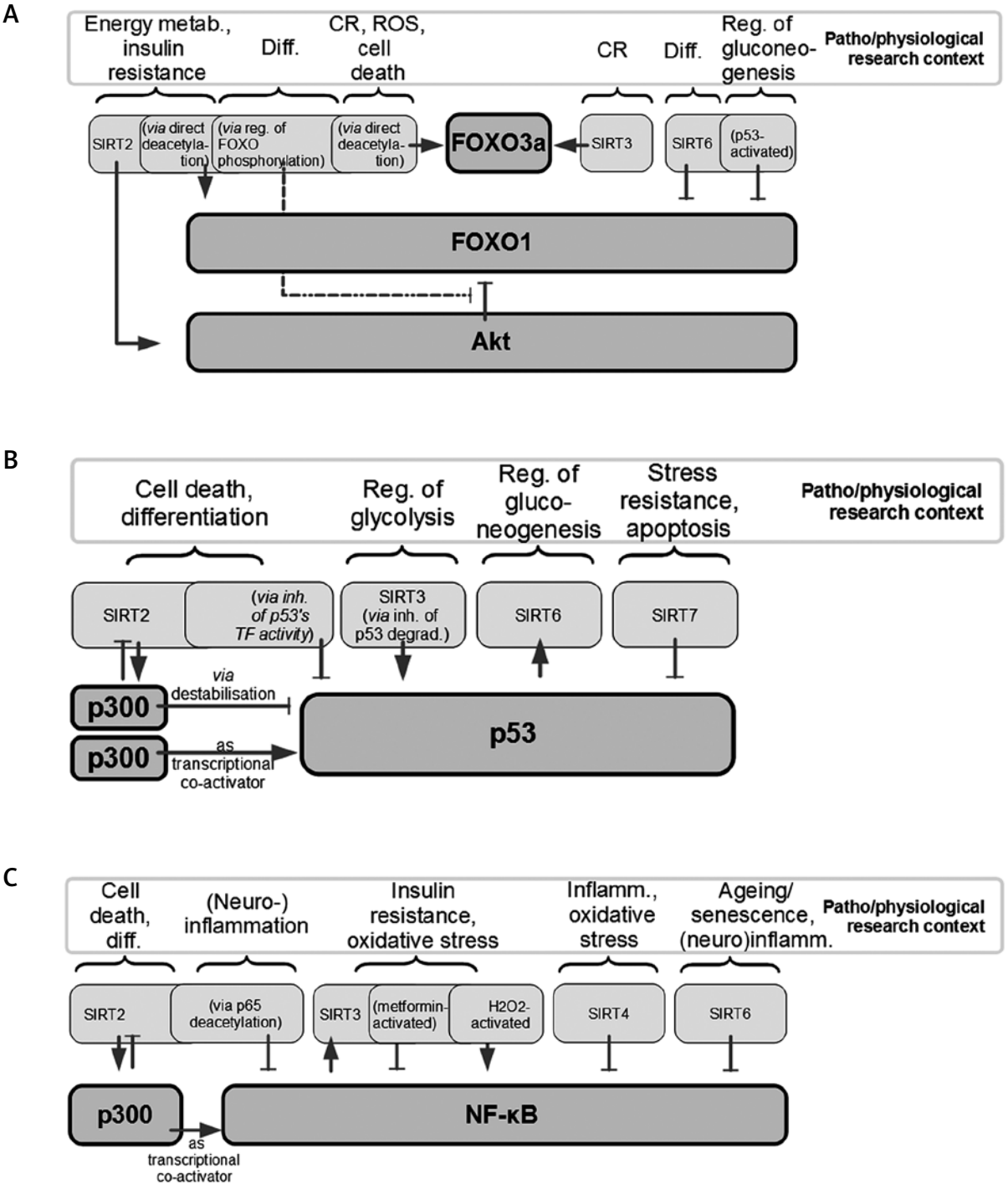
Interactions with transcription factors is a major mechanism of sirtuins' influence on metabolism and cell fate. The links between TFs of the FOXO family and sirtuins are extensive (Figs. 2 and 3) [219]. Sirtuins modulate FOXOs directly; moreover, sirtuins also add another level of FOXO regulation via modulation of the IIS pathway:

– SIRT1 deacetylates FOXO1 (Fig. 2) with varying effects on its activity: FOXO1 deacetylation increases its TF activity on SIRT1 and some other genes [219] while suppressing it in other situations (possibly due to different protein complex composition/promoter sequence) [228]. SIRT1 also modulates FOXO1 through enhancement of its nuclear presence [55] and probably changes its target gene spectrum [62]. SIRT2 in turn facilitates DNA binding by FOXOs [207]; deacetylation by SIRT2 inhibits the Akt-mediated nuclear sequestration of FOXO1 [88] (Fig. 3C). This enhances the inhibitory influence FOXO1 exerts on PPARγ, thus mediating the changes in adipose metabolism induced by nutrient deprivation or exposure to low temperature [208]. FOXO3 and FOXO4 are also deacetylated by SIRT1 and 2; this exerts a complex influence on their downstream mediators including superoxide dismutase, $p27^{kip1}$, and GADD45 (growth arrest and DNA damage 45) and target processes such as stress resistance cell cycle and death [25,78,101,173,207].
SIRT3 is a necessary partner in the mitochondrial gene expression control by FOXO3a. CR (caloric restriction) causes FOXO3a to accumulate in mitochondria, where it interacts with SIRT3 and with RNA polymerase to activate gene expression, which boosts mitochondrial respiration [155].
– FOXOs also are modulated indirectly via insulin(-like) signalling (IIS)/Akt. The outcome varies depending on the different sirtuins involved and cell lines used.



**PPARγ inhibition by SIRT1 exerts a much less clearly understood immunomodulatory role.*

Fig. 2. SIRT1 signalling targets with potential impact on neurodegenerative processes. According to [234], modified. BER, base excision (DNA) repair; DNA-PK, DNA-dependent protein kinase; inh., inhibition; NER, nucleotide excision repair; NHEJ, non-homologous end-joining (DNA repair); XPA, xeroderma pigmentosum group A; XPC, xeroderma pigmentosum group A; YY1, yin yang 1.



CR – caloric restriction, Diff. – cellular differentiation, inh. – inhibition, reg. – regulation, ROS – reactive oxygen species

Fig. 3. Signalling network of SIRT2 to -7. **A**) Interactions of sirtuins with p53 and its co-activator p300. **B**) Sirtuins, NF-κB and its co-activator p300. **C**) FOXO transcription factors and sirtuins.

SIRT1 enhances IIS signalling – it occurs through at least two ways:

- deacetylation of p53 leads to reduction of its protein levels, relieving IIS inhibition by the IGF-binding protein-3 [215];
- SIRT1 can also directly deacetylate Akt, restoring its ability to bind phosphoinositides and become activated by phosphoinositide-dependent protein kinase 1 [192]).

These dependencies have already been confirmed to impact metabolic deregulation, cardiac dysfunctions and tumour formation, and might result in inhibition of the IIS target FOXO1 [67].

In addition to SIRT1, also SIRT2 can physically interact with Akt; the sirtuins may be *exchanged* depending on the activation state of the IIS pathways. SIRT2 is necessary for full activation of Akt in response to insulin/growth factor signalling, while a deficient Akt response is noted in metabolic disturbances including insulin resistance [164]. Together with the above-mentioned results it suggests an image of extremely tightly regulated, multi-level influence of SIRT2 on FOXO-mediated events.

Besides direct interactions with FOXO3a, SIRT3 also has a potential indirect impact on FOXOs by moderating Akt overactivation by ROS [158].

SIRT6 has been shown to suppress IIS signalling-modulated genes [194], resulting in reduced FOXO1 expression [193]. SIRT6 also mediates p53-induced nuclear sequestration of FOXO1 in the regulation of energy metabolism [235].

The FOXOs' extensive interactions with various stress signalling and protein turnover pathways allow them to mediate a broad spectrum of homeostatic responses. Their role in the longevity/neuroprotective effects of IIS (insulin/insulin-like signalling)-dependent modulation of stress resistance is of particular importance. FOXOs' links may be crucial for the pathomechanism of a number of (mostly age-related) diseases associated with disturbed somatic maintenance, including AD, leading to suggestions that they could constitute targetable *integrating factors* influencing various neurodegenerative mechanisms [125].

The highly conserved tumour suppressor p53 and its paralogues (p63, p73) have long been known to take part in the DNA damage response, especially cell cycle arrest, cellular senescence, and death. These TFs are also capable of direct modulation of DNA repair genes and proteins [146]. Moreover, the p53 family could also be linked to ageing at the organism level [146,160]. Other emerging roles of p53 in glucose and lipid metabolism, ROS signalling and oxidative stress [64] suggest a significant functional overlap with SIRT pathways. p53 undergoes extensive post-translational modifications of several types; this makes it sensitive inter alia to inhibition and destabilisation via sirtuin-catalysed deacetylation (Figs. 2 and 3B). Moreover, SIRT1 binds and inhibits p53 promoter [52]; SIRT1's interactions with the senescence modulator *miRNA-34a* also allow a post-transcriptional influence on p53 [77,229], while both SIRT1 and p53 can be miRNA-34a's targets as well [229]. SIRT1 expression increases in the conditions of H_2O_2-induced oxidative stress, and sirtuin activation inhibits p53-dependent apoptosis [240]. Down-regulation of SIRT1's influence on p53 mediates responses to several stressors in other cell types [204,224] and to a range of age/hyperglycaemia-related vascular endothelial pathologies [107,233]. Similar mechanisms of age-related, glucose-elicited damage might also be involved in neurodegenerative disorders along with generalized oxidative/nitrosative stress. Indeed, it is suggested that a significant part of SIRT1's neuroprotective signalling could be mediated through p53 [234], including SIRT1's roles in AD and PD [39,98,151]. Sirtuin-mediated changes in p53 stability and TF activity also occur in an experimental model of hippocampal neuronal plasticity [112].

Less characterised sirtuin family members have also been noted to signal through p53 (Fig. 3B). Administration of a SIRT2 inhibitor resulted in increased p53 acetylation [226]. The influence of SIRT2 on p53 appears to be complex; it can either block its trans-activating influence on gene expression (via direct deacetylation) [87], or enhance its degradation [18], sometimes only when working in concert with SIRT1 [153]. SIRT3 is able to modulate p53 degradation mediated by MDM2 (mouse double minute 2 homolog), and the influence p53's role as a metabolic regulator [237]. SIRT6 also takes part in p53's modulation of energy metabolism via nuclear sequestration of FOXO1 [235]. A recently identified cytoplasmic pool of SIRT7 binds p53 in a complex with TPPII (tripeptidyl-peptidase II, also capable of modulating NF-κB) [141].

Moreover, sirtuins also interact with an important partner of p53 and NF-κB, p300 (Figs. 2 and 3B). p300 is a transcriptional co-activator able to block the interaction of histones with DNA through their acetylation. However, p300 is also able to reduce p53 stability via its negative regulator MDM2, in a manner that appears to depend on the type of upstream signals or on cell type [109]. SIRT1 can inhibit the acetylating activity of p300 [22], which might exert a pro-survival influence in AD [48]. However, the influence of SIRT2 on p300 appears to be opposite to that of SIRT1 [18], as mentioned above in the context of p53 degradation. In turn, p300 inhibits SIRT2 through acetylation, attenuating its negative influence on p53 [73].

The NF-κB pathway has been proposed to be a nearly universal booster of the innate immunity and pro-inflammatory responses that largely counteracts the FOXO system [173]. NF-κB activity often significantly contributes to neuronal damage in AD, ischaemia, and other disorders; the blockage of NF-κB-dependent gene transactivation by sirtuin signalling offers neuroprotection in amyloid β (Aβ) toxicity [32]. Moreover, the regulatory activities of NF-κB are altered during ageing [76], while NF-κB is capable of modulation of ageing/senescence largely via its sirtuin interactions [96]. Despite varying intracellular localisations and interactions repertoires, most sirtuins modulate NF-κB, often in a negative manner.

- SIRT1 inhibits NF-κB (Fig. 2) through:
  - deacetylation of the RelA subunit of NF-κB (this RelA modification is dependent on p300 or PCAF – the p300/CBP-associated factor) [230];
  - interactions with NF-κB's transcriptional co-repressor TLE1 (transducin-like enhancer protein 1) [61].
- SIRT2 is also able to inhibit the TF via deacetylation of p65 (Lys 310) (Fig. 3C); [117]. However, its known positive influence on p300 [18] suggests that the regulatory interactions between these proteins might be significantly more complex than currently known.
- SIRT3, itself a transcriptional target of NF-κB [116], mediates the inhibitory effect of metformin on NF-κB in a cellular model of oxidative stress and insulin resistance [185]. In contrast, in a different cell line SIRT3 has been found to activate H_2O_2-induced, NF-κB-dependent expression of, inter alia, superoxide dismutase [31], strongly suggesting that the interaction is promoter-specific and/or modified by further interactions.
- SIRT4 blocks the degradation of IκB (inhibitor of κB) [33] and reduces the nuclear translocation of NF-κB and resulting pro-oxidative and pro-inflammatory phenotype [196].
- SIRT6 binds RelA and is able to repress NF-κB target promoters that become activated during aging [96], and can delay cellular senescence [218]. However, the effect has not been observed in some other models/conditions [65], possibly due to the dynamic and interdependent character of the interaction with NF-κB [97].
- Besides these, the sirtuin target FoxO3a interacts with NF-κB [111] and with its PI-3K (phosphoinositide 3-kinase)/Akt-dependent upstream activator IKKβ (IκB kinase β) [154], which suggests additional paths of influence.

Sirtuins thus simultaneously impact the pro-inflammatory and potentially deleterious actions of NF-κB and activate FOXO somatic maintenance signalling [173]. The effect may modulate the stress resistance signals of IIS, which is able to regulate both FOXOs and NF-κB [70].

The family of hypoxia-inducible factors (HIFs) modulates, inter alia, energy metabolism and the stress response depending on oxygen concentration. SIRT1 inhibits HIF1 [110] but activates HIF2 (Fig. 2) [45], while SIRT6 may be a co-repressor for HIF-1α [242]. The significance of this discrepancy has not been extensively tested, but invertebrate data suggest engagement of HIFs in the modulation of ageing rates. Moreover, HIFs' transactivation targets include genes with known neuroprotective products, although it has been suggested that these TFs might play either protective or detrimental roles [54,86,140, 223].

The sirtuin interaction partners peroxisome proliferator-activated receptors (PPARα, PPARβ/δ, PPARγ) are a class of nuclear receptors, TFs whose intracellular localization and activity are regulated by ligand binding. PPAR roles include metabolic regulation in response to environmental cues, proliferation control, and cardiovascular homoeostasis; they modulate oxidative stress, inflammation, or insulin resistance. PPARs can antagonize neurodegeneration in AD/PD/cerebral ischaemia/brain trauma [139,161]. They may also be of therapeutic interest in the metabolic syndrome [58]. PPARs also modulate inflammation that partially mediates these pathologies

[58,139,161,165]. PPARs may also constitute plausible targets in diabetes and diabetes-linked neuropathy.

SIRT1 is involved in a two-directional interaction with PPARα. SIRT1 binds PPARα on its DNA response elements. The binding is tightly regulated depending on the DNA sequence [150]. The resulting deacetylation enhances PPARα activity [167] (Fig. 2). SIRT1 also facilitates the protein-protein interaction between PPARα and NF-κB (p65) [159]. *Sirt1* and *PPARα* genes are regulated in a coordinate manner by the ageing-linked *miRNA-22* [69] and *miRNA-34a* [44], while SIRT1 is able to modulate *miRNA-34a* in concert with p53 [77]. This suggests a precisely regulated feedback mechanism, but the potentially significant topic has not been explored much further. The widely used natural sirtuin activator resveratrol has been shown to bind and activate PPARα directly [195]. SIRT1 also reverses the p300-dependent acetylation of PPARγ [72] and seems to inhibit its transactivation function [156]. PPARα, PPARγ, and PPARδ agonists were able to increase SIRT1 expression [35,100,213]; PPARα activation also blocked SIRT1 export from the nucleus [213]. The *Sirt5* gene promoter contains potential PPARα-responsive sequences, and the PPARα agonist is able to increase its expression [26]. Besides SIRT1, also SIRT6 displays links with the signalling network of PPARs [225].

Not surprisingly, the interactions between sirtuin and PPAR pathways profoundly modulate energy metabolism [26] and appear to have an impact on a number of pathophysiological conditions (Fig. 2). SIRT1 is involved in a potential senescence-related feedback interaction with PPARγ [72]. PPARγ is widely present in the brain (neurons and microglia), lowers local levels of iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase-2), and might constitute an effective target in the treatment of ischaemia [42]. Moreover, the impact of metabolic stress on SIRT1-PPARγ signalling has been suggested to modulate β-secretase and thus the rate of amyloid β production in AD [211]. Additionally, differential expression of *Sirt1* and *PPARγ* has been noted in Aβ-treated glia, which would fit the above-mentioned antagonistic regulation of *Sirt1* by PPARγ; it has been proposed to mediate the neuroprotective reaction of astrocytes elicited by *in vitro* Aβ treatment [4]. Outside the brain, PPARα is one of the effectors of SIRT1's cardioprotective actions [159], although in some circumstances the SIRT1-PPARα interaction may actually promote heart hypertrophy [149].

PPARγ co-activator 1α (PGC-1α) is an important player in the PPAR network, capable of modulating respiration/oxidative stress resistance [183] and neuronal survival. Its ASN-induced [221] disturbances may be implicated in the pathogenesis of Parkinson's disease [40], and PGC-1α has been proposed as a therapeutic target in PD [239].

PGC-1α regulates mitochondrial biogenesis by working together with SIRT1 [8]. SIRT1 reverses the p300-mediated acetylation of PGC-1α in a unique nuclear-mitochondrial cross-talk [8]. Additionally, SIRT1 binds the PGC-1α promoter and takes part in its positive regulation loop [6]. An interesting interaction takes place between PGC-1α and SIRT6: the sirtuin deacetylates and activates the acetyltransferase GCN5 (general control non-repressed protein 5), which leads to increased acetylation of PGC-1α and inhibition of its transcriptional co-activator function [46]. PGC-1 has been proposed to mediate the protective SIRT1/PPAR-dependent action of Aβ-challenged astrocytes towards neurons (the increase of neuronal biogenesis of mitochondria and survival in the co-culture with astroglia) [4].

AP-1 (activator protein-1) is a dimeric TF consisting of proteins from Fos and Jun families, with a wide variety of roles in development, cell proliferation, survival and migration, and ROS (reactive oxygen species)/low oxygen signalling [133,181]. AP-1 has been implicated in the control of brain plasticity and damage [162], including a hypothesized central role in AD/PD [166], and of numerous peripheral functions.

SIRT1 exerts a varied, context-specific influence on the transactivation of genes by AP-1 to modulate processes ranging from cyclooxygenase expression to pathogen replication [168,236]. The *Sirt3* gene contains an AP-1 binding site [15] in its longevity-correlating intronic enhancer [16]. As alleles displaying the lowest activity of this enhancer are notably absent from the oldest old group, the interaction may have strong significance for the modulation of human lifespan [16]. SIRT6 (which has also been associated with lifespan modulation via IIS [92]) binds c-Jun, undergoes recruitment to its target promoters and reduces their activity via histone deacetylation [193]. c-Fos is able to induce transcription of the *Sirt6* gene; the sirtuin in turn represses survivin via NF-κB. The significance of apoptotic resistance regulation

by AP-1–SIRT6 signalling in the survival of pre-neoplastic lesions is further strengthened by the observation that both display specific expression patterns in pathological tissue samples [134].

Further elucidation should cast more light on sirtuin–AP-1 cross-talk, which could have significant consequences for, inter alia, brain development, homeostasis, learning and memory, and neurodegenerative conditions [162].

While microRNAs are an emerging mechanism of sirtuins' gene regulation, relatively little is known about the possible specific impact of sirtuins on miRNA metabolism (see above, PPAR section).

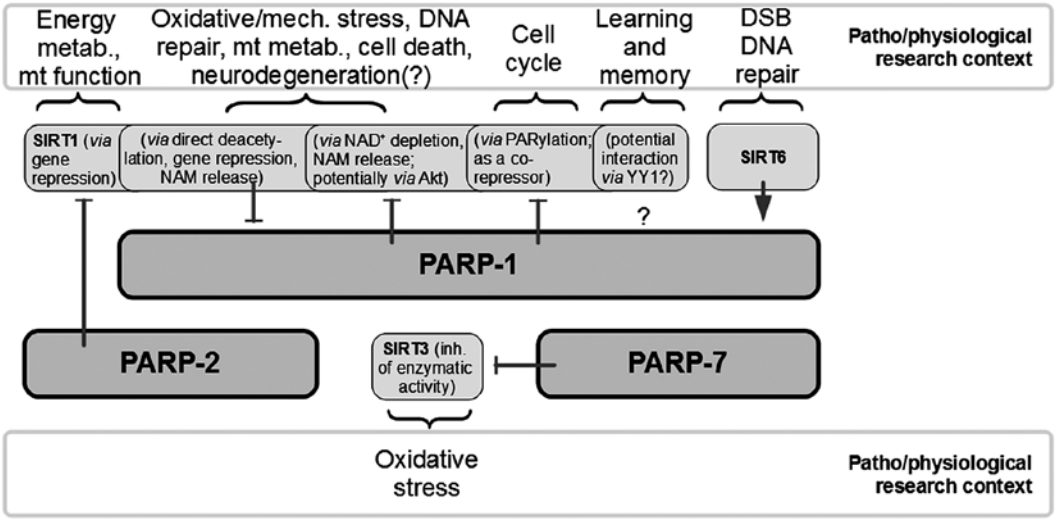
Sirtuins and DNA repair

The interaction with stress-related TFs may have vast significance for the regulation of DNA repair by sirtuins. Additionally, some TFs (such as FOXO3a, p53, NF-κB, E2F1, Sp1 – specificity protein-1, or some nuclear receptors) have also been implicated in the repair process itself, possibly via relaxation of chromatin structure, though the matter still needs some clarification [124,201]. However, sirtuins are able to directly influence proteins involved in the repair of macromolecular damage.

– Apurinic/apyrimidinic endonuclease 1 (APE1) is one of the crucial factors involved in the base excision repair (BER) pathway which removes the ubiquitous products of free radical-related damage from DNA. APE1 has been shown to be inactivated by acetylation at multiple sites [222]. SIRT1 binds APE1 and deacetylates two of its lysines. This stimulates APE1 to bind its partner XRCC1 (X-ray cross-complementing-1) and increases its activity in the BER complex. The net effect of sirtuin-mediated stimulation of APE1 is an improvement of the efficiency of this crucial repair mechanism, as measured by reduced levels of abasic sites in DNA [222].
– SIRT1 is also known to facilitate the activity of nucleotide excision repair (NER), a mechanism that removes a wide spectrum of DNA lesions/adducts and has demonstrated crucial significance in cancer prevention. SIRT1 deacetylates two lysines of the core NER protein XPA (xeroderma pigmentosum group A); this reaction is necessary for the full efficiency of UV damage removal [50]. SIRT1 also relieves the repression of the *XPC* gene coding for a protein that recognizes DNA lesion and recruits other NER components [135].

Table II. Mammalian PARP enzymes. According to [79,205], modified

Old name	New unified name	Activity – measured	Activity – postulated
PARP1	ARTD1	PARylation	
PARP2	ARTD2	PARylation	
PARP3	ARTD3	Mono(ADP-ribosyl)ation	PARylation
vPARP/PARP4	ARTD4	Mono(ADP-ribosyl)ation	PARylation
Tankyrase-1/PARP5a	ARTD5	PARylation	
Tankyrase-2/PARP5b/PARP6	ARTD6	PARylation	
PARP6	ARTD17	Mono(ADP-ribosyl)ation	
PARP7	ARTD14	Mono(ADP-ribosyl)ation	
PARP8	ARTD16	Mono(ADP-ribosyl)ation	
PARP9	ARTD9	Not detected	
PARP10	ARTD10	Mono(ADP-ribosyl)ation	
PARP11	ARTD11	Mono(ADP-ribosyl)ation	
PARP12	ARTD12	Mono(ADP-ribosyl)ation	
PARP13	ARTD13	Not detected	Mono(ADP-ribosyl)ation (mouse)
PARP14	ARTD8	Mono(ADP-ribosyl)ation	
PARP15	ARTD7	Mono(ADP-ribosyl)ation	
PARP16	ARTD15	Mono(ADP-ribosyl)ation	



Mt metab. – mitochondrial metabolic regulation, mech. stress – mechanical stress, NAM – nicotinamide

Fig. 4. Interactions between sirtuins and poly(ADP-ribose) polymerases.

– DNA-dependent protein kinase (DNA-PK) is involved in non-homologous end-joining (NHEJ) repair, which neutralises double-strand breaks, a highly mutagenic and lethal type of DNA lesion. DNA-PK is also an anti-apoptotic signalling protein. The Ku70 subunit of DNA-PK undergoes inhibitory acetylation on at least 8 lysines by, inter alia, PCAF (p300/CBP-associated factor), a histone acetyltransferase that also collaborates in DNA damage signalling with p53 [179]. SIRT1 associates with and deacetylates Ku70, thus activating DNA-PK in both its roles [41,85]. SIRT6 also appears to be involved in DNA maintenance [21] and modulates the binding of DNA-PK to regions of DNA double-strand breaks, thus facilitating the removal of these deleterious lesions [127].
– SIRT6 was observed to be an important factor in telomere maintenance through deacetylation of histone H3. Moreover, SIRT6 appears to stabilize the association of Werner protein with telomeric chromatin, further contributing to the regulation of its architecture [131].

Sirtuins and PARPs

Sirtuins interact in a complex way with the versatile family of Poly(ADP-ribose) polymerases (PARPs) (Table II, Fig. 4). The roles of various PARPs include DNA repair (modulated chiefly by PARP-1 to -3), regulation of gene transcription (PARP-1, -2, and structurally different *macroPARPs*: PARP-9, -14, -15) [128], RNA processing in the nucleus and cytoplasm (PARP-1, -7, -10, -12 to -15, tankyrase-1) [19], cellular RNA transport (probable role of vault PARP and PARP-10) [1], cellular transport of proteins (mainly PARP-16) [1], and telomere maintenance (somewhat ambiguously including PARP-1, tankyrase-1 and possibly tankyrase-2) [174,177].

The family's founding member PARP-1 detects DNA damage (single- and double-strand breaks, abnormal spatial structures) and post-translationally modifies histones to locally de-condensate chromatin, thus facilitating access for the repair machinery [190]. It also directly recruits and modulates DNA repair proteins involved in BER, NER, NHEJ, and homologous recombination DNA repair pathways, and numerous signalling proteins [188]. Besides regulating chromatin accessibility [199], PARPs can act more specifically, as activators/co-activators or (co-) repressors for numerous TFs. PARP-1 modulation of transcription factors impacts both gene regulation and the recently identified role of TFs in DNA repair [84,124].

The extensive network of interactions between PARP-1 and the p53 pathway cross-talks with other post-translational modifiers [216], possibly including sirtuins [138], with vast significance for most previously identified PARP functions [74]. The co-operation between PARP-1 and numerous TFs also includes NF-κB and is important for neurodegeneration in Alzheimer's disease [95], for brain ischaemia [80], etc.

Despite the pro-survival physiological significance of PARP-1, its excessive activation by DNA damage induced by ROS/RNS (reactive nitrogen species) [187], Aβ, or mutagens [189] has long been associated with cell death. The long-postulated theory of passive cellular demise via stress-induced energy imbalance suggested that PARP over-activation by intense DNA damage would lead to massive PARylation, depleting cellular stores of NAD^+ and consequently ATP (which is used to re-synthesize it). However, more recent works have suggested that in post-mitotic cells nuclear NAD^+ depletion itself could be more significant, inhibiting some crucial enzymes that utilise the nucleotide as a substrate [157]. PARP-1's K_M towards NAD^+ should be low enough to make it relatively insensitive to the changes of NAD^+ concentration and to allow continued activation despite ongoing metabolic disruption. In contrast, the nuclear SIRT1 displays K_M closer to the reported intracellular NAD^+ levels and thus should be significantly influenced by such pathophysiological changes [28,157]. Indeed, cell death caused by PARP over-activation was rescued by various interventions that boosted NAD^+ levels and occurred only in the presence of the intact SIRT1 orthologue Sir2α [157]. Increased activity of SIRT1 in PARP-$1^{-/-}$ mice was also noted [12]. The PARP–sirtuin substrate competition has already been confirmed to impact SIRT1 downstream events linked to the regulation of cell death/survival [157] or mitochondrial metabolism [12]. Disruption of the SIRT1-PGC-1α axis by (over)activated PARP-1 has been suggested to be of significance for the pathomechanism of several DNA repair disorders accompanied by neurodegeneration where mitochondrial abnormalities may play significant roles [51,178,200]. SIRT1 inhibition via NAD^+ depletion might also mediate other neurodegenerative insults such as the death of hippocampal cells in culture in a model of acute epileptic neuron loss [212].

Sirtuins other than SIRT1 also display K_M that would suggest dependency on PARP-induced NAD^+ fluctuations. However, the phenomenon of inactivation by PARP-mediated substrate competition appears to be restricted to SIRT1. The (in)sensitivity of various sirtuins to competition with PARP-1 might stem from several factors, including their intracellular localisation and their ability or not to pre-bind NAD^+ and thus escape the NAD^+ depletion [28]. Moreover, in some situations sirtuin inhibition by oxidative stress may be direct and not mediated by the competition with PARPs for the substrate [27].

Yet other mechanisms of cross-talk might exist, as both PARP-1 [147,148] and SIRT1 [17] interact with YY1 (yin yang 1). YY1 is an important regulator of miRNAs and protein-coding genes related to neuronal plasticity [59] and degeneration [104] as well as DNA repair [147]. A potentially significant topic for sirtuin regulation is the observed impact of PARP-1 on both upstream modulators and signalling targets of sirtuins. PARP-1 appears to be critically involved in the modulation of Akt activity [91,186]; however, despite its importance for, inter alia, neurodegeneration [130], or ischemic damage [105] the mechanism of this interaction has not been explored further. PARP-1 also directly binds and PARylates FOXO1, leading to suppression of FOXO1-dependent genes [172].

The more favourable K_M of PARP-1 should allow it to *out-perform* SIRT1 in the competition for NAD^+ in all situations [12]. However, both enzymes are able to block each other's activity by releasing the inhibitory by-product nicotinamide [103]. SIRT1 has also been able to mitigate the rapid PARP-1 activation in oxidative (H_2O_2-induced) stress while SIRT1 knock-out has led to enhanced apoptotic signalling and cell loss in these conditions [103]. The results obtained by Rajamohan suggest that depending on the conditions the difference in K_M could be negligible: the value for PARP-1 activated by pERK or the histone acetyltransferase PCAF (p300/CBP-associated factor) is just 10% to 20% lower than that of SIRT1 [163].

The activation of PARP-1 by PCAF in stress conditions occurs via acetylation [163], making it a good substrate for SIRT1. SIRT1 has been shown to interact with and de-acetylate PARP-1 [163], reversing its enzymatic stimulation and reducing it to nearly undetectable levels. Surprisingly, acetylation boosted only the basal activity of PARP-1 and not its maximum, DNA damage-induced activity. However, removal of this modification inhibited PARP's (mechanical stress-related) activation, thus potentially offering some cytoprotective potential [163]. Although the physical interaction between SIRT1 and PARP 1 is dependent on NAD^+ availability and gradually diminishes with its increasing concentration, SIRT1 pre-bound to NAD^+ is still able to bind PARP-1 physically (and possibly deactivate it) despite the lack of substrate. This suggests a potential mechanism for pre-

serving SIRT1 activity despite NAD^+ depletion [163]. Most work on SIRT1-mediated PARP-1 inhibition has been done on cell lines of non-neuronal origin. However, it has been shown that the influence of SIRT1 on PARP-1 can indeed be of significance in oxidative stress conditions, thus raising hopes for using it as a potential target in neurodegeneration. The absence of SIRT1 sensitized the cells via PARP to H_2O_2-induced death [103], while over-expression of SIRT1 in HeLa cells reduced PARP-mediated, DNA damage-induced death in a mode dependent on its deacetylase function [163].

SIRT1 is capable of modulating not only PARP-1 protein but also its gene expression. SIRT1 over-expression in cardiomyocytes has been shown to reduce *PARP-1* gene promoter activity and *PARP-1* mRNA, which translated into lower protein levels; deacetylase activity was necessary for the effect. SIRT1 did not appear to influence the degradation of PARP-1 protein, as shown in experiments with proteasomal and lysosomal inhibitors [163].

Other PARPs (Figs. 1B and 4; Table II), whose activities typically fall well below those of PARP-1, are able to modulate sirtuins in ways independent of NAD^+ fluctuations. [11]. PARP-2 is a direct negative regulator of the SIRT1 promoter, and its impact on the SIRT1 gene has direct consequences for energetic metabolism and mitochondrial function (Fig. 4) [137]. PARP-7, or tetrachlorodibenzo-p-dioxin-inducible poly(ADP-ribose) polymerase (TiPARP), appears to have the ability to inhibit SIRT3 activity (but not mRNA expression) in conditions of oxidative stress (Fig. 4); this leads to reduced expression of superoxide dismutase-2 and might further exacerbate the damage [75].

It is not clear if the acetylated residues present in PARPs other than PARP-1 could be targeted by sirtuins or if these isoforms are able to significantly affect SIRT activities.

The influence of SIRT2 to -7 on PARPs is not fully determined. A rather unusual interaction takes place between SIRT6 and PARP-1 [126]. SIRT6 resides largely in the heterochromatin; it is recruited to double-strand break sites and its expression is enhanced in response to DNA damage. Its stimulatory effect on DNA repair was visible both under resting and stress conditions evoked by paraquat (producing superoxide), neocarzinostatin (a single- and double-strand break inducer) or H_2O_2. SIRT6 physically binds PARP-1 in a manner enhanced by the damage and mono(ADP ribosyl)ates it on Lys521. PARP-1 enzymatic activity is stimulated by this interaction and mediates the positive effect of SIRT6 on the efficiency of NHEJ and homologous recombination repair (Fig. 4); [126]. Although SIRT6 did not influence the acetylation level of PARP1, both SIRT6 enzymatic activities have been found to take part in the regulation of DNA repair [126]. The opposite influence of SIRT1 and -6 on PARP activity prompted Cantó et al. to suggest that these proteins could constitute a signalling switch in the DNA repair network [28]. In an example scenario, ATM (ataxia-telangiectasia mutated), which senses DNA damage, would phosphorylate DBC-1 protein, facilitating its inhibitory influence on SIRT1. This would remove the inhibition of PARP-1, thus leaving only the positive influence of SIRT6 and allowing PARP-1 to efficiently perform its protective function [28].

The described unique characteristics of sirtuins correspond to their broad links to signalling pathways and enzymes involved in cellular maintenance and the stress/damage response. Some sirtuins localise to mitochondria and modulate their biogenesis as well as the function of the respiratory machinery. Moreover, sirtuins are capable of influencing anti-oxidative proteins and the unfolded protein response there, as well as the mitochondrial cell death signalling. A growing body of evidence links sirtuins to aging and neurodegenerative diseases, making these HDACs highly promising research and therapeutic targets.

Acknowledgments

The authors' work is supported by National Science Centre grant 2013/09/B/NZ3/01350.

Disclosure

Authors report no conflict of interest.

References

1. Abd Elmageed ZY, Naura AS, Errami Y, Zerfaoui M. The poly(ADP-ribose) polymerases (PARPs): new roles in intracellular transport. Cell Signal 2012; 24: 1-8.
2. Adamczyk A, Czapski GA, Jeśko H, Strosznajder RP. Non A beta component of Alzheimer's disease amyloid and amyloid beta peptides evoked poly(ADP-ribose) polymerase-dependent release of apoptosis-inducing factor from rat brain mitochondria. J Physiol Pharmacol 2005; 56 Suppl 2: 5-13.
3. Adamczyk A, Jeśko H, Strosznajder RP. Alzheimer's disease related peptides affected cholinergic receptor mediated

poly(ADP-ribose) polymerase activity in the hippocampus. Folia Neuropathol 2005; 43: 139-142.
4. Aguirre-Rueda D, Guerra-Ojeda S, Aldasoro M, Iradi A, Obrador E, Ortega A, Mauricio MD, Vila JM, Valles SL. Astrocytes protect neurons from Aβ1-42 peptide-induced neurotoxicity increasing TFAM and PGC-1 and decreasing PPAR-γ and SIRT-1. Int J Med Sci 2015; 12: 48-56.
5. Ahuja N, Schwer B, Carobbio S, Waltregny D, North BJ, Castronovo V, Maechler P, Verdin E. Regulation of insulin secretion by SIRT4, a mitochondrial ADP-ribosyltransferase. J Biol Chem 2007; 282: 33583-33592.
6. Amat R, Planavila A, Chen SL, Iglesias R, Giralt M, Villarroya F. SIRT1 controls the transcription of the peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α) gene in skeletal muscle through the PGC-1α autoregulatory loop and interaction with MyoD. J Biol Chem 2009; 284: 21872-21880.
7. Antoniali G, Lirussi L, D'Ambrosio C, Dal Piaz F, Vascotto C, Casarano E, Marasco D, Scaloni A, Fogolari F, Tell G. SIRT1 gene expression upon genotoxic damage is regulated by APE1 through nCaRE-promoter elements. Mol Biol Cell 2014; 25: 532-547.
8. Aquilano K, Vigilanza P, Baldelli S, Pagliei B, Rotilio G, Ciriolo MR. Peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) and sirtuin 1 (SIRT1) reside in mitochondria: possible direct function in mitochondrial biogenesis. J Biol Chem 2010; 285: 21590-21599.
9. Badi I, Burba I, Ruggeri C, Zeni F, Bertolotti M, Scopece A, Pompilio G, Raucci A. MicroRNA-34a Induces Vascular Smooth Muscle Cells Senescence by SIRT1 Downregulation and Promotes the Expression of Age-Associated Pro-inflammatory Secretory Factors. J Gerontol A Biol Sci Med Sci 2015; 70: 1304-1311.
10. Bae HJ, Chang YG, Noh JH, Kim JK, Eun JW, Jung KH, Kim MG, Shen Q, Ahn YM, Kwon SH, Park WS, Lee JY, Nam SW. DBC1 does not function as a negative regulator of SIRT1 in liver cancer. Oncol Lett 2012; 4: 873-877.
11. Bai P, Canto C, Brunyánszki A, Huber A, Szántó M, Cen Y, Yamamoto H, Houten SM, Kiss B, Oudart H, Gergely P, Menissier-de Murcia J, Schreiber V, Sauve AA, Auwerx J. PARP-2 regulates SIRT1 expression and whole-body energy expenditure. Cell Metab 2011; 13: 450-460.
12. Bai P, Cantó C, Oudart H, Brunyánszki A, Cen Y, Thomas C, Yamamoto H, Huber A, Kiss B, Houtkooper RH, Schoonjans K, Schreiber V, Sauve AA, Menissier-de Murcia J, Auwerx J. PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. Cell Metab 2011; 13: 461-468.
13. Barber MF, Michishita-Kioi E, Xi Y, Tasselli L, Kioi M, Moqtaderi Z, Tennen RI, Paredes S, Young NL, Chen K, Struhl K, Garcia BA, Gozani O, Li W, Chua KF. SIRT7 links H3K18 deacetylation to maintenance of oncogenic transformation. Nature 2012; 487: 114-118.
14. Baur JA, Ungvari Z, Minor RK, Couteur DGL, de Cabo R. Are sirtuins viable targets for improving healthspan and lifespan? Nat Rev Drug Discov 2012; 11: 443-461.
15. Bellizzi D, Covello G, Di Cianni F, Tong Q, De Benedictis G. Identification of GATA2 and AP-1 Activator elements within the enhancer VNTR occurring in intron 5 of the human SIRT3 gene. Mol Cells 2009; 28: 87-92.
16. Bellizzi D, Rose G, Cavalcante P, Covello G, Dato S, De Rango F, et al. A novel VNTR enhancer within the SIRT3 gene, a human homologue of SIR2, is associated with survival at oldest ages. Genomics 2005; 85: 258-263.
17. Bicker S, Schratt G. Not miR-ly aging: SIRT1 boosts memory via a microRNA-dependent mechanism. Cell Res 2010; 20: 1175-1177.
18. Black JC, Mosley A, Kitada T, Washburn M, Carey M. The SIRT2 deacetylase regulates autoacetylation of p300. Mol Cell 2008; 32: 449-455.
19. Bock FJ, Todorova TT, Chang P. RNA Regulation by Poly(ADP-Ribose) Polymerases. Mol Cell 2015; 58: 959-969.
20. Bonda DJ, Lee H-G, Camins A, Pallàs M, Casadesus G, Smith MA, Zhu X. The sirtuin pathway in ageing and Alzheimer disease: mechanistic and therapeutic considerations. Lancet Neurol 2011; 10: 275-279.
21. Bosch-Presegué L, Vaquero A. Sirtuin-dependent epigenetic regulation in the maintenance of genome integrity. FEBS J 2015; 282: 1745-1767.
22. Bouras T, Fu M, Sauve AA, Wang F, Quong AA, Perkins ND, Hay RT, Gu W, Pestell RG. SIRT1 deacetylation and repression of p300 involves lysine residues 1020/1024 within the cell cycle regulatory domain 1. J Biol Chem 2005; 280: 10264-10276.
23. Braidy N, Poljak A, Grant R, Jayasena T, Mansour H, Chan-Ling T, Smythe G, Sachdev P, Guillemin GJ. Differential expression of sirtuins in the aging rat brain. Front Cell Neurosci 2015; 9: 167.
24. Bräutigam L, Jensen LDE, Poschmann G, Nyström S, Bannenberg S, Dreij K, Lepka K, Prozorovski T, Montano SJ, Aktas O, Uhlén P, Stühler K, Cao Y, Holmgren A, Berndt C. Glutaredoxin regulates vascular development by reversible glutathionylation of sirtuin 1. Proc Natl Acad Sci U S A 2013; 110: 20057-20062.
25. Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer PL, Lin Y, Tran H, Ross SE, Mostoslavsky R, Cohen HY, Hu LS, Cheng HL, Jedrychowski MP, Gygi SP, Sinclair DA, Alt FW, Greenberg ME. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science 2004; 303: 2011-2015.
26. Buler M, Aatsinki S-M, Izzi V, Uusimaa J, Hakkola J. SIRT5 is under the control of PGC-1α and AMPK and is involved in regulation of mitochondrial energy metabolism. FASEB J 2014; 28: 3225-3237.
27. Caito S, Hwang J-W, Chung S, Yao H, Sundar IK, Rahman I. PARP-1 inhibition does not restore oxidant-mediated reduction in SIRT1 activity. Biochem Biophys Res Commun 2010; 392: 264-270.
28. Cantó C, Sauve AA, Bai P. Crosstalk between poly(ADP-ribose) polymerase and sirtuin enzymes. Mol Aspects Med 2013; 34: 1168-1201.
29. Cardinale A, de Stefano MC, Mollinari C, Racaniello M, Garaci E, Merlo D. Biochemical characterization of sirtuin 6 in the brain and its involvement in oxidative stress response. Neurochem Res 2015; 40: 59-69.
30. Ceolotto G, De Kreutzenberg SV, Cattelan A, Fabricio ASC, Squarcina E, Gion M, Semplicini A, Fadini GP, Avogaro A. Sirtuin 1 stabilization by HuR represses TNF-α- and glucose-induced E-selectin release and endothelial cell adhesiveness in vitro: relevance to human metabolic syndrome. Clin Sci 2014; 127: 449-461.

31. Chen C-J, Fu Y-C, Yu W, Wang W. SIRT3 protects cardiomyocytes from oxidative stress-mediated cell death by activating NF-κB. Biochem Biophys Res Commun 2013; 430: 798-803.
32. Chen J, Zhou Y, Mueller-Steiner S, Chen L-F, Kwon H, Yi S, Mucke L, Gan L. SIRT1 protects against microglia-dependent amyloid-beta toxicity through inhibiting NF-kappaB signaling. J Biol Chem 2005; 280: 40364-40374.
33. Chen Y, Wang H, Luo G, Dai X. SIRT4 inhibits cigarette smoke extracts-induced mononuclear cell adhesion to human pulmonary microvascular endothelial cells via regulating NF-κB activity. Toxicol Lett 2014; 226: 320-327.
34. Chen Z, Shentu TP, Wen L, Johnson DA, Shyy JY. Regulation of SIRT1 by oxidative stress-responsive miRNAs and a systematic approach to identify its role in the endothelium. Antioxid Redox Signal 2013; 19: 1522-1538.
35. Chiang MC, Cheng YC, Lin KH, Yen CH. PPARγ regulates the mitochondrial dysfunction in human neural stem cells with tumor necrosis factor alpha. Neuroscience 2013; 229: 118-129.
36. Choi SE, Fu T, Seok S, Kim D-H, Yu E, Lee KW, Kang Y, Li X, Kemper B, Kemper JK. Elevated microRNA-34a in obesity reduces NAD+ levels and SIRT1 activity by directly targeting NAMPT. Aging Cell 2013; 12: 1062-1072.
37. Choi SE, Kemper JK. Regulation of SIRT1 by microRNAs. Mol Cells 2013; 36: 385-392.
38. Chuang DM, Leng Y, Marinova Z, Kim HJ, Chiu CT. Multiple roles of HDAC inhibition in neurodegenerative conditions. Trends Neurosci 2009; 32: 591-601.
39. Cieślik M, Czapski GA, Strosznajder JB. The Molecular Mechanism of Amyloid β42 Peptide Toxicity: The Role of Sphingosine Kinase-1 and Mitochondrial Sirtuins. PLoS ONE 2015; 10: e0137193.
40. Ciron C, Zheng L, Bobela W, Knott GW, Leone TC, Kelly DP, Schneider BL. PGC-1α activity in nigral dopamine neurons determines vulnerability to α-synuclein. Acta Neuropathol Commun 2015; 3: 16.
41. Cohen HY, Lavu S, Bitterman KJ, Hekking B, Imahiyerobo TA, Miller C, Frye R, Ploegh H, Kessler BM, Sinclair DA. Acetylation of the C terminus of Ku70 by CBP and PCAF controls Bax-mediated apoptosis. Mol Cell 2004; 13: 627-638.
42. Culman J, Zhao Y, Gohlke P, Herdegen T. PPAR-gamma: therapeutic target for ischemic stroke. Trends Pharmacol Sci 2007; 28: 244-249.
43. Czapski GA, Adamczyk A, Strosznajder RP, Strosznajder JB. Expression and activity of PARP family members in the hippocampus during systemic inflammation: their role in the regulation of prooxidative genes. Neurochem Int 2013; 62: 664-673.
44. Ding J, Li M, Wan X, Jin X, Chen S, Yu C, Li Y. Effect of miR-34a in regulating steatosis by targeting PPARα expression in nonalcoholic fatty liver disease. Sci Rep 2015; 5: 13729.
45. Dioum EM, Chen R, Alexander MS, Zhang Q, Hogg RT, Gerard RD, Garcia JA. Regulation of hypoxia-inducible factor 2alpha signaling by the stress-responsive deacetylase sirtuin 1. Science 2009; 324: 1289-1293.
46. Dominy JE, Lee Y, Jedrychowski MP, Chim H, Jurczak MJ, Camporez JP, Ruan HB, Feldman J, Pierce K, Mostoslavsky R, Denu JM, Clish CB, Yang X, Shulman GI, Gygi SP, Puigserver P. The deacetylase Sirt6 activates the acetyltransferase GCN5 and suppresses hepatic gluconeogenesis. Mol Cell 2012; 48: 900-913.
47. Du J, Zhou Y, Su X, Yu JJ, Khan S, Jiang H, Kim J, Woo J, Kim JH, Choi BH, He B, Chen W, Zhang S, Cerione RA, Auwerx J, Hao Q, Lin H. Sirt5 is a NAD-dependent protein lysine demalonylase and desuccinylase. Science 2011; 334: 806-809.
48. Duclot F, Meffre J, Jacquet C, Gongora C, Maurice T. Mice knock out for the histone acetyltransferase p300/CREB binding protein-associated factor develop a resistance to amyloid toxicity. Neuroscience 2010; 167: 850-863.
49. Fan W, Fang R, Wu X, Liu J, Feng M, Dai G, Chen G, Wu G. Shear-sensitive microRNA-34a modulates flow-dependent regulation of endothelial inflammation. J Cell Sci 2015; 128: 70-80.
50. Fan W, Luo J. SIRT1 regulates UV-induced DNA repair through deacetylating XPA. Mol Cell 2010; 39: 247-258.
51. Fang EF, Scheibye-Knudsen M, Brace LE, Kassahun H, SenGupta T, Nilsen H, Mitchell JR, Croteau DL, Bohr VA. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD(+)/SIRT1 reduction. Cell 2014; 157: 882-896.
52. Feng Y, Liu T, Dong S-Y, Guo Y-J, Jankovic J, Xu H, Wu YC. Rotenone affects p53 transcriptional activity and apoptosis via targeting SIRT1 and H3K9 acetylation in SH-SY5Y cells. J Neurochem 2015; 134: 668-676.
53. Finley LWS, Haas W, Desquiret-Dumas V, Wallace DC, Procaccio V, Gygi SP, Haigis MC. Succinate dehydrogenase is a direct target of sirtuin 3 deacetylase activity. PLoS ONE 2011; 6: e23295.
54. Franke K, Kalucka J, Mamlouk S, Singh RP, Muschter A, Weidemann A, Iyengar V, Jahn S, Wieczorek K, Geiger K, Muders M, Sykes AM, Poitz DM, Ripich T, Otto T, Bergmann S, Breier G, Baretton G, Fong GH, Greaves DR, Bornstein S, Chavakis T, Fandrey J, Gassmann M, Wielockx B. HIF-1α is a protective factor in conditional PHD2-deficient mice suffering from severe HIF-2α-induced excessive erythropoiesis. Blood 2013; 121: 1436-1445.
55. Frescas D, Valenti L, Accili D. Nuclear trapping of the forkhead transcription factor FoxO1 via Sirt-dependent deacetylation promotes expression of glucogenetic genes. J Biol Chem 2005; 280: 20589-20595.
56. Fritz KS, Galligan JJ, Smathers RL, Roede JR, Shearn CT, Reigan P, Petersen DR. 4-Hydroxynonenal inhibits SIRT3 via thiol-specific modification. Chem Res Toxicol 2011; 24: 651-662.
57. Fu T, Seok S, Choi S, Huang Z, Suino-Powell K, Xu HE, Kemper B, Kemper JK. MicroRNA 34a inhibits beige and brown fat formation in obesity in part by suppressing adipocyte fibroblast growth factor 21 signaling and SIRT1 function. Mol Cell Biol 2014; 34: 4130-4142.
58. Fuentes E, Guzmán-Jofre L, Moore-Carrasco R, Palomo I. Role of PPARs in inflammatory processes associated with metabolic syndrome (Review). Mol Med Rep 2013; 8: 1611-1616.
59. Gao J, Wang W-Y, Mao Y-W, Gräff J, Guan J-S, Pan L, Mak G, Kim D, Su SC, Tsai LH. A novel pathway regulates memory and plasticity via SIRT1 and miR-134. Nature 2010; 466: 1105-1109.
60. Gerace E, Scartabelli T, Formentini L, Landucci E, Moroni F, Chiarugi A, Pellegrini-Giampietro DE. Mild activation of poly(ADP-ribose) polymerase (PARP) is neuroprotective in rat hippocampal slice models of ischemic tolerance. Eur J Neurosci 2012; 36: 1993-2005.

61. Ghosh HS, Spencer JV, Ng B, McBurney MW, Robbins PD. Sirt1 interacts with transducin-like enhancer of split-1 to inhibit nuclear factor kappaB-mediated transcription. Biochem J 2007; 408: 105-111.
62. Giannakou ME, Partridge L. The interaction between FOXO and SIRT1: tipping the balance towards survival. Trends Cell Biol 2004; 14: 408-412.
63. Gibson TM, Cotter MA, Cameron NE. Effects of poly(ADP-ribose) polymerase inhibition on dysfunction of non-adrenergic non-cholinergic neurotransmission in gastric fundus in diabetic rats. Nitric Oxide 2006; 15: 344-350.
64. Gonfloni S, Iannizzotto V, Maiani E, Bellusci G, Ciccone S, Diederich M. P53 and Sirt1: routes of metabolism and genome stability. Biochem Pharmacol 2014; 92: 149-156.
65. Grimley R, Polyakova O, Vamathevan J, McKenary J, Hayes B, Patel C, Smith J, Bridges A, Fosberry A, Bhardwaja A, Mouzon B, Chung CW, Barrett N, Richmond N, Modha S, Solari R. Over expression of wild type or a catalytically dead mutant of Sirtuin 6 does not influence NFκB responses. PLoS One 2012; 7: e39847.
66. Guarente L. Sirtuins as potential targets for metabolic syndrome. Nature 2006; 444: 868-874.
67. Günschmann C, Stachelscheid H, Akyüz MD, Schmitz A, Missero C, Brüning JC, Niessen CM. Insulin/IGF-1 controls epidermal morphogenesis via regulation of FoxO-mediated p63 inhibition. Dev Cell 2013; 26: 176-187.
68. Guo X, Williams JG, Schug TT, Li X. DYRK1A and DYRK3 promote cell survival through phosphorylation and activation of SIRT1. J Biol Chem 2010; 285: 13223-13232.
69. Gurha P, Wang T, Larimore AH, Sassi Y, Abreu-Goodger C, Ramirez MO, Reddy AK, Engelhardt S, Taffet GE, Wehrens XH, Entman ML, Rodriguez A. microRNA-22 promotes heart failure through coordinate suppression of PPAR/ERR-nuclear hormone receptor transcription. PLoS One 2013; 8: e75882.
70. Gustin JA, Korgaonkar CK, Pincheira R, Li Q, Donner DB. Akt regulates basal and induced processing of NF-kappaB2 (p100) to p52. J Biol Chem 2006; 281: 16473-16481.
71. Haigis MC, Mostoslavsky R, Haigis KM, Fahie K, Christodoulou DC, Murphy AJ, Valenzuela DM, Yancopoulos GD, Karow M, Blander G, Wolberger C, Prolla TA, Weindruch R, Alt FW, Guarente L. SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic beta cells. Cell 2006; 126: 941-954.
72. Han L, Zhou R, Niu J, McNutt MA, Wang P, Tong T. SIRT1 is regulated by a PPAR{γ}-SIRT1 negative feedback loop associated with senescence. Nucleic Acids Res 2010; 38: 7458-7471.
73. Han Y, Jin YH, Kim YJ, Kang BY, Choi HJ, Kim DW, Yeo CY, Lee KY. Acetylation of Sirt2 by p300 attenuates its deacetylase activity. Biochem Biophys Res Commun 2008; 375: 576-580.
74. Hassa PO, Hottiger MO. The functional role of poly(ADP-ribose) polymerase 1 as novel coactivator of NF-kappaB in inflammatory disorders. Cell Mol Life Sci 2002; 59: 1534-1553.
75. He J, Hu B, Shi X, Weidert ER, Lu P, Xu M, Huang M, Kelley EE, Xie W. Activation of the aryl hydrocarbon receptor sensitizes mice to nonalcoholic steatohepatitis by deactivating mitochondrial sirtuin deacetylase Sirt3. Mol Cell Biol 2013; 33: 2047-2055.
76. Helenius M, Hänninen M, Lehtinen SK, Salminen A. Changes associated with aging and replicative senescence in the regulation of transcription factor nuclear factor-kappa B. Biochem J 1996; 318 (Pt 2): 603-608.
77. Herbert KJ, Cook AL, Snow ET. SIRT1 modulates miRNA processing defects in p53-mutated human keratinocytes. J Dermatol Sci 2014; 74: 142-149.
78. van der Horst A, Tertoolen LGJ, de Vries-Smits LMM, Frye RA, Medema RH, Burgering BMT. FOXO4 is acetylated upon peroxide stress and deacetylated by the longevity protein hSir2(SIRT1). J Biol Chem 2004; 279: 28873-28879.
79. Hottiger MO, Hassa PO, Lüscher B, Schüler H, Koch-Nolte F. Toward a unified nomenclature for mammalian ADP-ribosyltransferases. Trends Biochem Sci 2010; 35: 208-219.
80. Hu G, Wu Z, Yang F, Zhao H, Liu X, Deng Y, Shi M, Zhao G. Ginsenoside Rd blocks AIF mitochondrio-nuclear translocation and NF-κB nuclear accumulation by inhibiting poly(ADP-ribose) polymerase-1 after focal cerebral ischemia in rats. Neurol Sci 2013; 34: 2101-2106.
81. Huang Z-P, Chen J, Seok HY, Zhang Z, Kataoka M, Hu X, Wang DZ. MicroRNA-22 regulates cardiac hypertrophy and remodeling in response to stress. Circ Res 2013; 112: 1234-1243.
82. Imai S, Armstrong CM, Kaeberlein M, Guarente L. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature 2000; 403: 795-800.
83. Ito T, Yagi S, Yamakuchi M. MicroRNA-34a regulation of endothelial senescence. Biochem Biophys Res Commun 2010; 398: 735-740.
84. Izhar L, Adamson B, Ciccia A, Lewis J, Pontano-Vaites L, Leng Y, Liang AC, Westbrook TF, Harper JW, Elledge SJ. A Systematic Analysis of Factors Localized to Damaged Chromatin Reveals PARP-Dependent Recruitment of Transcription Factors. Cell Reports 2015; 11: 1486-1500.
85. Jeong J, Juhn K, Lee H, Kim SH, Min BH, Lee KM, Cho MH, Park GH, Lee KH. SIRT1 promotes DNA repair activity and deacetylation of Ku70. Exp Mol Med 2007; 39: 8-13.
86. Jiang H, Huang Y, Xu H, Sun Y, Han N, Li QF. Hypoxia inducible factor-1α is involved in the neurodegeneration induced by isoflurane in the brain of neonatal rats. J Neurochem 2012; 120: 453-460.
87. Jin YH, Kim YJ, Kim DW, Baek KH, Kang BY, Yeo CY, Lee KY. Sirt2 interacts with 14-3-3 beta/gamma and down-regulates the activity of p53. Biochem Biophys Res Commun 2008; 368: 690-695.
88. Jing E, Gesta S, Kahn CR. SIRT2 regulates adipocyte differentiation through FoxO1 acetylation/deacetylation. Cell Metab 2007; 6: 105-114.
89. Jung HJ, Suh Y. Regulation of IGF-1 signaling by microRNAs. Front Genet 2015; 5: 472.
90. Kaidi A, Weinert BT, Choudhary C, Jackson SP. Human SIRT6 promotes DNA end resection through CtIP deacetylation. Science 2010; 329: 1348-1353.
91. Kalmar-Nagy K, Degrell P, Szabo A, Sumegi K, Wittmann I, Gallyas F, Sumegi B. PARP inhibition attenuates acute kidney allograft rejection by suppressing cell death pathways and activating PI-3K-Akt cascade. PLoS One 2013; 8: e81928.

92. Kanfi Y, Naiman S, Amir G, Peshti V, Zinman G, Nahum L, Bar-Joseph Z, Cohen HY. The sirtuin SIRT6 regulates lifespan in male mice. Nature 2012; 483: 218-221.
93. Kang H, Jung JW, Kim MK, Chung JH. CK2 is the regulator of SIRT1 substrate-binding affinity, deacetylase activity and cellular response to DNA-damage. PLoS One 2009; 4: e6611.
94. Kauppinen A, Suuronen T, Ojala J, Kaarniranta K, Salminen A. Antagonistic crosstalk between NF-κB and SIRT1 in the regulation of inflammation and metabolic disorders. Cell Signal 2013; 25: 1939-1948.
95. Kauppinen TM, Suh SW, Higashi Y, Berman AE, Escartin C, Won SJ, Wang C, Cho SH, Gan L, Swanson RA. Poly(ADP-ribose)polymerase-1 modulates microglial responses to amyloid β. J Neuroinflammation 2011; 8: 152.
96. Kawahara TLA, Michishita E, Adler AS, Damian M, Berber E, Lin M, McCord RA, Ongaigui KC, Boxer LD, Chang HY, Chua KF. SIRT6 links histone H3 lysine 9 deacetylation to control of NF-κB dependent gene expression and organismal lifespan. Cell 2009; 136: 62-74.
97. Kawahara TLA, Rapicavoli NA, Wu AR, Qu K, Quake SR, Chang HY. Dynamic chromatin localization of Sirt6 shapes stress- and aging-related transcriptional networks. PLoS Genet 2011; 7: e1002153.
98. Kim D, Nguyen MD, Dobbin MM, Fischer A, Sananbenesi F, Rodgers JT, Delalle I, Baur JA, Sui G, Armour SM, Puigserver P, Sinclair DA, Tsai LH. SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. EMBO J 2007; 26: 3169-3179.
99. Kim EJ, Kho JH, Kang MR, Um SJ. Active regulator of SIRT1 cooperates with SIRT1 and facilitates suppression of p53 activity. Mol Cell 2007; 28: 277-290.
100. Kim MY, Kang ES, Ham SA, Hwang JS, Yoo TS, Lee H, Paek KS, Park C, Lee HT, Kim JH, Han CW, Seo HG. The PPARδ-mediated inhibition of angiotensin II-induced premature senescence in human endothelial cells is SIRT1-dependent. Biochem Pharmacol 2012; 84: 1627-1634.
101. Kobayashi Y, Furukawa-Hibi Y, Chen C, Horio Y, Isobe K, Ikeda K, Motoyama N. SIRT1 is critical regulator of FOXO-mediated transcription in response to oxidative stress. Int J Mol Med 2005; 16: 237-243.
102. Kokkola T, Suuronen T, Molnár F, Määttä J, Salminen A, Jarho EM, Lahtela-Kakkonen M. AROS has a context-dependent effect on SIRT1. FEBS Lett 2014; 588: 1523-1528.
103. Kolthur-Seetharam U, Dantzer F, McBurney MW, de Murcia G, Sassone-Corsi P. Control of AIF-mediated cell death by the functional interplay of SIRT1 and PARP-1 in response to DNA damage. Cell Cycle 2006; 5: 873-877.
104. Korhonen P, Kyrylenko S, Suuronen T, Salminen A. Changes in DNA binding pattern of transcription factor YY1 in neuronal degeneration. Neurosci Lett 2005; 377: 121-124.
105. Kovacs K, Toth A, Deres P, Kalai T, Hideg K, Gallyas F, Sumegi B. Critical role of PI3-kinase/Akt activation in the PARP inhibitor induced heart function recovery during ischemia-reperfusion. Biochem Pharmacol 2006; 71: 441-452.
106. Li N, Muthusamy S, Liang R, Sarojini H, Wang E. Increased expression of miR-34a and miR-93 in rat liver during aging, and their impact on the expression of Mgst1 and Sirt1. Mech Ageing Dev 2011; 132: 75-85.
107. Li P, Zhang L, Zhou C, Lin N, Liu A. Sirt 1 activator inhibits the AGE-induced apoptosis and p53 acetylation in human vascular endothelial cells. J Toxicol Sci 2015; 40: 615-624.
108. Li X, Khanna A, Li N, Wang E. Circulatory miR34a as an RNA-based, noninvasive biomarker for brain aging. Aging (Albany NY) 2011; 3: 985-1002.
109. Li Y, Matsumori H, Nakayama Y, Osaki M, Kojima H, Kurimasa A, Ito H, Mori S, Katoh M, Oshimura M, Inoue T. SIRT2 down-regulation in HeLa can induce p53 accumulation via p38 MAPK activation-dependent p300 decrease, eventually leading to apoptosis. Genes Cells 2011; 16: 34-45.
110. Lim JH, Lee YM, Chun YS, Chen J, Kim JE, Park JW. Sirtuin 1 modulates cellular responses to hypoxia by deacetylating hypoxia-inducible factor 1alpha. Mol Cell 2010; 38: 864-878.
111. Lin L, Hron JD, Peng SL. Regulation of NF-kappaB, Th activation, and autoinflammation by the forkhead transcription factor Foxo3a. Immunity 2004; 21: 203-213.
112. Lisachev PD, Pustylnyak VO, Shtark MB. Sirt1 Regulates p53 Stability and Expression of Its Target S100B during Long-Term Potentiation in Rat Hippocampus. Bull Exp Biol Med 2016; 160: 432-434.
113. Liszt G, Ford E, Kurtev M, Guarente L. Mouse Sir2 homolog SIRT6 is a nuclear ADP-ribosyltransferase. J Biol Chem 2005; 280: 21313-21320.
114. Liu DJ, Hammer D, Komlos D, Chen KY, Firestein BL, Liu AY-C. SIRT1 knockdown promotes neural differentiation and attenuates the heat shock response. J Cell Physiol 2014; 229: 1224-1235.
115. Liu P, Wilson MJ. miR-520c and miR-373 target mTOR and SIRT1, activate the Ras/Raf/MEK/Erk pathway and NF-κB, with up-regulation of MMP9 in human fibrosarcoma cells. J Cell Physiol 2012; 227: 867-876.
116. Liu R, Fan M, Candas D, Qin L, Zhang X, Eldridge A, Zou JX, Zhang T, Juma S, Jin C, Li RF, Perks J, Sun LQ, Vaughan AT, Hai CX, Gius DR, Li JJ. CDK1-Mediated SIRT3 Activation Enhances Mitochondrial Function and Tumor Radioresistance. Mol Cancer Ther 2015; 14: 2090-2102.
117. Lo Sasso G, Menzies KJ, Mottis A, Piersigilli A, Perino A, Yamamoto H, Schoonjans K, Auwerx J. SIRT2 deficiency modulates macrophage polarization and susceptibility to experimental colitis. PLoS One 2014; 9: e103573.
118. Mahlknecht U, Ho AD, Letzel S, Voelter-Mahlknecht S. Assignment of the NAD-dependent deacetylase sirtuin 5 gene (SIRT5) to human chromosome band 6p23 by in situ hybridization. Cytogenet Genome Res 2006; 112: 208-212.
119. Mahlknecht U, Ho AD, Voelter-Mahlknecht S. Chromosomal organization and fluorescence in situ hybridization of the human Sirtuin 6 gene. Int J Oncol 2006; 28: 447-456.
120. Mahlknecht U, Voelter-Mahlknecht S. Chromosomal characterization and localization of the NAD+-dependent histone deacetylase gene sirtuin 1 in the mouse. Int J Mol Med 2009; 23: 245-252.
121. Mahlknecht U, Voelter-Mahlknecht S. Fluorescence in situ hybridization and chromosomal organization of the sirtuin 4 gene (Sirt4) in the mouse. Biochem Biophys Res Commun 2009; 382: 685-690.

122. Mahlknecht U, Voelter-Mahlknecht S. Genomic organization and localization of the NAD-dependent histone deacetylase gene sirtuin 3 (Sirt3) in the mouse. Int J Oncol 2011; 38: 813-822.
123. Mahlknecht U, Zschoernig B. Involvement of Sirtuins in Life-Span and Aging Related Diseases. In: Sensing in Nature. López-Larrea C (ed.). Springer, New York 2012; pp. 252-261.
124. Malewicz M, Perlmann T. Function of transcription factors at DNA lesions in DNA repair. Exp Cell Res 2014; 329: 94-100.
125. Manolopoulos KN, Klotz L-O, Korsten P, Bornstein SR, Barthel A. Linking Alzheimer's disease to insulin resistance: the FoxO response to oxidative stress. Mol Psychiatry 2010; 15: 1046-1052.
126. Mao Z, Hine C, Tian X, Van Meter M, Au M, Vaidya A, Seluanov A, Gorbunova V. SIRT6 promotes DNA repair under stress by activating PARP1. Science 2011; 332: 1443-1446.
127. McCord RA, Michishita E, Hong T, Berber E, Boxer LD, Kusumoto R, Guan S, Shi X, Gozani O, Burlingame AL, Bohr VA, Chua KF. SIRT6 stabilizes DNA-dependent protein kinase at chromatin for DNA double-strand break repair. Aging (Albany NY) 2009; 1: 109-121.
128. Mehrotra P, Riley JP, Patel R, Li F, Voss L 'erin, Goenka S. PARP-14 Functions as a Transcriptional Switch for Stat6-dependent Gene Activation. J Biol Chem 2011; 286: 1767-1776.
129. Menghini R, Casagrande V, Cardellini M, Martelli E, Terrinoni A, Amati F, Vasa-Nicotera M, Ippoliti A, Novelli G, Melino G, Lauro R, Federici M. MicroRNA 217 modulates endothelial cell senescence via silent information regulator 1. Circulation 2009; 120: 1524-1532.
130. Mester L, Szabo A, Atlasz T, Szabadfi K, Reglodi D, Kiss P, Racz B, Tamas A, Gallyas F Jr, Sumegi B, Hocsak E, Gabriel R, Kovacs K. Protection against chronic hypoperfusion-induced retinal neurodegeneration by PARP inhibition via activation of PI-3-kinase Akt pathway and suppression of JNK and p38 MAP kinases. Neurotox Res 2009; 16: 68-76.
131. Michishita E, McCord RA, Berber E, Kioi M, Padilla-Nash H, Damian M, Cheung P, Kusumoto R, Kawahara TL, Barrett JC, Chang HY, Bohr VA, Ried T, Gozani O, Chua KF. SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin. Nature 2008; 452: 492-496.
132. Michishita E, Park JY, Burneskis JM, Barrett JC, Horikawa I. Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. Mol Biol Cell 2005; 16: 4623-4635.
133. Milton VJ, Sweeney ST. Oxidative stress in synapse development and function. Dev Neurobiol 2012; 72: 100-110.
134. Min L, Ji Y, Bakiri L, Qiu Z, Cen J, Chen X, Chen L, Scheuch H, Zheng H, Qin L, Zatloukal K, Hui L, Wagner EF. Liver cancer initiation is controlled by AP-1 through SIRT6-dependent inhibition of survivin. Nat Cell Biol 2012; 14: 1203-1211.
135. Ming M, Shea CR, Guo X, Li X, Soltani K, Han W, He YY. Regulation of global genome nucleotide excision repair by SIRT1 through xeroderma pigmentosum C. Proc Natl Acad Sci U S A 2010; 107: 22623-22628.
136. Mitchell SJ, Martin-Montalvo A, Mercken EM, Palacios HH, Ward TM, Abulwerdi G, Minor RK, Vlasuk GP, Ellis JL, Sinclair DA, Dawson J, Allison DB, Zhang Y, Becker KG, Bernier M, de Cabo R. The SIRT1 activator SRT1720 extends lifespan and improves health of mice fed a standard diet. Cell Rep 2014; 6: 836-843.
137. Mohamed JS, Hajira A, Pardo PS, Boriek AM. MicroRNA-149 inhibits PARP-2 and promotes mitochondrial biogenesis via SIRT-1/PGC-1α network in skeletal muscle. Diabetes 2014; 63: 1546-1559.
138. Montero J, Dutta C, van Bodegom D, Weinstock D, Letai A. p53 regulates a non-apoptotic death induced by ROS. Cell Death Differ 2013; 20: 1465-1474.
139. Moran EP, Ma J-X. Therapeutic Effects of PPAR α on Neuronal Death and Microvascular Impairment. PPAR Res 2015; 2015: 595426.
140. Nagara Y, Tateishi T, Yamasaki R, Hayashi S, Kawamura M, Kikuchi H, Iinuma KM, Tanaka M, Iwaki T, Matsushita T, Ohyagi Y, Kira J. Impaired cytoplasmic-nuclear transport of hypoxia-inducible factor-1α in amyotrophic lateral sclerosis. Brain Pathol 2013; 23: 534-546.
141. Nahálková J. Novel protein-protein interactions of TPPII, p53, and SIRT7. Mol Cell Biochem 2015; 409: 13-22.
142. Nasrabady SE, Kuzhandaivel A, Akrami A, Bianchetti E, Milanese M, Bonanno G, Nistri A. Unusual increase in lumbar network excitability of the rat spinal cord evoked by the PARP-1 inhibitor PJ-34 through inhibition of glutamate uptake. Neuropharmacology 2012; 63: 415-426.
143. Nasrin N, Kaushik VK, Fortier E, Wall D, Pearson KJ, de Cabo R, Bordone L. JNK1 phosphorylates SIRT1 and promotes its enzymatic activity. PLoS One 2009; 4: e8414.
144. Nemoto S, Fergusson MM, Finkel T. Nutrient availability regulates SIRT1 through a forkhead-dependent pathway. Science 2004; 306: 2105-2108.
145. Nemoto S, Fergusson MM, Finkel T. SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1{alpha}. J Biol Chem 2005; 280: 16456-16460.
146. Nicolai S, Rossi A, Di Daniele N, Melino G, Annicchiarico-Petruzzelli M, Raschellà G. DNA repair and aging: the impact of the p53 family. Aging (Albany NY) 2015; 7: 1050-1065.
147. Oei SL, Shi Y. Transcription factor Yin Yang 1 stimulates poly(ADP-ribosyl)ation and DNA repair. Biochem Biophys Res Commun 2001; 284: 450-454.
148. Oei SL, Shi Y. Poly(ADP-ribosyl)ation of transcription factor Yin Yang 1 under conditions of DNA damage. Biochem Biophys Res Commun 2001; 285: 27-31.
149. Oka S, Alcendor R, Zhai P, Park JY, Shao D, Cho J, Yamamoto T, Tian B, Sadoshima J. PPARα-Sirt1 complex mediates cardiac hypertrophy and failure through suppression of the ERR transcriptional pathway. Cell Metab 2011; 14: 598-611.
150. Oka S, Zhai P, Yamamoto T, Ikeda Y, Byun J, Hsu CP, Sadoshima J. Peroxisome Proliferator Activated Receptor-α Association With Silent Information Regulator 1 Suppresses Cardiac Fatty Acid Metabolism in the Failing Heart. Circ Heart Fail 2015; 8: 1123-1132.
151. Okawara M, Katsuki H, Kurimoto E, Shibata H, Kume T, Akaike A. Resveratrol protects dopaminergic neurons in midbrain slice culture from multiple insults. Biochem Pharmacol 2007; 73: 550-560.
152. Park J, Chen Y, Tishkoff DX, Peng C, Tan M, Dai L, Xie Z, Zhang Y, Zwaans BM, Skinner ME, Lombard DB, Zhao Y. SIRT5-mediated lysine desuccinylation impacts diverse metabolic pathways. Mol Cell 2013; 50: 919-930.

153. Peck B, Chen CY, Ho KK, Fruscia PD, Myatt SS, Coombes RC, Fuchter MJ, Hsiao CD, Lam EW. SIRT Inhibitors Induce Cell Death and p53 Acetylation through Targeting Both SIRT1 and SIRT2. Mol Cancer Ther 2010; 9: 844-855.
154. Perkins ND. Integrating cell-signalling pathways with NF-kappaB and IKK function. Nat Rev Mol Cell Biol 2007; 8: 49-62.
155. Peserico A, Chiacchiera F, Grossi V, Matrone A, Latorre D, Simonatto M, Fusella A, Ryall JG, Finley LW, Haigis MC, Villani G, Puri PL, Sartorelli V, Simone C. A novel AMPK-dependent FoxO3A-SIRT3 intramitochondrial complex sensing glucose levels. Cell Mol Life Sci 2013; 70: 2015-2029.
156. Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, Leid M, McBurney MW, Guarente L. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. Nature 2004; 429: 771-776.
157. Pillai JB, Isbatan A, Imai S, Gupta MP. Poly(ADP-ribose) polymerase-1-dependent cardiac myocyte cell death during heart failure is mediated by NAD+ depletion and reduced Sir2alpha deacetylase activity. J Biol Chem 2005; 280: 43121-43130.
158. Pillai VB, Sundaresan NR, Gupta MP. Regulation of Akt signaling by Sirtuins: Its implication in cardiac hypertrophy and aging. Circ Res 2014; 114: 368-378.
159. Planavila A, Iglesias R, Giralt M, Villarroya F. Sirt1 acts in association with PPARα to protect the heart from hypertrophy, metabolic dysregulation, and inflammation. Cardiovasc Res 2011; 90: 276-284.
160. Priami C, De Michele G, Cotelli F, Cellerino A, Giorgio M, Pelicci PG, Migliaccio E. Modelling the p53/p66Shc Aging Pathway in the Shortest Living Vertebrate Nothobranchius Furzeri. Aging Dis 2015; 6: 95-108.
161. Quintanilla RA, Utreras E, Cabezas-Opazo FA. Role of PPARγ in the Differentiation and Function of Neurons. PPAR Res 2014; 2014: 768594.
162. Raivich G, Behrens A. Role of the AP-1 transcription factor c-Jun in developing, adult and injured brain. Prog Neurobiol 2006; 78: 347-363.
163. Rajamohan SB, Pillai VB, Gupta M, Sundaresan NR, Birukov KG, Samant S, Hottiger MO, Gupta MP. SIRT1 promotes cell survival under stress by deacetylation-dependent deactivation of poly(ADP-ribose) polymerase 1. Mol Cell Biol 2009; 29: 4116-4129.
164. Ramakrishnan G, Davaakhuu G, Kaplun L, Chung WC, Rana A, Atfi A, Miele L, Tzivion G. Sirt2 deacetylase is a novel AKT binding partner critical for AKT activation by insulin. J Biol Chem 2014; 289: 6054-6066.
165. Ramanan S, Kooshki M, Zhao W, Hsu F-C, Riddle DR, Robbins ME. The PPARalpha agonist fenofibrate preserves hippocampal neurogenesis and inhibits microglial activation after whole-brain irradiation. Int J Radiat Oncol Biol Phys 2009; 75: 870-877.
166. Ramanan VK, Saykin AJ. Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer's disease, Parkinson's disease, and related disorders. Am J Neurodegener Dis 2013; 2: 145-175.
167. Rebollo A, Roglans N, Baena M, Sánchez RM, Merlos M, Alegret M, Laguna JC. Liquid fructose downregulates Sirt1 expression and activity and impairs the oxidation of fatty acids in rat and human liver cells. Biochim Biophys Acta 2014; 1841: 514-524.
168. Ren JH, Tao Y, Zhang ZZ, Chen WX, Cai XF, Chen K, Ko BC, Song CL, Ran LK, Li WY, Huang AL, Chen J. Sirtuin 1 regulates hepatitis B virus transcription and replication by targeting transcription factor AP-1. J Virol 2014; 88: 2442-2451.
169. Ren Y, Shan TZ, Zhu LN, Wu T, Guo J, Wang YZ. Effect of breed on the expression of Sirtuins (Sirt1-7) and antioxidant capacity in porcine brain. Animal 2013; 7: 1994-1998.
170. Rodriguez-Ortiz CJ, Baglietto-Vargas D, Martinez-Coria H, LaFerla FM, Kitazawa M. Upregulation of miR-181 decreases c-Fos and SIRT-1 in the hippocampus of 3xTg-AD mice. J Alzheimers Dis 2014; 42: 1229-1238.
171. Rokavec M, Li H, Jiang L, Hermeking H. The p53/miR-34 axis in development and disease. J Mol Cell Biol 2014; 6: 214-230.
172. Sakamaki J, Daitoku H, Yoshimochi K, Miwa M, Fukamizu A. Regulation of FOXO1-mediated transcription and cell proliferation by PARP-1. Biochem Biophys Res Commun 2009; 382: 497-502.
173. Salminen A, Ojala J, Huuskonen J, Kauppinen A, Suuronen T, Kaarniranta K. Interaction of aging-associated signaling cascades: inhibition of NF-kappaB signaling by longevity factors FoxOs and SIRT1. Cell Mol Life Sci 2008; 65: 1049-1058.
174. Salvati E, Scarsella M, Porru M, Rizzo A, Iachettini S, Tentori L, Graziani G, D'Incalci M, Stevens MF, Orlandi A, Passeri D, Gilson E, Zupi G, Leonetti C, Biroccio A. PARP1 is activated at telomeres upon G4 stabilization: possible target for telomere-based therapy. Oncogene 2010; 29: 6280-6293.
175. Saunders LR, Sharma AD, Tawney J, Nakagawa M, Okita K, Yamanaka S, Willenbring H, Verdin E. miRNAs regulate SIRT1 expression during mouse embryonic stem cell differentiation and in adult mouse tissues. Aging (Albany NY) 2010; 2: 415-431.
176. Sayed D, Abdellatif M. AKT-ing via microRNA. Cell Cycle 2010; 9: 3213-3217.
177. Sbodio JI, Lodish HF, Chi NW. Tankyrase-2 oligomerizes with tankyrase-1 and binds to both TRF1 (telomere-repeat-binding factor 1) and IRAP (insulin-responsive aminopeptidase). Biochem J 2002; 361: 451-459.
178. Scheibye-Knudsen M, Croteau DL, Bohr VA. Mitochondrial deficiency in Cockayne syndrome. Mech Ageing Dev 2013; 134: 275-283.
179. Schiltz RL, Nakatani Y. The PCAF acetylase complex as a potential tumor suppressor. Biochim Biophys Acta 2000; 1470: M37-M53.
180. Sharma A, Diecke S, Zhang WY, Lan F, He C, Mordwinkin NM, Chua KF, Wu JC. The role of SIRT6 protein in aging and reprogramming of human induced pluripotent stem cells. J Biol Chem 2013; 288: 18439-18447.
181. Shaulian E, Karin M. AP-1 as a regulator of cell life and death. Nat Cell Biol 2002; 4: E131-136.
182. Shi T, Wang F, Stieren E, Tong Q. SIRT3, a mitochondrial sirtuin deacetylase, regulates mitochondrial function and thermogenesis in brown adipocytes. J Biol Chem 2005; 280: 13560-13567.
183. Siddiqui A, Chinta SJ, Mallajosyula JK, Rajagopolan S, Hanson I, Rane A, Melov S, Andersen JK. Selective binding of nuclear alpha-synuclein to the PGC1alpha promoter under conditions of oxidative stress may contribute to losses in mitochondrial function: implications for Parkinson's disease. Free Radic Biol Med 2012; 53: 993-1003.
184. Smit-McBride Z, Forward KI, Nguyen AT, Bordbari MH, Oltjen SL, Hjelmeland LM. Age-dependent increase in miRNA-34a

expression in the posterior pole of the mouse eye. Mol Vis 2014; 20: 1569-1578.
185. Song Y, Shi J, Wu Y, Han C, Zou J, Shi Y, Liu Z. Metformin ameliorates insulin resistance in L6 rat skeletal muscle cells through upregulation of SIRT3. Chin Med J 2014; 127: 1523-1529.
186. Song ZF, Chen DY, Du B, Ji XP. Poly (ADP-ribose) polymerase inhibitor reduces heart ischaemia/reperfusion injury via inflammation and Akt signalling in rats. Chin Med J 2013; 126: 1913-1917.
187. Strosznajder JB, Jeśko H, Strosznajder RP. Effect of amyloid beta peptide on poly(ADP-ribose) polymerase activity in adult and aged rat hippocampus. Acta Biochim Pol 2000; 47: 847-854.
188. Strosznajder RP, Czubowicz K, Jesko H, Strosznajder JB. Poly(ADP-ribose) metabolism in brain and its role in ischemia pathology. Mol Neurobiol 2010; 41: 187-196.
189. Strosznajder RP, Jesko H, Adamczyk A. Effect of aging and oxidative/genotoxic stress on poly(ADP-ribose) polymerase-1 activity in rat brain. Acta Biochim Pol 2005; 52: 909-914.
190. Strosznajder RP, Jesko H, Zambrzycka A. Poly(ADP-ribose) polymerase: the nuclear target in signal transduction and its role in brain ischemia-reperfusion injury. Mol Neurobiol 2005; 31: 149-167.
191. Strum JC, Johnson JH, Ward J, Xie H, Feild J, Hester A, Alford A, Waters KM. MicroRNA 132 regulates nutritional stress-induced chemokine production through repression of SirT1. Mol Endocrinol 2009; 23: 1876-1884.
192. Sundaresan NR, Pillai VB, Wolfgeher D, Samant S, Vasudevan P, Parekh V, Raghuraman H, Cunningham JM, Gupta M, Gupta MP. The deacetylase SIRT1 promotes membrane localization and activation of Akt and PDK1 during tumorigenesis and cardiac hypertrophy. Sci Signal 2011; 4: ra46.
193. Sundaresan NR, Vasudevan P, Zhong L, Kim G, Samant S, Parekh V, Pillai VB, Ravindra PV, Gupta M, Jeevanandam V, Cunningham JM, Deng CX, Lombard DB, Mostoslavsky R, Gupta MP. The sirtuin SIRT6 blocks IGF-Akt signaling and development of cardiac hypertrophy by targeting c-Jun. Nat Med 2012; 18: 1643-1650.
194. Takasaka N, Araya J, Hara H, Ito S, Kobayashi K, Kurita Y, Wakui H, Yoshii Y, Yumino Y, Fujii S, Minagawa S, Tsurushige C, Kojima J, Numata T, Shimizu K, Kawaishi M, Kaneko Y, Kamiya N, Hirano J, Odaka M, Morikawa T, Nishimura SL, Nakayama K, Kuwano K. Autophagy induction by SIRT6 through attenuation of insulin-like growth factor signaling is involved in the regulation of human bronchial epithelial cell senescence. J Immunol 2014; 192: 958-968.
195. Takizawa Y, Nakata R, Fukuhara K, Yamashita H, Kubodera H, Inoue H. The 4'-hydroxyl group of resveratrol is functionally important for direct activation of PPARα. PLoS One 2015; 10: e0120865.
196. Tao Y, Huang C, Huang Y, Hong L, Wang H, Zhou Z, Qiu Y. SIRT4 Suppresses Inflammatory Responses in Human Umbilical Vein Endothelial Cells. Cardiovasc Toxicol 2015; 15: 217-223.
197. Tong L, Denu JM. Function and metabolism of sirtuin metabolite O-acetyl-ADP-ribose. Biochim Biophys Acta 2010; 1804: 1617-1625.
198. Tsai Y-C, Greco TM, Boonmee A, Miteva Y, Cristea IM. Functional proteomics establishes the interaction of SIRT7 with chromatin remodeling complexes and expands its role in regulation of RNA polymerase I transcription. Mol Cell Proteomics 2012; 11: 60-76.
199. Tulin A, Stewart D, Spradling AC. The Drosophila heterochromatic gene encoding poly(ADP-ribose) polymerase (PARP) is required to modulate chromatin structure during development. Genes Dev 2002; 16: 2108-2119.
200. Valentin-Vega YA, Maclean KH, Tait-Mulder J, Milasta S, Steeves M, Dorsey FC, Cleveland JL, Green DR, Kastan MB. Mitochondrial dysfunction in ataxia-telangiectasia. Blood 2012; 119: 1490-1500.
201. Vélez-Cruz R, Johnson DG. E2F1 and p53 Transcription Factors as Accessory Factors for Nucleotide Excision Repair. Int J Mol Sci 2012; 13: 13554-13568.
202. Voelter-Mahlknecht S, Ho AD, Mahlknecht U. FISH-mapping and genomic organization of the NAD-dependent histone deacetylase gene, Sirtuin 2 (Sirt2). Int J Oncol 2005; 27: 1187-1196.
203. Voelter-Mahlknecht S, Letzel S, Mahlknecht U. Fluorescence in situ hybridization and chromosomal organization of the human Sirtuin 7 gene. Int J Oncol 2006; 28: 899-908.
204. Volonte D, Zou H, Bartholomew JN, Liu Z, Morel PA, Galbiati F. Oxidative Stress-induced Inhibition of Sirt1 by Caveolin-1 Promotes p53-dependent Premature Senescence and Stimulates the Secretion of Interleukin 6 (IL-6). J Biol Chem 2015; 290: 4202-4214.
205. Vyas S, Matic I, Uchima L, Rood J, Zaja R, Hay RT, Ahel I, Chang P. Family-wide analysis of poly(ADP-ribose) polymerase activity. Nat Commun 2014; 5: 4426.
206. Wang C, Chen L, Hou X, Li Z, Kabra N, Ma Y, Nemoto S, Finkel T, Gu W, Cress WD, Chen J. Interactions between E2F1 and SirT1 regulate apoptotic response to DNA damage. Nat Cell Biol 2006; 8: 1025-1031.
207. Wang F, Nguyen M, Qin FX-F, Tong Q. SIRT2 deacetylates FOXO3a in response to oxidative stress and caloric restriction. Aging Cell 2007; 6: 505-514.
208. Wang F, Tong Q. SIRT2 Suppresses Adipocyte Differentiation by Deacetylating FOXO1 and Enhancing FOXO1's Repressive Interaction with PPARγ. Mol Biol Cell 2009; 20: 801-808.
209. Wang HF, Li Q, Feng RL, Wen TQ. Transcription levels of sirtuin family in neural stem cells and brain tissues of adult mice. Cell Mol Biol (Noisy-le-grand) 2012; Suppl 58: OL1737-1743.
210. Wang J, Fivecoat H, Ho L, Pan Y, Ling E, Pasinetti GM. The role of Sirt1: at the crossroad between promotion of longevity and protection against Alzheimer's disease neuropathology. Biochim Biophys Acta 2010; 1804: 1690-1694.
211. Wang R, Li JJ, Diao S, Kwak YD, Liu L, Zhi L, Büeler H, Bhat NR, Williams RW, Park EA, Liao FF. Metabolic stress modulates Alzheimer's β-secretase gene transcription via SIRT1-PPARγ-PGC-1 in neurons. Cell Metab 2013; 17: 685-694.
212. Wang S, Yang X, Lin Y, Qiu X, Li H, Zhao X, Cao L, Liu X, Pang Y, Wang X, Chi Z. Cellular NAD depletion and decline of SIRT1 activity play critical roles in PARP-1-mediated acute epileptic neuronal death in vitro. Brain Res 2013; 1535: 14-23.
213. Wang WR, Liu EQ, Zhang JY, Li YX, Yang XF, He YH, Zhang W, Jing T, Lin R. Activation of PPAR alpha by fenofibrate inhibits apoptosis in vascular adventitial fibroblasts partly through SIRT1-mediated deacetylation of FoxO1. Exp Cell Res 2015; 338: 54-63.

214. Wang Y, Pang WJ, Wei N, Xiong Y, Wu WJ, Zhao CZ, Shen QW, Yang GS. Identification, stability and expression of Sirt1 antisense long non-coding RNA. Gene 2014; 539: 117-124.
215. Wang Y, Zhao X, Shi D, Chen P, Yu Y, Yang L, Xie L. Overexpression of SIRT1 promotes high glucose-attenuated corneal epithelial wound healing via p53 regulation of the IGFBP3/IGF-1R/AKT pathway. Invest Ophthalmol Vis Sci 2013; 54: 3806-3814.
216. Wesierska-Gadek J, Wojciechowski J, Schmid G. Phosphorylation regulates the interaction and complex formation between wt p53 protein and PARP-1. J Cell Biochem 2003; 89: 1260-1284.
217. Wu M, Seto E, Zhang J. E2F1 enhances glycolysis through suppressing Sirt6 transcription in cancer cells. Oncotarget 2015; 6: 11252-11263.
218. Wu Y, Chen L, Wang Y, Li W, Lin Y, Yu D, et al. Overexpression of Sirtuin 6 suppresses cellular senescence and NF-κB mediated inflammatory responses in osteoarthritis development. Sci Rep 2015; 5: 17602.
219. Xiong S, Salazar G, Patrushev N, Alexander RW. FoxO1 mediates an autofeedback loop regulating SIRT1 expression. J Biol Chem 2011; 286: 5289-5299.
220. Xu J, Li L, Yun H, Han Y. MiR-138 promotes smooth muscle cells proliferation and migration in db/db mice through down-regulation of SIRT1. Biochem Biophys Res Commun 2015; 463: 1159-1164.
221. Yakunin E, Kisos H, Kulik W, Grigoletto J, Wanders RJA, Sharon R. The regulation of catalase activity by PPAR γ is affected by α-synuclein. Ann Clin Transl Neurol 2014; 1: 145-159.
222. Yamamori T, DeRicco J, Naqvi A, Hoffman TA, Mattagajasingh I, Kasuno K, Jung SB, Kim CS, Irani K. SIRT1 deacetylates APE1 and regulates cellular base excision repair. Nucleic Acids Res 2010; 38: 832-845.
223. Yan J, Huang Y, Lu Y, Chen J, Jiang H. Repeated administration of ketamine can induce hippocampal neurodegeneration and long-term cognitive impairment via the ROS/HIF-1α pathway in developing rats. Cell Physiol Biochem 2014; 33: 1715-1732.
224. Yang H, Yan B, Liao D, Huang S, Qiu Y. Acetylation of HDAC1 and degradation of SIRT1 form a positive feedback loop to regulate p53 acetylation during heat-shock stress. Cell Death Dis 2015; 6: e1747.
225. Yang SJ, Choi JM, Chae SW, Kim WJ, Park SE, Rhee EJ, Lee WY, Oh KW, Park SW, Kim SW, Park CY. Activation of peroxisome proliferator-activated receptor gamma by rosiglitazone increases sirt6 expression and ameliorates hepatic steatosis in rats. PLoS One 2011; 6: e17057.
226. Yang T, Chen X, Jin H, Sethi G, Go ML. Functionalized tetrahydro-1H-pyrido[4,3-b]indoles: A novel chemotype with Sirtuin 2 inhibitory activity. Eur J Med Chem 2015; 92: 145-155.
227. Yang Y, Fu W, Chen J, Olashaw N, Zhang X, Nicosia SV, Bhalla K, Bai W. SIRT1 sumoylation regulates its deacetylase activity and cellular response to genotoxic stress. Nat Cell Biol 2007; 9: 1253-1262.
228. Yang Y, Hou H, Haller EM, Nicosia SV, Bai W. Suppression of FOXO1 activity by FHL2 through SIRT1-mediated deacetylation. EMBO J 2005; 24: 1021-1032.
229. Ye Z, Fang J, Dai S, Wang Y, Fu Z, Feng W, Wei Q, Huang P. MicroRNA-34a induces a senescence-like change via the down-regulation of SIRT1 and up-regulation of p53 protein in human esophageal squamous cancer cells with a wild-type p53 gene background. Cancer Lett 2016; 370: 216-221.
230. Yeung F, Hoberg JE, Ramsey CS, Keller MD, Jones DR, Frye RA, Mayo MW. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J 2004; 23: 2369-2380.
231. Yin H, Liang X, Jogasuria A, Davidson NO, You M. miR-217 regulates ethanol-induced hepatic inflammation by disrupting sirtuin 1-lipin-1 signaling. Am J Pathol 2015; 185: 1286-1296.
232. Yuan F, Xie Q, Wu J, Bai Y, Mao B, Dong Y, Bi W, Ji G, Tao W, Wang Y, Yuan Z. MST1 promotes apoptosis through regulating Sirt1-dependent p53 deacetylation. J Biol Chem 2011; 286: 6940-6945.
233. Zhang E, Guo Q, Gao H, Xu R, Teng S, Wu Y. Metformin and Resveratrol Inhibited High Glucose-Induced Metabolic Memory of Endothelial Senescence through SIRT1/p300/p53/p21 Pathway. PLoS ONE 2015; 10: e0143814.
234. Zhang F, Wang S, Gan L, Vosler PS, Gao Y, Zigmond MJ, et al. Protective effects and mechanisms of sirtuins in the nervous system. Prog Neurobiol 2011; 95: 373-395.
235. Zhang P, Tu B, Wang H, Cao Z, Tang M, Zhang C, et al. Tumor suppressor p53 cooperates with SIRT6 to regulate gluconeogenesis by promoting FoxO1 nuclear exclusion. Proc Natl Acad Sci USA 2014; 111: 10684-10689.
236. Zhang R, Chen H-Z, Liu J-J, Jia Y-Y, Zhang Z-Q, Yang R-F, et al. SIRT1 suppresses activator protein-1 transcriptional activity and cyclooxygenase-2 expression in macrophages. J Biol Chem 2010; 285: 7097-7110.
237. Zhao K, Zhou Y, Qiao C, Ni T, Li Z, Wang X, et al. Oroxylin A promotes PTEN-mediated negative regulation of MDM2 transcription via SIRT3-mediated deacetylation to stabilize p53 and inhibit glycolysis in wt-p53 cancer cells. J Hematol Oncol 2015; 8: 41.
238. Zhao W, Zhao J, Hou M, Wang Y, Zhang Y, Zhao X, et al. HuR and TIA1/TIAL1 are involved in regulation of alternative splicing of SIRT1 pre-mRNA. Int J Mol Sci 2014; 15: 2946-2958.
239. Zheng B, Liao Z, Locascio JJ, Lesniak KA, Roderick SS, Watt ML, et al. PGC-1α, A Potential Therapeutic Target for Early Intervention in Parkinson's Disease. Sci Transl Med 2010; 2: 52ra73.
240. Zheng T, Lu Y. SIRT1 Protects Human Lens Epithelial Cells Against Oxidative Stress by Inhibiting p53-Dependent Apoptosis. Curr Eye Res 2015; : 1-8.
241. Zheng Y, Xu Z. MicroRNA-22 induces endothelial progenitor cell senescence by targeting AKT3. Cell Physiol Biochem 2014; 34: 1547-1555.
242. Zhong L, D'Urso A, Toiber D, Sebastian C, Henry RE, Vadysirisack DD, et al. The histone deacetylase Sirt6 regulates glucose homeostasis via Hif1alpha. Cell 2010; 140: 280-293.