REVIEW

Sirtuin 1 (SIRT1) and steroid hormone receptor activity in cancer

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Abstract

Sirtuins, which are class III NAD-dependent histone deacetylases that regulate a number of physiological processes, play important roles in the regulation of metabolism, aging, oncogenesis, and cancer progression. Recently, a role for the sirtuins in the regulation of steroid hormone receptor signaling is emerging. In this mini-review, we will summarize current research into the regulation of estrogen, androgen, progesterone, mineralocorticoid, and glucocorticoid signaling by sirtuins in cancer. Sirtuins can regulate steroid hormone signaling through a variety of molecular mechanisms, including acting as co-regulatory transcription factors, deacetylating histones in the promoters of genes with nuclear receptor-binding sites, directly deacetylating steroid hormone nuclear receptors, and regulating pathways that modify steroid hormone receptors through phosphorylation. Furthermore, disruption of sirtuin activity may be an important step in the development of steroid hormone-refractory cancers.

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Introduction

Steroid hormone receptors, such as the estrogen (ER) and androgen receptors (AR), as well as the progesterone (PR), glucocorticoid (GR), and mineralocorticoid receptors (MR) are part of a large nuclear receptor family of eukaryotic transcription factors (Tsai & Omalley 1994, Mangelsdorf *et al.* 1995, Aoyagi & Archer 2008). Steroid hormone receptors play essential roles in numerous biological processes, such as homeostasis, metabolism, cell growth, and development (Tsai & Omalley 1994, Mangelsdorf *et al.* 1995, Chawla *et al.* 2001).

Initiation of steroid hormone receptor activity normally requires the binding of a specific ligand, such as estrogen in the case of the ER. The steroid hormone receptors then dimerize and in some cases undergo post-translational modifications, translocate to the nucleus, and bind to their cognate hormone-responsive elements in the promoter or other regulatory regions of their target genes. The promoter-bound steroid hormone receptor then recruits transcriptional co-regulatory proteins and ultimately RNA polymerase II and other components of the transcriptional machinery, eliciting a transcriptional response (Tsai & Omalley 1994, Kinyamu & Archer 2004, Perissi & Rosenfeld 2005).

Regulation of steroid hormone receptor signaling is complex. Disruption in the physiological functions of these receptors can lead to several types of malignancies such as breast cancer, leukemia and lymphoma, prostate cancer, ovarian cancer, and lung cancer among others (Miller & Langdon 1997, Gronemeyer *et al.* 2004, Huang *et al.* 2010).

Understanding of the steroid hormone dependency of certain cancer cells and the mechanisms underlying their subsequent evolution to a hormone-refractory state is an important and challenging goal of molecular oncology. Abnormal function of the AR has been linked to both the pathogenesis and the progression of human prostate cancer (Edwards & Bartlett 2005, Wang *et al.* 2005, Fu *et al.* 2006), and the ER plays a similar role in pathogenesis and progression of breast cancer. In the healthy mammary glands, ER-positive cells are largely quiescent. Estrogen stimulates these cells to produce growth factors that cause the growth of neighboring ER-negative cells through paracrine effects involving stromal–epithelial cell interaction. ER-positive breast cancer cells are stimulated to proliferate in response to estrogen. Estrogen not only stimulates growth in these cells, but also suppresses apoptosis. One early step in the neoplastic transformation of the breast epithelium is the autocrine mechanism becoming predominant (Streuli & Haslam 1998, Fuqua *et al.* 2000, Aghmesheh *et al.* 2005, Song & Santen 2006). Prostate cancer progression can evolve through a similar pattern, including autocrine production of androgens, and eventual activation of AR signaling in a ligand-independent fashion (Prins & Putz 2008).

Post-translational modification of the steroid hormone receptors can play a role in the evolution of steroid

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responsiveness and independence in these tumors, by regulating signaling in response to steroid hormones. These modifications include phosphorylation, ubiquitination, glycosylation, and acetylation. For example, PRMT1-mediated acetylation of ERα is required for recruitment of the co-effector molecules SRC, PI_3K, and Fak (Le Romancer *et al.* 2008). ERα can be acetylated by p300 on two lysine residues located in the hinge region of the molecule *in vitro*. Acetylation at these sites decreases the hormone sensitivity of the receptor (Wang *et al.* 2001, Margueron *et al.* 2004). A mutation at one of these acetylation sites, lysine 303, has been linked to premalignant lesions of the breast (Fuqua *et al.* 2000, Wang *et al.* 2001). It has not yet been determined whether acetylation affects ERα stability, intracellular localization, or its ability to interact with co-activators or co-repressors (Margueron *et al.* 2004).

Sirtuins

The sirtuins comprise a family of enzymes with increasing relevance to the regulation of steroid hormone receptor activity. The sirtuins are encoded by a family of genes that has remained highly conserved from archaebacteria to eukaryotes (Frye 1999, 2000). In yeast, there are four other sirtuins in addition to Sir2p, whereas seven homologs have been identified in mammals, SIRT1–7 (Frye 1999, 2000, Ford *et al.* 2005, Yamamoto *et al.* 2007). Sirtuin activities are not limited to histone deacetylation; SIRT members can also deacetylate nonhistone proteins and have diverse functions in multiple cellular compartments. Sirtuin (SIRT) 1, 6, and 7 localize to the nucleus, whereas SIRT3, SIRT4, and SIRT5 are mitochondrial, and SIRT2 is primarily cytoplasmic (Liu *et al.* 2005, Michishita *et al.* 2005, 2008). SIRT6 has been found to deacetylate histone H3, thereby regulating transcription and maintaining genomic stability (Liu *et al.* 2005, Michishita *et al.* 2005, 2008, Lombard *et al.* 2008, Kawahara *et al.* 2009). SIRT7 regulates RNA polymerase I-mediated expression of ribosomal RNA genes. SIRT7 has also been linked to angiogenesis (Ford *et al.* 2006, Potente *et al.* 2007). SIRT2 is involved in cell-cycle regulation, can deacetylate histone H4, and also acts as a tumor suppressor in certain gliomas (Dryden *et al.* 2003, Hiratsuka *et al.* 2003, Vaquero *et al.* 2006). Mice carrying inactivating mutations of SIRT1, SIRT2, or SIRT3 develop cancers, predominantly in the mammary glands and the liver, accompanied by genomic instability and/or abnormal energy metabolism. SIRT2-deficient mice initially develop normally, but develop mammary tumors and hepatocellular carcinoma as they age (Deng *et al.* 2011). The functions of SIRT3–5 are, as yet, unknown. Substrates for these sirtuins include acetyl-coenzyme A synthetase 2, glutamate dehydrogenase, and cytochrome *c* (Haigis & Guarente 2006, Haigis *et al.* 2006, Hallows *et al.* 2006, Schlicker *et al.* 2008, Schwer & Verdin 2008, Hirschey *et al.* 2010). Of all the sirtuins, SIRT1 remains the most intensively studied, and its actions on steroid hormone signaling will be the focus of this review (Table 1).

SIRT1

SIRT1 is a nicotinamide adenosine dinucleotide (NAD/NADH)-dependent histone deacetylase (HDAC) that functions by deacetylating histone (H1, H3, and H4) and nonhistone proteins. SIRT1 has been linked to control of longevity, gene silencing, cell-cycle progression, apoptosis, and energy homeostasis (Haigis & Guarente 2006, Yang *et al.* 2006, Dali-Youcef *et al.* 2007, Yamamoto *et al.* 2007, Greiss & Gartner 2009). SIRT1 also has functions relating to inflammation and neurodegeneration (Yamamoto *et al.* 2007). SIRT1 interacts with nuclear steroid hormone receptor co-activator proteins such as p300, PPARγ and PGC-α in the differentiation of muscle cells, adipogenesis, fat storage, and metabolism in the liver (Fulco *et al.* 2003, Picard *et al.* 2004, Puigserver *et al.* 2005, Rodgers *et al.* 2005).

Recently, our understanding of the physiological control of SIRT1 activity in the cell and its consequences on steroid hormone receptor activity is expanding. Endogenous SIRT1 activity in normal cells is regulated by the absolute levels of SIRT1 protein (which do not generally appear to change temporally among cells of the same type), and more importantly by the ability of SIRT1 to act as a cellular energy sensor controlled by the intracellular NAD/NADH ratio. Whether changes in the energy state of the cell thereby have an effect on the function of steroid hormone receptors, however, has not yet been explored. Furthermore, in tumor

Table 1 Summary of actions of SIRT1 on steroid hormone receptor activity

	SIRT1 regulation	Deacetylase activity dependent	Physiological function of SIRT1
Estrogen receptor	SIRT1 inhibits ligand-independent activation	Yes	Represses transcription
Androgen receptor	SIRT1 regulates AR ability to transform prostate cells	Yes	Represses transcription
Progesterone receptor	SIRT1 regulates nucleocytoplasmic shuttling of the receptor as well as the induction of slow vs rapid progesterone response genes	Yes	Transcriptional regulator
Glucocorticoid receptor	SIRT1 regulation protects cells from the stress response	Yes	Cell metabolism and survival
Mineralocorticoid receptor	SIRT1 regulates the tissue damage response	No	Cell metabolism and survival

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cells there exist a number of other possible levels of SIRT1 regulation, ranging from overexpression of the protein, which is common in tumor cells, to dramatic changes in subcellular localization and post-translational modifications of SIRT1 itself (Byles *et al.* 2010), and aberrant control of SIRT1 gene transcription.

The transcription of SIRT1 is regulated at the SIRT1 promoter by FOXO3a and p53, among other transcription factors. Upon activation, cytoplasmic FOXO3a translocates to the nucleus and induces the removal of p53 from two binding sites present at the *SIRT1* promoter (Nemoto *et al.* 2004). E2F1 is a crucial positive regulator of *SIRT1* transcription, with two E2F1 binding sites within the *SIRT1* promoter. In non-neoplastic cells, SIRT1 binds to and deacetylates E2F1, deactivating it and also decreasing transcription and expression of *SIRT1*, thus forming a negative-feedback loop (Wang *et al.* 2006).

SIRT1 also regulates its own expression through other mechanisms. SIRT1 can form a complex with, and deacetylate, the hypermethylated in cancer-1 (HIC-1) protein at residue L314, thereby activating the transcriptional repressor functions of HIC-1. HIC-1 then negatively regulates SIRT1 transcription (Stankovic-Valentin *et al.* 2007). HIC-1 is of particular interest in the regulation of the estrogen response because of its role in the response of breast cancer cells to estrogen antagonists. In estrogen-antagonist sensitive cells, estrogen antagonists induce HIC-1 expression via a c-Jun N-terminal kinase 1 – and prohibitin-mediated signaling pathways. It is therefore possible that when SIRT1 activity is inhibited, the repressive functions of HIC-1 are also impaired, but this is yet to be established. Investigation of the relationship between SIRT1 and HIC-1 in both estrogen-dependent and estrogen-independent breast cancer cells may elucidate important reciprocal roles for these molecules.

In addition, SIRT1 is post-translationally modified by phosphorylation via *cyclin B/Cdk1* (Sasaki *et al.* 2008) and sumoylation (Kwon & Oft 2008). Phosphorylation of SIRT1 increases its deacetylase activity. Mutations at residues T530 and S540 that eliminate phosphorylation at those residues disturb normal cell-cycle progression. Sumoylation also increases SIRT1 activity (Yang *et al.* 2007). Whether there are post-translational modifications to SIRT1 in response to steroid hormone receptor activity, which in some cells promotes cell-cycle progression and ultimately cyclin B activation, has not yet been studied.

SIRT1 and cancer

SIRT1 has been linked to cancer in several ways, through its regulation of tumor cell apoptosis, senescence and the DNA damage response, all promoting tumor cell survival. SIRT1 associates with the tumor suppressor protein p53 (Bouras *et al.* 2005, Nemoto *et al.* 2005, Rodgers *et al.* 2005, Haigis & Guarente 2006, Yamamoto *et al.* 2007), and regulates protein levels of p53 through deacetylation of residue L382, which destabilizes p53, thereby promoting cell survival (Zhao *et al.* 2008). Accordingly, overexpression of SIRT1 has been found in cancer cells to promote tumor cell survival (Ford *et al.* 2005, Ota *et al.* 2006*a*,*b*). SIRT1 can deacetylate the DNA repair factor Ku70, which sequesters the pro-apoptotic protein BAX in the mitochondria, thus preventing apoptosis (Cohen *et al.* 2004*a*). In addition, SIRT1 can deacetylate FOXO family proteins, which repress the transcription of Bim, a pro-apoptotic protein (Luo *et al.* 2001, Brunet *et al.* 2004, Cohen *et al.* 2004*a*,*b*, Motta *et al.* 2004, Yi & Luo 2010).

SIRT1 also regulates epigenetic mechanisms in the transformation and progress of cancer. SIRT1 localizes to the promoters of several aberrantly silenced, densely hypermethylated tumor suppressor genes (TSGs) *SFRP1* and *SFRP2* in MCF-7 and MDA-231 breast cancer cell lines. Interestingly, SIRT1 does not localize to these same promoters in normal or tumor cell lines in which these genes are not hypermethylated. Inhibition of SIRT1 in breast and colon cancer cells causes increases in H4K16 and H3K9 acetylation at endogenous promoters and subsequent re-expression of silenced TSGs. Surprisingly, this reactivation occurs despite the fact that the hypermethylated state of the promoter remains unchanged. These results indicate that SIRT1 may comprise a new form of epigenetic silencing that may link some of the epigenetic changes found in aging with those found in cancers. In the future, this action of SIRT1 may prove to be important for the therapeutic targeting and reactivation of these TSGs (Pruitt *et al.* 2006).

SIRT1 activity increases the expression of drug resistance-promoting genes in drug-resistant cancer cell lines. Conversely, suppression of SIRT1 by siRNA decreases the drug-resistant phenotype (Chu *et al.* 2005). These results indicate that SIRT1 may be involved in the transformation of cancer cells from drug-responsive to drug-refractory phenotypes, an ongoing clinical challenge in the treatment of many types of cancer. SIRT1 may play a role in determining drug resistance or sensitivity, and thus SIRT1 activity may prove to be important as a prognostic indicator of responses to chemotherapeutics.

In *Sirt1*-transgenic mice, *Sirt1* is able to protect from aging-associated spontaneous cancer development, as well as from metabolic syndrome-associated liver cancer (Pfluger *et al.* 2008, Serrano 2011). This beneficial effect of *Sirt1* appears due to its impact on both metabolism (Pfluger *et al.* 2008, Herranz *et al.* 2010) and genomic integrity (Pfluger *et al.* 2008). However, there are other experimental scenarios in which *Sirt1* overexpression is able to accelerate tumorigenesis in certain tissues (tissues that also show higher *Sirt1* expression when malignant), and these observations constitute the first *in vivo* demonstrations of a potentially oncogenic role for *Sirt1* (Serrano 2011).

The transformation of steroid hormone-responsive cancer cells from a responsive to a refractory state is an important step in the progression of breast and prostate cancers. For example, estrogen-dependent cancers are defined by the presence of the ER and the requirement of estrogen for cell survival and

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growth (Davidson 1992, Osborne 1998, Osborne & Schiff 2005, Osborne *et al.* 2005, Skliris *et al.* 2008). Estrogen-dependent cancers are considered treatable and are associated with a more favorable prognosis, although these initial estrogen-dependent tumors generally transform over time to estrogen independence. Breast cancers which are ER negative at diagnosis have lost ERα expression, most often due to gene silencing, and are capable of proliferating in the absence of estrogen. Estrogen-independent cancers are generally more aggressive and associated with a less favorable prognosis. These cancer phenotypes are the least treatable (Cleator *et al.* 2007). Prostate cancers also inevitably undergo an evolution from hormone responsive to hormone independent (castration-resistant cancer), although loss of AR expression is rare (Scher *et al.* 2004, Bennett *et al.* 2010, Risbridger *et al.* 2010). Several lines of evidence suggest that SIRT1 activity may be required to prevent the transition of cancer cells from a steroid hormone-dependent to an -independent state (Dai *et al.* 2007, 2008, Wang *et al.* 2008, Byles *et al.* 2010). An understanding of SIRT1/steroid hormone receptor interactions may thus provide new approaches to the clinical problem of hormone independence in breast and prostate tumors.

Regulation of AR activity by SIRT1

Prostate cancer, like breast cancer, requires gonadal steroids for initiation and early development. Tumors that arise from both breast and prostate tissues are typically hormone dependent, and the underlying cellular biology of these two tumors is often strikingly similar. Prostate cancer cells are initially dependent on androgen, and the tumor cells predictably progress to a hormone-refractory state within 18 months of the institution of endocrine-based therapies. The primary treatment modality for prostate cancer is androgen-ablation therapy, which utilizes anti-androgenic approaches such as the androgen antagonists flutamide and casodex, suppression of the hypothalamic/gonadal axis, or castration (Risbridger *et al.* 2010).

The AR is a DNA-binding transcription factor that governs male sexual development and differentiation. The induction of AR activity is regulated by androgenic hormones, including dihydrotestosterone (DHT), which enhances co-activator (p300 and SRC, among others) association and reduces co-repressor protein (NCOR, HDAC, and SMAD) association with the AR (Dai *et al.* 2008).

Deacetylation of the AR by SIRT1 inactivates its ability to transform prostate cells. SIRT1 binds to and deacetylates the AR at a conserved lysine motif, downregulating its levels in the cell and repressing androgen-induced AR transcription (Popov *et al.* 2007). Furthermore, a recent report found that SIRT1 regulates DHT-responsive miRNAs with putative binding sites within crucial developmental genes, such as the homeobox gene *NKX3-1*. Interestingly, this regulation appears to be AR independent. This suggests that SIRT1 not only can regulate androgen signaling, which in turn effects DHT-dependent cellular proliferation and growth, but also regulate the expression of specific homeobox genes essential for normal prostate development (Powell *et al.* 2009).

SIRT1 is required for androgen antagonist-mediated transcriptional repression and growth suppression of prostate cancer cells (Dai *et al.* 2007). Androgen antagonists promote the physical association of SIRT1 with the AR and NCoR, and androgen antagonist-bound AR then recruits SIRT1 and NCoR to AR-responsive promoters, and deacetylates histone H3K9 locally in the AR-responsive promoters. SIRT1 recruitment to these promoters is required for androgen antagonist-mediated transcriptional repression. SIRT1 down-regulation by pharmacological means or by siRNA increased the sensitivity of androgen-responsive genes to androgen stimulation, and enhanced the sensitivity of prostate cancer cell proliferation in response to androgens. This finding was the first demonstration of ligand-dependent recruitment of a class III HDAC into a co-repressor transcriptional complex, and of a necessary functional role for a class III HDAC as a transcriptional co-repressor in AR antagonist-induced transcriptional repression. While deacetylation at K632/K633 reduces the affinity of AR to androgen *in vitro* (Fu *et al.* 2000), it has not yet been determined whether the proliferative effects observed following inhibition of SIRT1 activity are due in part to direct deacetylation of AR by SIRT1 *in vivo*.

This activity of SIRT1 on AR signaling suggests that SIRT1 itself may serve as a TSG product in prostate cancer cells – loss of SIRT1 eliminates repression of AR-regulated gene activity and renders hormone-antagonist therapy ineffective. The role(s) of SIRT1 in prostate cancer may, therefore, be pleiotropic and may depend in part on its aberrant subcellular localization in cancer cells. SIRT1 is overexpressed in many prostate cancer cells, as well as many other steroid hormone-dependent or -independent cancer cell phenotypes. This overexpression is the result of SIRT1 expression in the cytoplasmic compartment, rather than being restricted to the nucleus. This predominant cytoplasmic localization of SIRT1 is regulated by elevated mitotic activity and PI_3K/IGF1R signaling in cancer cells, producing increased SIRT1 protein stability. SIRT1 is required for PI_3K-mediated prostate cancer cell growth and promotes prostate cancer cell survival (Byles *et al.* 2010). Conversely, a separate study employing HeLa cells suggests that enforced cytoplasmic expression of SIRT1, achieved through truncation of nuclear localization motifs, enhances sensitivity of the cells to apoptosis (Jin *et al.* 2007). Interestingly, this pro-apoptotic activity of the truncated SIRT1 is not dependent on its deacetylase activity.

Regulation of ER activity by SIRT1

A significant and increasingly important role for SIRT1 in the development and progression of breast cancer is emerging. SIRT1 transcription and activity are repressed by the deleted

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in breast cancer-1 (DBC-1) protein. In nonmalignant cells, SIRT1 and DBC-1 expression are balanced. However, in many cancers, and particularly breast cancer, DBC-1 is dysregulated, while SIRT1 is highly upregulated (Zhao *et al.* 2008, Sung *et al.* 2010). A role for SIRT1 as a potential tumor promoter in breast cancer has therefore been proposed. Conversely, activation of SIRT1 elicits a more profound inhibitory effect on *BRCA1*-mutant cancer cells than on *BRCA1*-wild-type cancer cells both *in vitro* and *in vivo*, suggesting a tumor suppressor role for SIRT1 in *BRCA1*-mutant breast cancer development (Wang *et al.* 2008).

ERα and ERβ both belong to the steroid/nuclear superfamily of ligand-regulated transcription factors. ERα contains six domains, termed A–F, which can be divided into a hormone-independent activation function (AF-1) region, a DNA-binding domain (DBD), a hinge region that contains the three nuclear localization sequences that mediate the translocation of the receptor from the cytoplasm to the nucleus, and a hormone-binding domain (HBD) on the C-terminus of the receptor. This latter region is responsible for the dimerization of ERα and hormone-dependent activation function. Binding of estrogen to the HBD leads to a series of conformational changes in the protein structure. The changes uncover areas on the external surface of ERα that are responsible for the binding of co-activator molecules (Carroll *et al.* 2006, Song & Santen 2006).

One report has suggested that SIRT1 inhibition leads to inhibition of ER signaling (Yao *et al.* 2010), implying that SIRT1 serves as an ERα co-activator. Repression of SIRT1 activity in that study led to lower estrogen-responsive gene activity and thus slower breast cancer cell growth. Those findings are inconsistent, however, with other reports in the literature. In a different experimental system, for example, exposure of breast cancer cells to resveratrol, a phytoestrogen and an activator of SIRT1 (albeit not a specific one), led to an inhibition of breast cancer cell growth and an upregulation of SIRT1 mRNA and protein expression, suggesting that instead of being an ERα co-activator, SIRT1 actually serves as an ERα repressor (Lin *et al.* 2010). Our own work, using much more specific SIRT1 inhibitors such as sirtinol and splitomicin as well as anti-SIRT1 siRNA, has demonstrated that SIRT1 activity represses estrogen-independent ERα-regulated gene activity in breast cancer cells, represses PI_3K/AKT-dependent ERα activation (as assayed by ERα phosphorylation at S118 and ERα nuclear translocation), and represses cell growth in the absence of estrogen, via an ERα-dependent mechanism.

One study found that human breast cancer tissues exhibited reduced levels of SIRT1, SIRT2, and SIRT3, suggesting a potential tumor suppressor role for these proteins in breast tissue (Deng *et al.* 2011). Another recent report found that DBC-1 and SIRT1 were expressed in 71% (87/122) and 67% (82/122) of human breast carcinomas, respectively, and DBC-1 and SIRT1 expression was significantly associated with chemotherapeutic resistance, distant metastatic relapse in ER-positive tumors, and a shorter relapse-free survival rate in ER-negative tumors (Lee *et al.* 2011). Collectively, these findings support the theory that SIRT1 generally serves a tumor suppressor function in certain types of aging-associated cancers (including breast and prostate cancer) and in metabolic syndrome-associated cancers, through, in part, its effects on steroid hormone receptor signaling, and consequently that disruption of SIRT1 expression and activity has oncogenic potential (Herranz & Serrano 2010, Yi & Luo 2010).

These findings also highlight a potential role for SIRT1 in decreasing breast cancer cell dependency on estrogen. When considered together with the reports that SIRT1 activity increases the expression of drug-resistance genes, SIRT1 levels in tumors may represent a useful biomarker with regard to prognosis, or for tailoring patient-specific treatment regimens (Chu *et al.* 2005). Furthermore, pharmacological modulation of SIRT1 activity in breast tumors may prove useful in future breast cancer therapeutic strategies.

It is therefore important to note the gaps in our understanding of the role of SIRT1 in ERα signaling. The molecular mechanism directly linking SIRT1 activity and ER-dependent signaling has not yet been established. A direct enzymatic action of SIRT1 on ERα is not likely to be the mechanism, as acetylation or deacetylation of the ER itself produces only modest effects, at best, on ERα activity (Cui *et al.* 2004, Popov *et al.* 2007, Ma *et al.* 2010). Furthermore, although there is clearly an effect of SIRT1 activation on PI_3K regulation and subsequent downstream AKT-mediated activation/phosphorylation of ERα, the pathway linking SIRT1 and PI_3K has not yet been rigorously established. For example, any functional effects of acetylation on the PI_3K pathway components p85, p110, or AKT have not been established.

SIRT1 has, however, been directly linked to one PI_3K co-regulatory protein, phosphatase and tensin homolog (PTEN). PTEN is a lipid phosphatase that inhibits PI_3K activation by specifically dephosphorylating the three positions of phosphatidylinositols (PI_3P, $PI_{3,4}P_2$, and $PI_{3,4,5}P_3$), which are the product of PI_3K, thereby inhibiting PI_3K signaling (Maehama & Dixon 1998, Myers *et al.* 1998, Stambolic *et al.* 1998, Medema *et al.* 2000, Ikenoue *et al.* 2008). SIRT1 deacetylates PTEN at residue L402, thereby inactivating PTEN and relieving its repression of PI_3K signaling (Ikenoue *et al.* 2008). One would expect PTEN activity to increase in response to SIRT1 inhibition, thus decreasing PI_3K signaling. However, our unpublished findings demonstrate an increase in PI_3K activity in response to SIRT1 inhibition, making it unlikely that PTEN plays a role in SIRT1-mediated repression of estrogen-independent PI_3K activity.

Regulation of PR activity by SIRT1

The PR is an intracellular steroid hormone receptor that specifically binds progesterone (Misrahi *et al.* 1987). The PR has two main isoforms, A and B (Gadkar-Sable *et al.* 2005,

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Sachdeva *et al.* 2005). The acetylation state of the PR has been linked to modest degrees of functional modulation. Acetylation of the PR regulates the nuclear-cytoplasmic shuttling of the receptor as well as the transcriptional activation of 'slow' vs 'rapid' progesterone-responsive genes. For instance, constitutive-acetylation-mimic mutations at the PR hinge region display delayed nuclear entry upon progesterone binding compared with wild type, whereas acetylation-defective mutants induce more rapid induction of *c-MYC* gene expression (c-*MYC* is a prototypical 'rapid' progesterone-responsive gene), compared with wild type or constitutive-acetylation-mimic mutants (Daniel *et al.* 2010). These results indicate that acetylation of the hinge region of the PR regulates the kinetics of PR nucleocytoplasmic transport, and thereby subsequent transcriptional activity.

In addition, c-MYC binds to the SIRT1 promoter, increasing SIRT1 expression, while at the same time, SIRT1 deacetylates c-MYC, decreasing its stability, and compromising the transformative ability of c-MYC. Thus, the c-MYC/SIRT interaction comprises a negative-feedback loop. This not only suggests that SIRT1 has a role(s) in PR 'rapid-response' regulation, but also supports the notion that SIRT1 acts as a tumor suppressor (Yuan *et al.* 2009). It will be therefore of great interest to further investigate the role(s) SIRT1 expression and activity have in the ability of c-MYC to transform PR-expressing cells.

It has yet to be determined whether SIRT1 plays a major role in the deacetylation of the PR itself. When breast cancer cells were treated with nicotinamide (NAM), a SIRT1 inhibitor, progesterone-dependent transcription decreased, suggesting that SIRT1 activity is necessary for PR-mediated transcription. However, when more specific suppression of SIRT1 activity by knockdown with siRNA was employed, the reduction of PR-dependent signaling in response to NAM treatment was shown to be independent of SIRT1. The authors suggested that NAM inhibits the coordination of basal transcription machinery assembly after chromatin remodeling of the progesterone-responsive promoter by a SIRT1-independent mechanism (Aoyagi & Archer 2008). As NAM is a very nonspecific SIRT1 inhibitor, it is likely that any actions on PR-mediated transcription as a result of SIRT1 inhibition by NAM are masked by the off-target effects of NAM. To conclusively determine whether SIRT1 has a role in regulating basal PR-dependent gene activity, more selective inhibitors of SIRT1 should be employed.

SIRT1 regulation of the GRs and MRs

The GR is widely expressed and is pleiotropic in its functions, depending in part on when in development, and in what tissue, it is expressed (Tsai & Omalley 1994). The interaction between SIRT1 activity and GR function is best characterized in myocyte metabolism.

In skeletal muscle cells, glucocorticoids play a major role in the response of skeletal muscle to catabolic conditions such as sepsis, severe injury, or burn. Glucocorticoids are important mediators of muscle wasting and mitochondrial dysfunction in such conditions (Hasselgren 1999). Glucocorticoids activate transcription of uncoupling protein-3 (UCP3), a mitochondrial membrane transporter that protects muscle cells from an overload of fatty acids and protects against excessive production of reactive oxygen species (Brand & Esteves 2005, Amat *et al.* 2007).

GR activity, induced by ligand binding, activates p300, a histone acetylase, and SIRT1 co-regulatory protein, as well as releasing class I and II HDACs, resulting in increased *UCP3* gene transcription. Interestingly, SIRT1 deacetylase activity is required for the repression of *UCP3* gene transcription. SIRT1 represses *UCP3* gene transcription by inhibiting the interaction between GR and the co-activator p300 at the promoter. Furthermore, the SIRT1 activator resveratrol is able to completely inhibit the induction of the *UCP3* gene upon treatment with glucocorticoids (Amat *et al.* 2007). (Due to the inherent lack of specificity of resveratrol, however, this result should be verified with other SIRT1 activators.) Collectively, it therefore appears that, in contrast to the roles of SIRT1 in ERα and AR signaling, which in turn regulate proliferation and differentiation, the functional endpoint of SIRT1 and GR interactions is a metabolic one. SIRT1 activity in turn is controlled by the metabolic state of the cell, acting as an energy sensor controlled by the NAD/NADH ratio, in this case linking transcriptional regulation of metabolic genes to the stress response.

The MR and its steroid hormone ligand, aldosterone, regulate electrolyte balance in the kidney (Nakano *et al.* 2010). Aldosterone increases renal tubular Na^+ absorption in large part by increasing transcription of the epithelial Na^+ channel α-subunit (α-ENaC) expressed in the apical membrane of collecting duct principal cells in the kidney (Zhang *et al.* 2009).

SIRT1 has recently been identified as a modulator of the aldosterone-signaling pathway (Zhang *et al.* 2009). SIRT1 plays an essential role in the genesis of aldosterone-induced renal injury. This renal injury is the result of cellular senescence in renal tissue secondary to an MR/SIRT1-dependent signaling pathway involving the cyclin-dependent kinase inhibitor p21 and p53. The resulting renal damage is due to delayed repair of tubular cells (Nakano *et al.* 2010).

The physical interaction between SIRT1 and disruptor of telomeric silencing-1 (Dot1), a histone-methyltransferase, results in global H3K79 hypermethylation in chromatin along the *α-ENaC* 5′-flanking region and inhibition of *α-ENaC* gene transcription. Interestingly, this effect appears to be mediated by an action of SIRT1 to support the distributive methyltransferase activity of Dot1 on H3K79 methylation. Surprisingly, however, the deacetylase activity of SIRT1 is not required for this action. SIRT1 also inhibits aldosterone-induced *α-ENaC* gene transcription via a pathway that is largely independent of MR (Zhang *et al.* 2009). The authors assert that SIRT1 is therefore able to regulate proteins that do not serve as substrates for its deacetylase or ADP-ribosylase

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activities (Zhang *et al.* 2009). Thus, in some cases, the actual physical interaction of SIRT1 with other proteins confers actions beyond its catalytic activity.

SIRT1 regulation of steroid hormone receptor FOXO co-regulatory proteins, and the PI_3K activation pathway

Many avenues of research have demonstrated that FOXO proteins are involved in the regulation of steroid hormone receptor signaling, and that many FOXO proteins are in turn regulated by SIRT1. FOXO proteins are members of the forkhead superfamily of proteins. Since the first member of this family of genes was discovered in *Drosophila melanogaster*, more than 100 structurally related forkhead transcription factors have been identified. Forkhead proteins share a conserved 100-residue DBD called the forkhead (FKH) domain. Crystal structure analysis indicates that this domain contains three major α-helices and two large wing-like loops, leading to these genes also being called winged-helix transcription factors (Weigel *et al.* 1989, Clark *et al.* 1993, Lai *et al.* 1993, Huang & Tindall 2007).

FOXO proteins are tightly regulated transcription factors that are able to stimulate expression of proteins involved in cell-cycle arrest or initiation of apoptosis (Lengyel *et al.* 2007). FOXO proteins in turn are regulated by growth factors and cellular stress. Growth factors regulate FOXO proteins by threonine/serine phosphorylation and nuclear exclusion (Brownawell *et al.* 1999, Kops *et al.* 1999). Cellular stresses result in FOXO acetylation, deactivating FOXO activity (Brunet 2004, Brunet *et al.* 2004, Daitoku *et al.* 2004, Motta *et al.* 2004, Huang & Tindall 2007). Whereas deacetylation of transcription factors is normally associated with a decrease in their activity, deacetylation of the FOXO proteins results in an increase in their activity. SIRT1 targets many FOXO proteins, including FOXO1 and FOXO3a (Brunet *et al.* 2004, Daitoku *et al.* 2004, Giannakou & Partridge 2004, Huang & Tindall 2007).

SIRT1, which is a sensor of cellular energy/stress levels, is a selective activator of FOXO signaling (Giannakou & Partridge 2004, Yeung *et al.* 2004, Berdichevsky & Guarente 2006). Interplay between FOXOs and SIRT1 potentiates cellular resistance to oxidative stress and enhances cell-cycle arrest in response to stress conditions, which promotes cellular survival and longevity (Frescas *et al.* 2005).

FOXO proteins interact with many of the steroid hormone receptors. For example, the amino-terminal domain of FOXO3a (amino acids 1–300) binds to ERα, suggesting that FOXO3a could possibly repress ERα activity directly. When FOXO3a is overexpressed in estrogen-treated MCF-7 cells, expression of ER-regulated genes is decreased. FOXO3a interacts with, and regulates, FOXOM1, which has a binding site on the ERα promoter and can regulate ERα expression (Madureira *et al.* 2006, Delpuech *et al.* 2007). Furthermore, silencing of endogenous FOXO3a can convert non-tumorigenic, estrogen-dependent breast cancer cells into tumorigenic, estrogen-independent cells. Wild-type MCF-7 cells injected into the footpads of female athymic mice are not able to form tumors without being given supplemental estradiol. MCF-7 cells transduced by retroviruses expressing siRNA against human FOXO3a, however, were able to form and promote tumor growth without the addition of supplemental estradiol. This observation has been taken as evidence that FOXO3a serves as a tumor suppressor and that endogenous FOXO3a may normally prevent hormone-independent cell growth of breast cancer cells *in vivo* (Zou *et al.* 2008). FOXO3a repression of estrogen-independent breast cancer cell proliferation parallels the effects of SIRT1 on repression of estrogen-independent breast cancer cell proliferation, engendering the hypothesis that SIRT1 and FOXO3a are both components of the same regulatory pathway governing ER-mediated signaling; both SIRT1 and FOXO3a together would be necessary to repress ligand-independent ERα activation, through the PI_3K pathway (Table 2).

The PI_3K/AKT pathway is an important component of many of the steroid hormone signaling pathways, both up- and downstreams of the steroid receptor. PI_3K/AKT activity is required for phosphorylation and activation of certain steroid hormone receptors (Ward & Weigel 2009). Subsequently, PI_3K/AKT is activated as a consequence of steroid hormone receptor activation (Dillon *et al.* 2007, Wang *et al.* 2007), generating a positive-feedback loop. In the case of prostate cancer cells, the AR-signaling pathway and the PI_3K/AKT pathway cross-talk through FOXO proteins, among other routes (Wang *et al.* 2007).

Table 2 Similarities between SIRT1- and FOXO3a-mediated regulation of breast cancer cell proliferation suggesting the potential interaction of the two pathways

Similarities between SIRT1- and FOXO3a-mediated regulation of breast cancer cell proliferation

SIRT1-mediated repression of breast cancer cell proliferation	FOXO3a-mediated repression of breast cancer cell proliferation
SIRT1 represses estrogen-regulated gene expression	FOXO3a represses estrogen-regulated gene expression
Repression of proliferation by SIRT1 is ERα dependent	FOXO3a binds to and represses ERα activity
SIRT1 represses estrogen-independent PI_3K/AKT activation	FOXO3a represses PI_3K/AKT activity
SIRT1 represses estrogen-independent cell growth	FOXO3a represses estrogen-independent cell growth
SIRT1 expression is regulated by FOXO3a	FOXO3a regulates SIRT1 expression
SIRT1 regulates FOXO3a activity	FOXO3a activity is regulated by SIRT1

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FOXO proteins and the PI_3K/AKT signaling pathway play a similar role in the catabolic actions of the GR in the regulation of genes involved in myopathy (Schakman *et al.* 2008). Muscle atrophy is an important consequence of many diseases. Glucocorticoids induce insulin resistance and subsequent activation of the ubiquitin-proteosome pathway. Elevated glucocorticoid production results in increased expression of atrogenes such as *IRS1*, *IRS2*, *AT-1*, and *UBC*. FOXO3a mediates cross-talk among the PI_3K/AKT, MEK/ERK, and GR signaling pathways (Zheng *et al.* 2010).

Discussion

SIRT1 activity has been linked to steroid hormone receptor sensitivity to ligands, activation, and function. The literature to date suggests that SIRT1 in general functions to repress steroid hormone receptor activity. In the case of the ER, SIRT1 represses ligand-independent activation. In the case of AR and GR, SIRT1 regulates ligand sensitivity and the subsequent transcriptional response to androgen and glucocorticoids respectively. In the case of the PR, it is likely that SIRT1 regulates the kinetics of nucleocytoplasmic shuttling and, consequently, 'slow' vs 'rapid' progesterone-responsive gene transcription. In the case of the MR, SIRT1 represses MR-induced gene transcription and can also cause cellular senescence and subsequent renal injury (Fig. 1).

However, for the most part, direct deacetylation of steroid hormone receptors by SIRT1 has not been demonstrated, or the functional effects of such a direct interaction (receptor acetylation status) have been modest. In the case of the PR and ER, SIRT1 regulation of receptor activity appears independent of direct SIRT1 acetylation. Moreover, regulation of the MR activity by SIRT1 is independent of SIRT1 deacetylase activity. It is rather more likely that the SIRT1 regulation of steroid hormone receptor activity is 'indirect'. For at least one steroid hormone receptor, AR, SIRT1 appears to serve as a transcriptional cofactor. The AR, upon binding of an androgen antagonist, physically associates with SIRT1 and the co-repressor NCoR, and recruits these proteins to the promoter of AR-responsive genes, repressing their transcription.

SIRT1 appears to regulate the ER through a different indirect mechanism, via modulation of a PI_3K-dependent pathway, thus activating AKT, which in turn phosphorylates and activates ERα. In this case, and potentially for other steroid hormone receptors, the FOXO proteins may provide a critical link between SIRT1 activity and signaling pathways that activate or inactivate steroid hormone receptors.

In prostate cancer cells, SIRT1 inhibition via selective inhibitors or siRNA produces an increase of FOXO1 expression and acetylation, resulting in a decrease in cell viability that is independent of p53 (Jung-Hynes & Ahmad 2009). FOXO proteins may thus provide an important or even necessary co-regulatory component linking steroid hormone receptor activity and SIRT1 activity.

A recent study reports that SIRT1 is expressed in 67% (82/122) of breast carcinomas investigated, and with concurrent expression of DBC-1, is significantly associated with distant metastatic relapse and a shorter relapse-free survival rate (Lee *et al.* 2011). In addition, activation of SIRT1 elicits a more profound inhibitory effect on *BRCA1*-mutant cancer cells (women possessing genetic mutations in BCRA1 have an 80% risk of developing breast cancer in their lifetime) than on *BRCA1*-wild-type cancer cells both *in vitro* and *in vivo* (Wang *et al.* 2008). When considered together with

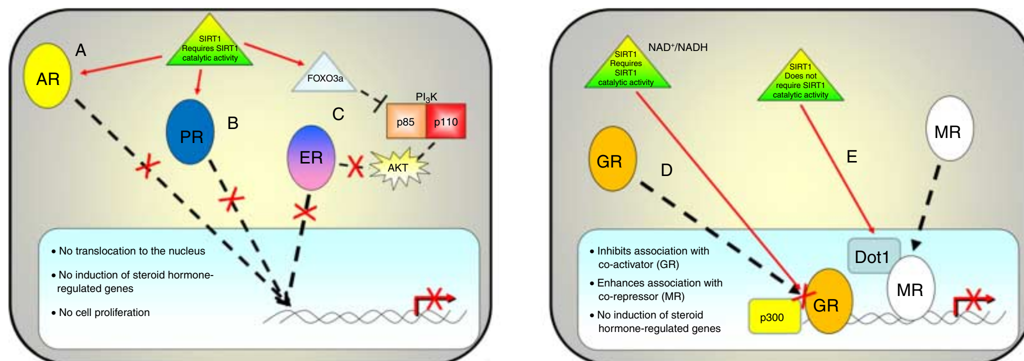

Figure 1 Model of SIRT1 regulation of steroid hormone receptor activity. SIRT1 regulates individual steroid hormone receptors via different mechanisms. (A) SIRT1 regulates the AR through direct deacetylation, thereby inhibiting AR activation and translocation and the transcription of AR-dependent genes. (B) SIRT1 inhibits the PR by regulating the nucleocytoplasmic translocation of the receptor, and thereby the downstream activation of PR-regulated genes. (C) SIRT1 regulates ERα by inhibiting the PI_3K/AKT (p85/p110) pathway, possibly through FOXO3a. This inhibits the translocation of ERα from the cytoplasm to the nucleus, thus decreasing ERα binding to DNA and ERα-dependent gene transcription. (D) The energy-sensing capabilities of SIRT1 regulate its effect on GR signaling. The cellular NAD/NADH ratio regulates SIRT1-mediated deacetylation of the GR and thus its ability to interact with the co-activator p300. (E) SIRT1 regulates the MR by binding DOT1, thereby enhancing DOT1-mediated repression of MR-regulated genes. SIRT1 regulation of MR is independent of SIRT1 deacetylase activity. Full colour version of this figure available via http://dx.doi.org/10.1530/JOE-11-0217.

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the reports that SIRT1 activity increases the expression of drug-resistance genes (Chu *et al*. 2005), SIRT1 expression and modulation may have important clinical implications for breast cancer patients, and potentially other steroid hormone-dependent cancer patients as well.

Understanding the effects of physiological and pathological changes in SIRT1 activity on steroid receptor function in normal and tumor cells is therefore of potentially great importance. New methods of pharmacological or genetic modulation of SIRT1 activity are under active development for a number of potential applications. In particular, SIRT1 may prove to be an important target molecule for new therapies of diseases of steroid hormone signaling and endocrine-related cancers.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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