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Mini Review

Dysregulation of sirtuins in cancer

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Abstract

Sirtuins have been shown to be dysregulated in tumor cells. Most information is available for the subform SIRT1, which is strongly upregulated in many tumors. This is, at least in part, explained by epigenetic silencing of SIRT1-targeting microRNAs and of transcriptional repressors of the *Sirt1* gene. Elevated SIRT1 expression has numerous consequences, from deacetylation of regulatory proteins, changes in histone acetylation and, secondarily, histone methylation, to DNA methylation patterns in promoters. Additionally, the tumor-specific rises in SIRT1 have to be seen in connection with dysfunctional circadian oscillators, which result from silencing of tumor suppressor genes that are oscillator components. These changes eliminate the circadian control of cell division and permit unrestrained proliferation. The chronobiotic melatonin, which acts on circadian oscillators, has been shown to suppress the elevated levels of SIRT1 in tumor cells. Studies on SIRT2 and SIRT6 are encouraging for investigating these and other sirtuin subforms in the future.

Introduction

Sirtuins have been discovered as anti-aging factors [1-4]. In enzymological terms, they act mostly as protein deacetylases, which accept many acetylated regulatory proteins as substrates and modify chromatin structure by deacetylation of histones. In this role, they are listed as class III histone deacetylases (HDACs). Alternately, they can act as mono-ADP-ribosyltransferases, which is plausible with regard to the identical substrate NAD^+ (nicotinamide adenine dinucleotide) that is required for either reaction. The latter reaction is, e.g., important for a participation in DNA repair. In mammals, seven sirtuin subforms, SIRT1–SIRT7, are known, which differ in their intracellular localization and spectrum of actions. Meanwhile, numerous additional effects of sirtuins have been described, which include antioxidant, anti-inflammatory, mitochondrial as well as metabolism-modulating properties and, additionally, a substantial role in the functioning of cellular circadian oscillators [5-7]. These actions are usually considered as being beneficial and contributing to healthy aging. However, sirtuins have also a dark side, particularly in carcinogenesis and the maintenance of the transformed state of tumor cells. It has been debated to what extent and under which conditions sirtuins have to be regarded as tumor suppressors or tumor-promoting agents [8]. Antiproliferative effects of SIRT1 have been reported in the specific case of DNA-binding fusion proteins of lysine-specific methyltransferase 2A (KMT2A), which are formed by genetic rearrangements in mixed-lineage leukemia [9]. However, in the majority of cases, SIRT1 is associated with increased proliferation in tumor cells, as will be outlined below.

The dark side extends to oxidative stress. In colorectal cancer cell lines, hydrogen peroxide was shown to upregulate SIRT1, but this effect that might otherwise be interpreted as being beneficial, turned out to reduce K16 acetylation at histone H4, reportedly via inhibition of histone acetyltransferase hMOF, a change that results in decreased expression of DNA repair genes [10]. Notably, a low level of H4K16ac is a hallmark of human cancers [11]. Moreover, SIRT1 was shown to act as a positive regulator of telomere length and to interact with telomeric repeats in vivo [12]. This effect that may be of advantage in the context of aging can be assumed to be unfavorable in cancer, with regard to continuing replicative activity. Elevated SIRT1 expression was also reported to favor microsatellite instability [13].

This short article cannot provide a comprehensive overview on sirtuins in cancer. Instead, a few important aspects of their actions and relationships to other regulatory players will be addressed, on the basis of selected examples. Some of these aspects are frequently overlooked or disregarded.

Upregulation of SIRT1 in tumor cells

SIRT1 expression and activity are known since long to be upregulated in many cancer cells, in conjunction with oncogene overexpression and/or dysfunctional tumor suppressor genes [14], because of either mutation or epigenetic silencing. SIRT1 has even been classified as an oncogene in breast cancer [15]. In mammary epithelial cells, it is overexpressed in a model of epithelial-mesenchymal transition (EMT), an effect attributed, at least in part, to epigenetic silencing of the SIRT1-targeting miR-200a [15]. Transformation of these cells was not only prevented by SIRT1 knockdown, but also by restoration of miR-200a expression. These treatments inhibited anchorage-independent growth and cell migration [15]. Processes leading to EMT are associated with E-cadherin gene silencing, promotion of tumor cell migration and invasion. All these alterations involve histone H4K16ac deacetylation by SIRT1, an effect that is mechanistically connected to H3K9 methylation and DNA methylation in promoters of tumor suppressor genes [16]. SIRT1-targeting microRNAs seem to be more generally repressed by DNA methylation of CpG islands in their promoters, a mechanistic connection to malignant SIRT1 elevation by

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cancer-induced epigenetic silencing [17]. The involvement of SIRT1 in cancer biology further extends to cancer stem cells, in which this sirtuin exhibits particularly high expression [18]. Moreover, high levels of SIRT1 were found to predict a decreased probability of survival in patients with hepatocellular carcinoma [18].

Role of sirtuins in DNA methylation of tumor cells

Although sirtuins are primarily protein deacetylases, they have indirect effects on DNA methylation. This is particularly important as far as CpG islands in control regions are affected, especially in promoters. Depending on the binding of transcription-promoting or -inhibiting proteins that is prevented by methylation, these modifications can either silence the respective genes or increase their expression. SIRT1 overexpression can lead to the CpG island methylator phenotype (CIMP), as shown, e.g., in colorectal cancer [13]. SIRT1 promotes DNA methylation, at least, by presumably two mechanisms. Hypermethylation is known to be executed by polycomb repressive complexes (PRCs) that contain DNA methyltransferase-1 (DNMT1), and SIRT1 is part of PRC4 [19,20]. Moreover, SIRT1 interacts physically with DNMT1 and deacetylates this substrate protein at K1349 and K1415, changes that enhance the methyltransferase activity and strengthen silencing, especially of tumor suppressor genes [21].

Moreover, malignant transformation can also cause hypermethylation or demethylation of certain genes, among them some that regulate SIRT1 expression. The erasure of methylcytosines is known to involve ten-eleven-translocation (Tet) enzymes, via sequential modification to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), followed by excision by thymine DNA glycosylase (TDG) and repair [22-24]. The *Sirt1* promoter was, in fact, shown to become demethylated in cancers, e.g., in B cell lymphoma 6 [25]. However, this is not necessarily associated with increased Tet activity, but can result from a balance between DNA methylation and erasure, which may shift upon changes in expression of genes that control *Sirt1* transcription. Among such genes, a relevant role has been ascribed to HIC1 (hypermethylated in cancer-1), which acts as a transcriptional repressor of *Sirt1*. Hypermethylation at the *Hic1* promoter, as known for various types of cancer, strongly decreases its expression, which eliminates the inhibition of *Sirt1* transcription [26,27]. Methyl groups at the disinhibited *Sirt1* promoter are erased by time. Hypermethylation of CpG islands in the genes of *Sirt1* mRNA-targeting miRNAs contribute to SIRT1 overexpression in tumor cells at the post-transcriptional level [17].

SIRT1 and open euchromatin

The epigenetic control of gene expression includes changes in chromatin structure via histone modification. The transcriptional repressor promyelocytic leukemia zinc finger protein (PLZF) is deacetylated by SIRT1, which leads to a loss of PLZF DNA binding activity. Therefore, promoters of PLZF target genes that are involved in oncogenesis undergo a change from heterochromatin to open euchromatin that allows transcription [28]. With regard to the role of E-cadherin repression in EMT, the interaction of SIRT1 with MPP8 (M-phase phosphoprotein 8) is of particular interest. SIRT1 deacetylates MPP8 at K439 and, thereby protects it from ubiquitin-proteasome-mediated degradation. Moreover, MPP8 recruits SIRT1 to deacetylate H4K16ac at target promoters. E-cadherin silencing by MPP8 is achieved by a coupled effect of H3K9 methylation and DNA methylation [16], the latter being mediated by binding of MPP8 to the dimethylated DNA methyltransferase DNMT3aK44me2 [29].

The role of dysregulated circadian oscillators

The upregulation of SIRT1 in tumor cells has an additional aspect concerning circadian oscillators, a nexus that is frequently not perceived. Circadian oscillators are cellular machineries, which control, among numerous other functions, DNA replication and cell division, which are coupled, in normal cells, to certain temporal phases. Moreover, cells undergo circadian cycles of chromatin remodeling that sets temporal limits to the expression of various genes. Importantly, several clock genes act as tumor suppressors and have to be silenced, in tumor cells, by hypermethylation or altered methylation in their promoters, as summarized elsewhere [6,30]. The tumor suppressing property was first detected for the important clock gene period-2 (*Per2*), whose dysfunction makes a mouse cancer-prone [31,32]. Moreover, SIRT1 participates in the circadian oscillator mechanism as an important component that can enhance circadian amplitudes. Its role depends on the transcriptional cycle of nicotinamide phosphoribosyltransferase (NAMPT), the key enzyme of NAD^+ synthesis in the NAD^+ salvage pathway. This results in a cycle in the concentration of the SIRT substrate and activator NAD^+, which drives the activities of sirtuins [33-36]. The extremely high levels of SIRT1 in tumor cells are associated with epigenetic silencing of the *Per2* gene, indicating that the oscillator is severely dysregulated and more or less fixed in a state that allows replication and mitosis [6,30]. In this state, in which *Per2* is silenced, normal rhythmicity is impossible and the oscillator has presumably escaped from the normal trajectory. In addition to SIRT1, the pro-replicative oscillator component, CLOCK, is strongly upregulated [6,30].

Sirtuins and melatonin

SIRT1 overexpression in tumor cells has consequences for its response to melatonin, a chronobiotic that modulates both central and peripheral circadian oscillators [37]. Moreover, the overexpression strongly contrasts to an entirely different situation in aging mammals, in which SIRT1 expression is declining, along with decreases in melatonin and a progressively deteriorating circadian system [6,7]. Under the conditions of aging, exogenous melatonin upregulates SIRT1 expression, as has been repeatedly shown and reviewed [6,30,38]. On the contrary, overexpressed SIRT1 of cancer cells is strongly downregulated by melatonin, in conjunction with reduced proliferative activity and additional proapoptotic effects [39-41]. This difference to nontumor cells of aging mammals has been explained on the basis of the dysregulated oscillator [6,30]. It remains to be clarified to what extent and for how long melatonin is capable to partially reactivate the oscillator and whether melatonin treatment may upregulate PER2 again.

In the context of nontumor cells, increasing evidence shows that SIRT1 functions as a mediator of several actions of melatonin, because various effects of melatonin can be suppressed by sirtuin inhibitors such as sirtinol or EX527 or by knockdown by *Sirt1* siRNA [6]. However, this relationship should be excluded for tumor cells.

Sirtuins and drug resistance

Despite the general observation that SIRT1 is typically upregulated in tumor cells and various reports on a contribution of SIRT1 to therapeutic resistance [14,18,42], the situation may be more complicated in those tumors which have already developed the drug resistance. In such cases, SIRT1 may secondarily decline. This was observed in cisplatin-resistant H1299 non-small cell lung cancer and P31 mesothelioma cells. It was found to be associated with progressively

reduced mitochondrial abundance, which explains resistance because of less production of reactive oxygen species [43]. The reasons for the secondary SIRT1 decline remain to be further studied, but especially SIRT1 and SIRT3 are associated with mitochondrial proliferation and function.

Expression *vs.* activity, a frequently overlooked but relevant aspect

A particular aspect that would deserve clarification in a number of studies concerns the fact that SIRT1 activity is rarely measured, but instead SIRT1 expression. One of the major misconceptions frequently observed in modern, gene-oriented cell biology is to believe that expression levels reflect the activity of the gene product, such as enzyme activity. Although the incorrectness of this assumption is absolutely clear from a fundamental point of view, many researchers prefer to study expression without also determining activity. Especially in the case of sirtuins, it is important remain aware of the fact that expression is not decisive, but rather enzyme activity, which depends in these enzymes on NAD^+ availability, as outlined above. Under conditions of aging, when SIRT1 expression has declined and may have become rate-limiting, an upregulation of SIRT1 may correlate with an increased SIRT1 activity, especially if increased effects can be shown to be suppressed by sirtuin inhibitors. However, this is not necessarily the case under conditions of strongly upregulated SIRT1 in tumor cells. An example for this problem has been published in a study on the effect of BRCA1 (breast cancer 1, early onset) on SIRT1 in ovarian cancer [44]. Inactivation of BRCA1was associated with decreased SIRT1 expression, but increased NAD^+ concentrations levels and, consequently, increased SIRT1 activity, whereas BRCA1 overexpression caused rises in SIRT1 expression, but decreases in NAD^+ levels and SIRT1 activity. It remains to be clarified whether a decrease in NAD^+ results from elevated consumption of the substrate or has other causes, but the findings illustrate that changes in sirtuin expression should be accompanied by measurements of the respective enzyme activities or, at least, checked for suppression of sirtuin effects by inhibitors like sirtinol or EX527.

Other sirtuins

Studies on other sirtuin subforms have been conducted much less than those on SIRT1. A certain functional overlap seems to exist between SIRT1 and SIRT2, since the latter has been shown to also deacetylate H4K16ac [45]. Moreover, SIRT2 was shown to reduce, by deacetylation at K90, the activity of the *N*-lysine methyltransferase KMT5A (alias PR/SET domain-containing protein 07; PR-Set7), which leads to a reduction of H4K20me1 that interferes with mitosis. SIRT2-deficient mice display genomic instability and are cancer-prone. Hence, SIRT2 was classified as a tumor suppressor [45]. This conclusion was confirmed by investigating keratinocyte differentiation and intracutaneous tumor suppression [46,47].

The constitutively chromatin-associated SIRT6 was also studied in keratinocytes and, particularly, in squamous cell carcinomas [48]. The microRNA miR-34a, which participates in keratinocyte differentiation, is downregulated in squamous cell carcinomas. In human keratinocytes, SIRT6 was shown to be directly targeted by miR-34a. In breast cancer, SIRT6 was shown to be downregulated at the mRNA level, but promoter methylation was not different from that in matched normal tissue [49]. More studies are needed for understanding the roles of the other sirtuin subforms in cancer.

Conclusion

All available data demonstrate a substantial relevance of sirtuin dysregulation in cancer. This includes roles in tumorigenesis, epithelial-mesenchymal transition and also therapeutic resistance. Most investigations have addressed the changes in SIRT1, but the few publications on other sirtuins indicate that further studies on these subforms would yield promising results for the understanding of cancer biology. SIRT1 is upregulated in many types of cancer. In addition to the regulatory alterations at the *Sirt1* gene, the role of the circadian oscillator deserves attention, as the strong upregulation of SIRT1 is associated with, and presumably caused by the dysregulation of cellular oscillators, which is necessary for tumor cells to avoid the expression of tumor suppressor genes in the oscillator machinery, such as *Per2*. Notably, the chronobiotic melatonin behaves in tumor cells entirely differently, compared to nontumor cells, by strongly downregulating SIRT1 and, thereby, exerting anti-tumor effects. Therefore, the dynamics of SIRT1 activity has to be considered in studies on this sirtuin. This should also be done when investigating other sirtuin subforms, which are likewise driven by NAD^+ availability. Especially under the condition of strong upregulations of sirtuins, as demonstrated for SIRT1 in tumor cells, it will be necessary to not only study sirtuin expression, but also activity, because they do not always correlate and may even be inversely coupled. Disregard of this possibility may lead to false conclusions.

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