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Sirt1: recent lessons from mouse models

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PREFACE

The family of protein deacetylases represented by yeast Sir2 has been the focus of intense investigation because of its longevity activity in yeast, worms and flies. Research in mammals has mainly focused on Sirt1, the closest homologue of Sir2. Emerging evidence from mouse models is yielding a sharper picture where Sirt1 is a potent protector from aging associated-pathologies, such as diabetes, liver steatosis, cardiovascular disease, neurodegeneration, osteoporosis and, importantly, various types of cancer.

INTRODUCTION

Over the past ten years, the aging research community has developed a growing interest in the mammalian sirtuin family (formed by paralogues Sirt1 to Sirt7), and more specifically in Sirt1, the closest homologue of yeast Sir2[1]. This interest stems from pioneer reports linking Sir2 to lifespan regulation in lower organisms. In particular, genetic overexpression of Sir2 was shown to increase lifespan in yeast[2], worms[3] and flies[4]. This remarkable effect was further corroborated in studies using purported Sir2-chemical activators, most notably resveratrol, that extended lifespan in yeast[5], worms and flies[6] in a Sir2-dependent manner. Moreover, calorie restriction (CR), which is the most effective dietary intervention to extend lifespan in different organisms[1], was shown to require Sir2, both in yeast[7] and flies[4], in order to produce lifespan extension. All these studies led to the appealing hypothesis that Sir2 is an evolutionary conserved longevity gene that mediates CR effects. If this was the case, then Sirt1 activation in mammals might improve aging without the necessity to reduce food intake. As discussed below, recent research in genetically-modified mice has demonstrated clear positive effects of Sirt1 on a variety of aspects related to mammalian health, including aging-associated diseases. Yet, current evidence does not support that Sirt1 can increase mammalian longevity.

Tidal changes

The story of Sirt1 has had its tidal changes, which should not be surprising when dealing with proteins that integrate and coordinate multiple stimuli and responses. Often, expectations run too high, and this is inevitably followed by counter expectations that go too low. In the case of Sirt1, the high expectations on its role in longevity were dimmed by studies that challenged the notion that *S. cerevisiae* Sir2 mediates CR-associated lifespan extension[8,9] and, subsequently, by a report that failed to reproduce lifespan extension by resveratrol in *D. melanogaster* and *C. elegans*[10]. Regarding mammals, resveratrol was shown to have beneficial effects on health, including improved glucose tolerance and protection from fatty liver, but without extending lifespan[11-13]. However, accumulating evidence indicates that resveratrol is not a direct activator of Sirt1[14-16], but rather acts

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indirectly through AMPK[17,18] (see Box1). Together, these conflictive results have casted a shadow on the relevance of Sirt1 in mammalian aging[19].

Another aspect that has generated debate is the relationship between Sirt1 and cancer, which, in turn, has its roots at the interplay between Sirt1 and p53. Early studies with *in vitro* cultured cells showed that Sirt1 is able to interact with and deacetylate the tumour suppressor protein p53, therefore inhibiting its transactivation potential[20,21]. In support of this, studies in Sirt1 knockout mice showed p53 hyperactivation, leading to increased thymocyte apoptosis[22], although this could not be confirmed by other investigators[23]. Moreover, Sirt1 is upregulated in several types of human tumours (reviewed in[24]), which has further supported the idea that Sirt1 could be oncogenic. However, contrary to this, all the currently available data indicate that Sirt1 is a tumour suppressor *in vivo*[25-28] and the possible consequences of Sirt1 on p53-mediated tumour suppression remain to be elucidated.

The above controversies highlight the importance of genetically-modified mouse models to address Sirt1 effects in the context of the organism. In this Progress, we discuss recent studies using genetic mouse models of Sirt1, which have shed new light into the field. For more comprehensive reviews on Sirt1, the reader is referred to recent reviews[29,30].

Sirt1 and metabolism

Sirt1 effects in metabolism are the best-characterized ones. A considerable amount of recent literature based on a variety of genetically-modified mouse models has solidly demonstrated a protective role for Sirt1 against pathologies associated to high dietary fat intake (HFD, high fat diet), such as glucose intolerance and liver steatosis (also known as fatty liver) (Table 1).

The first mouse models that linked Sirt1 to improved glucose tolerance were studies in which Sirt1 overexpression was restricted, in one case, to pancreatic β-cells[31] and, in the other one, to brain and adipose tissue[32]. The effect of Sirt1 on metabolism has been further explored in mice with whole-body transgenic expression of moderately increased levels of Sirt1 (2-3 x-fold) under its own endogenous transcriptional regulation[33,34]. Importantly, these Sirt1 transgenic mice were protected from diabetes associated to diet-induced obesity[33,34] or to genetically-induced obesity[34]. The impact of moderate systemic Sirt1 overexpression on protection from high dietary fat goes beyond glucose tolerance. In fact, whole body Sirt1 transgenic mice are remarkably protected from developing liver steatosis[33]. Consistent with this, mice deficient in Dbc1, a negative regulator of Sirt1, are also protected from fatty liver[35] and, conversely, Sirt1 heterozygous mice are prone to develop this disease[36]. Mice with tissue-specific deletion of Sirt1 have further refined the picture and have indicated that Sirt1 exerts its protective metabolic effects through its actions on multiple tissues. Namely, myeloid lineage-specific deletion of Sirt1 resulted in insulin resistance[37]; brain-specific Sirt1 deletion increased aging-associated glucose intolerance[38]; Sirt1 deletion in the pro-opiomelanocortin (POMC) neurons, that control food intake and energy expenditure, resulted in leptin resistance in these neurons and increased susceptibility to diet-induced obesity[39]; and, finally, liver-specific deletion of Sirt1 protected mice from steatosis[40]. However, regarding the latter, it should be mentioned that other investigators have reported the opposite phenotype using the same genetic model of Sirt1 deficiency in the liver[41]; the basis for these conflictive results are unclear. A separate note must be made of the few metabolic studies using whole-body Sirt1-null mice because of their paradoxical results. In particular, Sirt1-null presented higher glucose tolerance[42] and protection from fatty liver induced by LXR agonists[43], which is in sharp contrast with all above-described evidence indicating that Sirt1 protects from glucose intolerance and fatty liver. However, interpretation of the results obtained with whole-body Sirt1-null mice is

highly complex given that the majority of these mice die in the perinatal period and the survivors have developmental defects[22,44] that may obscure the role of Sirt1 in a normal physiological context. In summary, as listed in Table 1, most studies using a variety of mouse models have concluded that Sirt1 is a robust metabolic protector acting at several systems, including not only the liver, but also the brain and the immune system.

A recurrent mechanistic finding in the above-described mouse models linking Sirt1 to protection from diabetes and fatty liver is a reduced inflammatory response associated to lower levels of NFκB activity[33,35-37,40] (Figure 1). This fully supports in mice the earlier finding in cultured cells that Sirt1 binds, deacetylates and inhibits NFκB[45]. Another recurrent mechanism is the deacetylation and activation of key transcription factors involved in lipid metabolism, such as Foxo1[34] and the nuclear receptors PPARα[40], LXR[43], and FXR[46], as well as, their general co-activator PGC1α[33,40,47] (Figure 1). Numerous additional mechanisms implicating Sirt1 in metabolism have been also reported, but their detailed discussion goes beyond the scope of this Progress article. Briefly, these additional mechanisms include increased insulin production by repression of Ucp2[31,42]; deacetylation and inhibition of SREBP[33,40,48,49]; repression of the *Pparg* promoter[50]; activation of the *Sirt6* promoter[51] which, in turn, may contribute to protect from metabolic damage as demonstrated in Sirt6-overexpressing mice[52]; and deacetylation and activation of Lkb1[53,54].

Diabetes and fatty liver are diseases that often occur concurrently, and in association with other pathologies, notably including cardiovascular disease. This group of associated pathologies is referred to as the metabolic syndrome[55]. In this regard, it is worth mentioning that there is also evidence from Sirt1-mouse models indicating that Sirt1 can improve cardiovascular function[56-59]. The metabolic syndrome is characteristic of aged individuals chronically exposed to high caloric intake and low physical activity, a lifestyle of increasing prevalence that explains the high incidence of metabolic syndrome-associated diseases worldwide[55]. Based on the above-mentioned data in genetically-modified mice, Sirt1 activation is an attractive target for pharmaceutical interventions aimed to delay or ameliorate the pathologies associated to the metabolic syndrome.

Sirt1 and cancer

The analysis of cancer in mice with genetically-modified Sirt1 levels has consistently supported the concept that Sirt1 possesses strong tumour suppressive activity (Table 1). In particular, increased or decreased Sirt1 expression results, respectively, in delayed or accelerated sarcoma and lymphoma development in a p53-heterozygous background[27,28]. Interestingly, both studies obtained supporting *in vitro* evidence indicating that this tumour suppressive activity reflected the ability of Sirt1 to preserve genomic integrity in the face of p53 deficiency[27,28]. Upon DNA damage, chromatin-bound Sirt1 relocates from repeated elements to the actual DNA damaged sites, presumably repressing transcription[27] (Figure 1).

Following on the reported functions of Sirt1 in protection from DNA damage and in protection from fatty liver, whole-body Sirt1 transgenic mice were subjected to a novel carcinogenic treatment that models metabolic syndrome-associated liver cancer. Feeding mice with a high fat diet (HFD) dramatically increases the incidence of liver carcinomas in mice previously treated with a hepatic carcinogen (diethylnitrosamine, DEN) which on its own has poor carcinogenic activity[26,60]. Importantly, Sirt1 transgenic mice were remarkably protected from metabolic syndrome-driven liver carcinogenesis[26]. This protection was due to the combined effects of Sirt1, first, in reducing DNA damage by the hepatic mutagen and, then, in preventing inflammation and fatty liver by HFD[26] (Figure 1). Dietary obesity leads to liver inflammation by enhancing the expression of IL-6 and TNFα, well known targets of NFκB, and this inflammation promotes tumorigenesis[60]. Sirt1 transgenic mice show decreased NFκB activation and, concomitantly, decreased inflammation in the liver

resulting in the observed protection from liver tumorigenesis[26,33]. Of note, human liver cancers present decreased levels of Sirt1 compared to normal liver[28]. It remains to be elucidated whether Sirt1 would protect from inflammation-associated tumorigenesis in general or just from carcinogenesis associated to dietary-induced inflammation.

On another line of research, Sirt1 overexpression in enterocytes protected from intestinal tumours in the $Apc^{+/min}$ model[25]. This observation led to discovery that Sirt1 deacetylates and inhibits β-catenin in the intestine of these mice[25] (Figure 1). In further support of this, subsequent studies showed that Sirt1 suppresses the growth of colon tumour xenografts assays using human colon cancer lines[61]. Of note, recent studies using Sirt1-null mice revealed no difference in tumour development when combined with the $Apc^{+/min}$ mutation[62]. It is formally possible that Sirt1 overexpression could protect from intestinal tumorigenesis, while in the absence of Sirt1, compensatory mechanisms could supply the missing activity of Sirt1. As briefly alluded above, caution must be taken when interpreting the phenotypes observed in whole-body Sirt1-null strains due to their developmental defects[22,44].

Finally, regarding aging-associated spontaneous cancer, whole-body Sirt1 transgenic mice displayed a global decrease in cancer incidence[26]. This protection, however, was restricted to carcinomas and sarcomas, while lymphoma development was not affected by Sirt1 dosage. This differential effect is currently not well understood and it contrasts with the previously mentioned Sirt1-dependent protection from p53-deficient lymphomas. The aging-associated lymphomas developed in a p53-functional context are conceivably less aggressive and less genetically unstable than the lymphomas developed in the absence of p53. Hence, the ability of Sirt1 to preserve genomic stability could be less relevant in the context of aging-associated lymphomas. In addition to aging-associated lymphomas, Sirt1 was also found to be neutral regarding chemically-induced fibrosarcomas[26]. Apart from these two cancer models in which Sirt1 levels do not seem to affect tumorigenesis, the general finding in the above-summarized studies is that Sirt1 protects from cancer through a number of mechanisms, including protection from DNA damage, protection from diet-induced inflammation, and inhibition of the oncogenic activity of β-catenin (Figure 1). At present, there are no reports of mouse models of cancer in which Sirt1 plays an oncogenic role (Table 1).

Sirt1 and aging

The effect of Sirt1 on mammalian aging is a long-sought result in the field. Importantly, mice moderately overexpressing Sirt1 (3x-fold) under its own transcriptional regulatory elements do not live longer under standard diet conditions, but they show a healthier aging[26]. In particular, aged Sirt1 transgenic mice showed improved glucose homeostasis, better preservation of bone mineralization, reduced incidence of sarcomas and carcinomas, and reduced levels in molecular markers of aging, such as $p16^{Ink4a}$ or DNA damage[26]. Moreover, recent studies in mice have also demonstrated a protective role for Sirt1 against Alzheime's disease and amyotrophic lateral sclerosis[63,64]. The emerging picture is one in which Sirt1, through its well-established protective activities against diet-induced metabolic damage, genomic instability, and cancer, improves some aspects of aging and delays or ameliorates a number of aging-associated diseases such as metabolic syndrome, Alzheimer or some types of cancer. In summary, although current evidence does not allow to categorize Sirt1 as a "longevity" gene, it clearly is a beneficial gene for aging and aging-associated diseases.

A related issue is whether Sirt1 mediates the effects of calorie restriction (CR) on aging. Only one report has addressed this directly using Sirt1-null mice under CR[65]. As mentioned above, most Sirt1-null mice die in the perinatal period and those that survive have

developmental defects[22,44], including a shortened lifespan (median lifespan of approximately 1 year)[65]. Interestingly, CR started between 5-7 months of age did not have an impact on the longevity of Sirt1-null mice[65]. Although suggestive, the abnormally short lifespan of Sirt1-null mice makes it difficult to interpret their lack of response to CR. Additionally, some of the beneficial effects of Sirt1 on metabolism are also characteristically produced by CR, such as improved insulin sensitivity. Finally, a number of studies have reported a variety of molecular and phenotypic effects of CR that are mediated by Sirt1 in mice[38,65-69]. Overall, there is growing suggestive evidence indicating that Sirt1 participates in CR.

Conclusions and future perspectives

Recent work with genetically-modified mice has firmly established Sirt1 as a protector of metabolic syndrome and as a tumour suppressor in a wide range of cancers. Moreover, emerging evidence implicate Sirt1 in protection from cardiovascular disease[56-59] and neurodegeneration[63,64]. The fact that Sirt1 impinges on such a variety of aging-associated diseases suggests that it could be a longevity gene, although direct evidence for this is still lacking in mammals. The only available study of longevity in a mouse model with systemic Sirt1 overexpression (3x-fold) reported improved health during aging, but normal longevity[26]. In this regard, it would be interesting to test whether higher levels of Sirt1 overexpression or contemporaneous overexpression of several sirtuins could extend longevity.

Regarding metabolism, it would be of critical importance to know if, once diabetes has developed, Sirt1 activation could be used as a treatment. To this end, and until potent Sirt1 activators are developed, Sirt1 inducible knock-in mice could be used to explore this possibility. If these activators showed a benefit in diabetic patients, and given the cancer protection activity of Sirt1, it is tempting to speculate that they could diminish cancer incidence concomittantly. Precedence for this can be found in the anti-diabetic drug metformin that decreases cancer incidence both in mice[63,64] and humans[63,64].

With respect to cancer, genetic studies published so far support a protective role for Sirt1 in many types of cancer. However, this is not general and there are examples of mouse cancer types where Sirt1 does not play a role (Table 1). Besides, numerous studies based on *in vitro* cultured cancer cell lines have suggested that Sirt1 has oncogenic activities[24]. Although this has not been confirmed yet in a more physiological setting, it remains possible that future studies could reveal oncogenic activities of Sirt1 *in vivo*. Finally, a key pending question is whether Sirt1 activators have therapeutic activity on cancer.

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Box1: Resveratrol and Sirt1

Resveratrol has been widely used as a Sirt1 activator, yet a number of studies have concluded that resveratrol is not a direct activator of Sirt1[14-16]. This does not invalidate the concept that resveratrol, through indirect mechanisms, can activate Sirt1 *in vivo*. In fact, earlier reports more than 10 years ago already indicated that resveratrol was an inhibitor of mitochondrial ATP synthase[70] and this was corroborated by the crystallographic structure of ATP synthase complexed with resveratrol[71]. Inhibition of ATP synthase is predicted to increase AMP levels and therefore activate AMPK. In fact, resveratrol has been recently demonstrated to activate AMPK[18], and, finally, it is now known that AMPK increases NAD^+ levels and this, in turn, activates Sirt1[17]. This chain of events now provides a rationale for how resveratrol, albeit indirectly, can activate Sirt1.

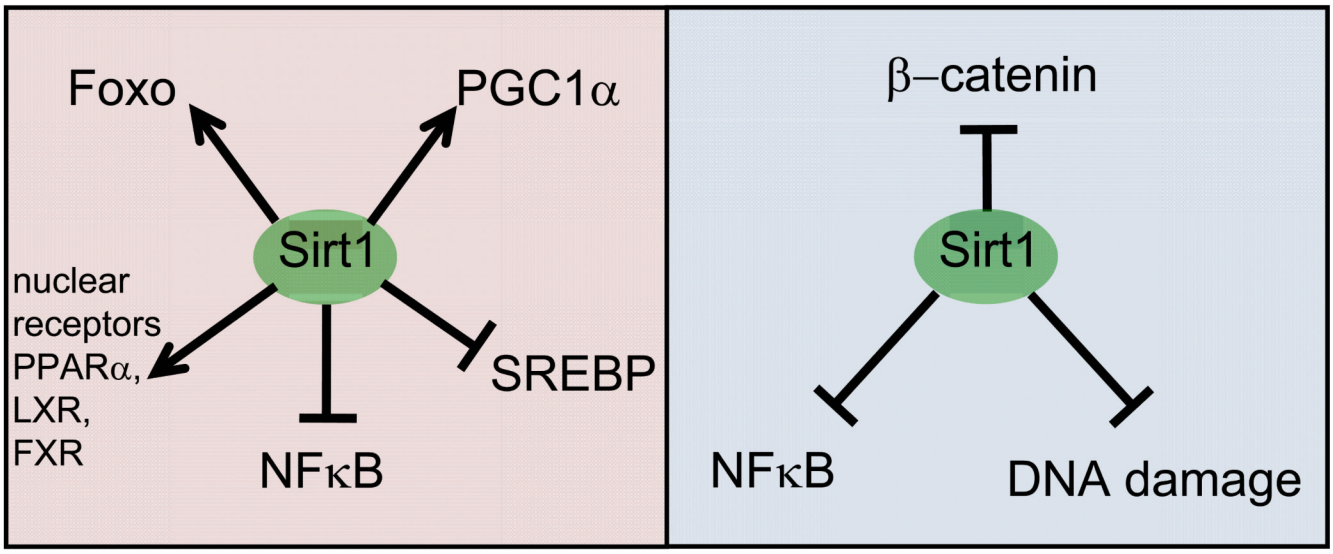

Figure 1. Summary of the main mechanisms through which Sirt1 protects from metabolic damage and cancer

The left panel shows the main mechanisms by which Sirt1, through direct deacetylation, protects from metabolic damage. Other mechanisms are mentioned in the text. The right panel shows the three mechanisms reported so far supporting cancer protection by Sirt1 in mice.

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Table 1

Sirt1 mouse models and their effects on cancer and metabolism

Modification of Sirt1 levels	Mouse model	Cancer phenotypes (*)	Metabolic phenotypes (*)	Ref.
Whole-body overexpression	Whole-body Sirt1-tg	*Decreased aging associated carcinomas and sarcomas *Decreased metabolic-syndrome associated cancer *No effect in chemically-induced fibrosarcomas *No effect in aging associated lymphomas	*Protection from glucose intolerance (associated to aging, diet-induced obesity, and genetically-induced obesity) *Protection from fatty liver disease (induced by HFD) *Decreased inflammation in WAT and liver (induced by HFD)	26,33,34
Tissue-specific overexpression	β-cells Sirt1-tg	Not explored	*Increased insulin secretion	31
	Brain and adipose tissue Sirt1-tg	Not explored	*Increased glucose tolerance *Decreased body weight	32
	Intestinal Sirt1-tg combined with $Apc^{+/min}$	*Decreased intestinal polyp formation	Not explored	25
Whole-body deficiency	Whole-body Sirt1-null	*No effect in $Apc^{+/min}$ -induced intestinal polyps *No effect in chemically-induced papillomas	*Decreased insulin production *Improved glucose tolerance *Protection from fatty liver (induced by LXR agonists)	42,43,62
	Whole-body Sirt1-het	Not explored	*Increased fatty liver disease (induced by HFD) *Increased body weight *Increased liver inflammation	36
	Whole-body Sirt1-het combined with p53-het	*Increased incidence of sarcomas and lymphomas associated to p53 deficiency	Not explored	28
Tissue-specific deficiency	Liver Sirt1-null	Not explored	*Protection from glucose intolerance (induced by HFD) *Decreased liver weight with HFD *Decreased body weight with HFD	41
	Liver Sirt1-null	Not explored	*Increased fatty liver disease (induced by HFD) *Increased inflammation and ER-stress in liver (induced by HFD) *Increased body weight with HFD	40
	Myeloid lineage Sirt1-null	Not explored	*Increased glucose intolerance (induced by HFD) *Increased inflammation in WAT and liver (induced by HFD)	37
	Brain Sirt1-null	Not explored	*Increased glucose intolerance (associated to aging)	38
	POMC neurons Sirt1-null	Not explored	*Protection from diet-induced obesity	39

(*) Phenotypes in green colour are those that imply a beneficial effect of Sirt1, on the contrary, those in red imply a detrimental effect of Sirt1.