tumors particularly benefit from pharmacologic EPO antagonism? The authors speculate that PDGF-B–specific and EPO-specific neutralizing agents could overcome the drug resistance associated with VEGF-specific antibody therapy. Yet evidence is strongest for stromal PDGF-C, and not PDGF-B, production in response to VEGF inhibitors[16]. Further, therapeutic use of EPO neutralization could be limited by the induction of excessive anemia.

Several key questions remain. Do spontaneous tumors that express PDGF-B, either in mice or in humans, also exploit stromal EPO circuitry similar to the engineered PDGF-B–overexpressing tumors used in the current study? Could PDGF-B–induced EPO production promote tumorigenesis by stimulating EPO receptors on tumor cells as well as on endothelium? The further characterization of the EPO-producing stromal cell types would be of interest, as the stromal cell secreting EPO seem to be poorly defined, except for PDGFR-β expression and negative staining for various stromal markers. Overall, the description of tumor stromal EPO synthesis clearly expands the known repertoire of EPO-producing cell types[5,6] with implications for neoplastic progression. Additionally, the studies of Xue *et al.*[5] should provide a strong platform for the further definition of functions of PDGF-B–regulated stromal EPO production in both the malignant and nonmalignant settings.

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# Finding a sirtuin truth in Huntington's disease

Albert R La Spada

**The search for compounds to treat neurodegenerative disorders is especially pressing given the rapidly growing elderly human population and has led to the consideration of sirtuin proteins as potential therapeutic candidates. Two studies now report that modulating the expression of the sirtuin Sirt1 has therapeutic benefit in Huntington's disease mouse models and identify putative downstream targets of Sirt1 involved in improved disease outcomes (pages 159–165 and 153–158).**

The sirtuins are a conserved family of primarily NAD-dependent deacetylase proteins and have garnered much attention since the first report that the yeast sirtuin Sir2 can extend lifespan in this organism[1]. After more than 15 years of study, a central role for sirtuins in nutrient sensing is well established, and there is strong evidence to suggest that sirtuins are an integrative link between metabolic control and transcriptional regulation, although the importance of sirtuins in promoting lifespan extension is debatable[2]. Sirtuins have been shown to be necessary for mediating the beneficial effects of caloric restriction, and caloric restriction in mouse models of neurodegeneration was found to ameliorate disease symptoms and pathology, leading to the controversial notion that sirtuins might represent important therapeutic targets for neurodegenerative disorders.

In this issue of *Nature Medicine*, two reports by Jeong *et al.*[3] and Jiang *et al.*[4] show that the mammalian sirtuin Sirt1 can protect against mutant huntingtin neurotoxicity in three different mouse models of Huntington's disease. These studies provide new insights into the neuroprotective functions of sirtuins and may thus have important implications for the development of neurotherapeutics.

Huntington's disease is a dominantly inherited neurodegenerative disorder characterized by uncontrolled movements, cognitive decline and psychiatric abnormalities. It is caused by the expansion of a CAG repeat in the gene encoding huntingtin, leading to the expression of huntingtin with expanded glutamine tracts[5]. Huntingtin bearing an expanded polyglutamine stretch adopts an altered conformation, resulting in protein aggregation. Huntington's disease is one of nine polyglutamine diseases that share this feature of aberrant proteostasis with a larger class of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.

Several mouse models that recapitulate features of Huntington's disease have been generated by the transgenic expression of a severely truncated N-terminal huntingtin fragment or the full-length huntingtin protein. Jeong *et al.*[3] focused on R6/2 mice, one of the truncation models, and crossed them to a brain-specific knockout (BSKO) of Sirt1 or a model in which Sirt1 was knocked in to the endogenous β-actin locus (Sirt1-KI). They found that BSKO-R6/2 mice suffered from a more severe neurodegenerative and neuropathological phenotype than R6/2 mice, but the Sirt1-KI–R6/2 mice showed the opposite outcome: an amelioration of neuronal atrophy and protein aggregation, accompanied by a 30% extension in survival. By comparison, Jiang *et al.*[4] used a different truncation model, N171-82Q mice, and a full-length model in which huntingtin was expressed from a bacterial artificial chromosome (BAC-HD mice), and crossed each of these models with a different Sirt1 transgenic model from the one used by Jeong *et al.*[3]. They found that Sirt1

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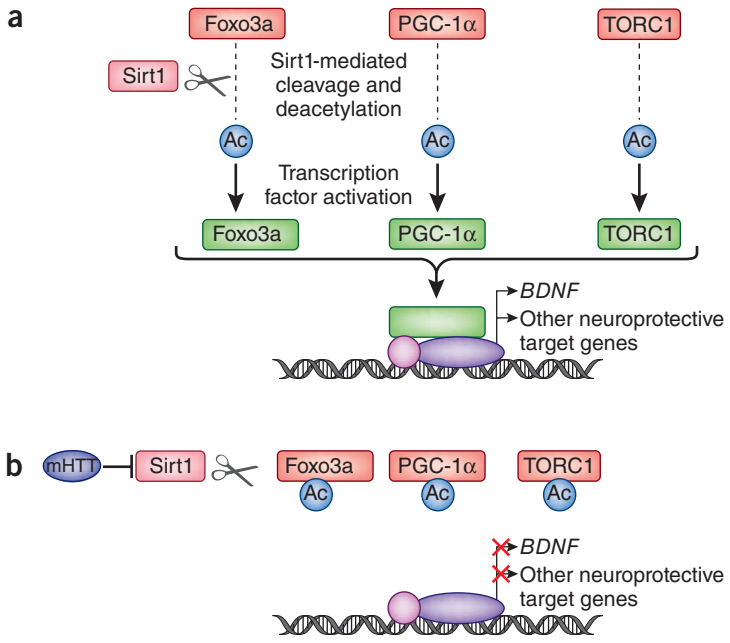


**Figure 1** Inhibition of Sirt1 contributes to Huntington's disease pathogenesis. (**a**) Sirt1 has a deacetylase domain, and Sirt1-mediated removal of key acetyl groups from certain regulatory transcription factors activates these proteins, allowing them to promote the expression of neurotrophic factors, BDNF and neuroprotective genes in the central nervous system. (**b**) The work of Jeong *et al.*[3] and Jiang *et al.*[4] indicates that Huntington's disease pathogenesis involves interference with Sirt1 deacetylation of such target proteins, and the authors present evidence that Foxo3a and TORC1, a transcriptional co-activator of CREB, are repressed in Huntington's disease. PGC-1α, an established Sirt1 target that has already been implicated in Huntington's disease is also shown, although these two studies did not directly address the status of PGC-1α. Mutant huntingtin (mHTT) carrying a polyglutamine expansion physically interacts with Sirt1 to inhibit its deacetylase activity. This prevents the activation of Sirt1 target proteins, which results in decreased expression of neurotrophic and neuroprotective factors, leading to Huntington's disease neurodegeneration.

overexpression significantly attenuated motor phenotypes and reduced neuronal atrophy in both Huntington's models. Together, these two independent studies strongly support that Sirt1 expression is a powerful modifier of Huntington's disease phenotypes in transgenic mice.

How does Sirt1 mediate neuroprotection in Huntington's disease? To answer this question, both groups considered brain-derived neurotrophic factor (BDNF), whose reduced expression has been strongly implicated in Huntington's disease striatal degeneration[6]. Jeong *et al.*[3] identified BDNF using an expression array analysis of striatal samples from Sirt1-KI–R6/2 mice, leading them to perform a detailed analysis of BDNF transcription regulation. This work yielded evidence that Sirt1 transactivates BDNF expression at a promoter region that is also regulated by the cyclic AMP response element binding (CREB) transcription factor. This finding led Jeong *et al.*[3] to investigate whether transducer of regulated CREB activity 1 (TORC1), a transcriptional coactivator known to enhance CREB function[7] (not to be confused with the mTORC1 complex), is involved in Sirt1-mediated regulation of BDNF transcription. Through a comprehensive biochemical analysis, they determined that Sirt1-mediated deacetylation of TORC1 at certain lysine residues (particularly Lys13) promotes TORC1's interaction with CREB and that mutant huntingtin interferes with Sirt1 through a physical interaction that may be dependent on polyglutamine length[3].

Jiang *et al.*[4] had previously implicated BDNF in the rescue of the Huntington's disease phenotype, prompting them to examine the BDNF receptor and discover that Sirt1 overexpression favored the phosphorylation and consequent activation of Trk-B, a neurotrophic tyrosine kinase. They also evaluated the effects of Foxo3a, which is a well-known Sirt1 target and candidate neuroprotective factor, and found that Sirt1 restoration of ATP production in cultured Huntington's disease striatal-like neurons depends upon Foxo3a, and that Foxo3a overexpression is linked to the recovery of BDNF and DARPP32 (a dopamine pathway protein) expression in Huntington's disease cells. Akin to Jeong *et al.*[3], Jiang *et al.*[4] also found that Sirt1 deacetylase activity is crucial for neuroprotection in the Huntington's disease cells, presumably via its activation of Foxo3a, although Sirt1 could also act on other targets, such as PGC-1α, for which a role in Huntington's disease pathogenesis is well established[4].

Thus, on the basis of these two studies, a model for Sirt1 dysfunction in Huntington's disease would include the following key elements: physical interaction of mutant huntingtin protein with Sirt1, inhibition of Sirt1 deacetylase activity, inactivation of Sirt1 downstream targets such as TORC1 and Foxo3a, and reduced expression of crucial neurotrophic factors and metabolic regulators (**Fig. 1**).

The role of sirtuins in neurodegeneration has been heavily debated, and conflicting reports have argued that sirtuin activation or inhibition can be neuroprotective. This has even been the case in Huntington's disease, in which studies in *Caenorhabditis elegans* support a neuroprotective role for sirtuins but studies in *Drosophila* do not[8,9]. In terms of mammalian relevance, Sirt1 activation in a mouse model with some features of Alzheimer's disease has been shown to be potentially neuroprotective[10]. However, the fact that sirtuins have diverse physiological roles and affect a range of metabolic processes confounds investigations with Sirt1 and its pharmacological activators. Many neurodegenerative disease models actually show non-neural phenotypes, including metabolic abnormalities. Indeed, small body size and reduced body weight have been observed in most mouse models for such disorders, and Huntington's disease mouse models also show perturbed glucose metabolism and insulin pathway regulation. As Sirt1 can elicit multiple divergent effects in the central nervous system and periphery, different outcomes might occur, depending on how, when and where Sirt1 is activated.

A comparison of the work of Jeong *et al.*[3] and Jiang *et al.*[4] reveals that although the Sirt1-KI–R6/2 mice did not show increased body weight, Sirt1 overexpression in the BAC-HD mice attenuated weight loss and abnormal glucose regulation[3,4]. Furthermore, there is a disconnect between the observed effects of Sirt1 on protein aggregation, with Sirt1 overexpression or knockout modulating inclusion formation in the brain of the R6/2 mice, but Sirt1 has no effect on aggregation in the N171-82Q mice. These findings underscore the complexity inherent in working with alternative Huntington's disease models and varying types of Sirt1 mouse models in which Sirt1 modulation is accomplished in different ways.

Nonetheless, the two studies provide compelling support that Sirt1 has a neuroprotective effect in Huntington's disease, and they also raise important questions. Perhaps the

most imperative issue is whether there are broader implications of Sirt1's neuroprotective effects for other neurodegenerative diseases. Jeong *et al.*[3] and Jiang *et al.*[4] propose that Sirt1 inhibition is driven by a physical interaction between mutant huntingtin and Sirt1. Of course, delineating the nature of this interaction, for example, whether it is direct or indirect, and why it occurs with normal huntingtin, will be important topics for future studies. But if only the Sirt1–mutant huntingtin interaction accounts for Sirt1 dysfunction, then Huntington's disease may represent a special case, and other neurodegenerative disorders may not be as affected by alterations in Sirt1, unless the mutated proteins responsible for those diseases also interact with Sirt1. Despite this caveat, Sirt1 deserves careful consideration as a therapeutic candidate based on the neuroprotective potency of its targets. Indeed, interfering with PGC-1α function may contribute to both Huntington's and Parkinson's diseases[11], and Foxo3a can promote motor neuron survival when mutant neurodegenerative disease causing proteins are present[12]. Hence, although many questions remain about Sirt1 and other mammalian sirtuins, these two new studies suggest that sirtuins should receive even more attention, especially from investigators seeking treatments for neurodegenerative disorders.

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# Telomerase at the center of collapsing glomerulopathy

Sumant S Chugh & Lionel C Clement

**Collapsing glomerulopathy, the classic kidney lesion in HIV-associated nephropathy, is characterized by the closure of glomerular capillary loops and epithelial cell proliferation. A new study shows that upregulation of TERT, the reverse transcriptase component of telomerase, in podocytes, the key filtration cells in the kidney, plays a major part in the development of this condition by activating Wnt signaling (pages 111–119).**

The kidney condition collapsing glomerulopathy was first noted in people infected with HIV[1], and was later also shown to occur independently of HIV infection (non-HIV collapsing glomerulopathy)[2]. HIV-associated collapsing glomerulopathy is characterized by the presence of protein in the affected individual's urine (proteinuria) and rapid loss of kidney function. Since the use of antiretroviral therapy became widespread, the incidence of this condition has declined. Nevertheless, it continues to be a substantial cause of morbidity in people with HIV[3]. The identification[4] and characterization[5] of glomerular lesions in transgenic mice that express HIV-1 genes two decades ago brought hope that the pathogenic mechanisms of collapsing glomerulopathy would finally be unraveled. However, despite some progress in this area and the development of additional transgenic models for individual HIV genes, the major mechanisms of this disease have not been elucidated.

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In this issue of *Nature Medicine*, Shkreli *et al.*[6] describe a major breakthrough in understanding the pathogenesis of HIV-associated collapsing glomerulopathy. Using a mouse model in which TERT could be overexpressed in multiple organs in an inducible manner, the authors showed that these mice developed glomerular collapse (**Fig. 1**) without substantial structural and functional changes in most other organs[6]. Moreover, human kidney tissue samples from individuals with HIV or idiopathic collapsing glomerulopathy showed TERT upregulation. The authors found that TERT overexpression led to activation of Wnt signaling and that the glomerular phenotype could be reversed by switching off the TERT transgene or blocking Wnt signaling[6], suggesting that targeting the Wnt pathway may be of clinical benefit in people with HIV-associated collapsing glomerulopathy.

In additional mutant mice that were deficient in TERC, the RNA component of telomerase, or that overexpressed a mutant form of TERT that was catalytically inactive, Shkreli *et al.*[6] revealed that the TERT-mediated glomerular effect is independent of TERC and the reverse transcriptase activity of TERT. The phenotype of the inducible mice could be reversed after switching off TERT overexpression. Consistent with the observations in mice, biopsies from individuals with HIV-associated and idiopathic collapsing glomerulopathy showed elevated TERT expression in podocytes. By contrast, kidney tissues from people with classic focal and segmental glomerulosclerosis, a glomerular pathology that is not associated with podocyte proliferation, had similar levels of TERT expression to controls without kidney disease.

How does TERT overexpression lead to glomerular pathology? Mature podocytes are normally quiescent, but Shkreli *et al.*[6] found that overexpression of TERT led to dedifferentiation and proliferation of podocytes. The authors had previously shown that TERT can modulate transcriptional responses regulated by the Wnt pathway[7]. In the current study they found that mouse podocytes overexpressing TERT showed upregulated expression of and increased nuclear localization of the Wnt factor β-catenin, as well as activation of Wnt target genes[6]. The authors also found evidence of Wnt pathway activation in HIV-transgenic mice, and kidney biopsies from patients with HIV and non-HIV collapsing glomerulopathy. Moreover, inhibition of the Wnt pathway in the inducible TERT-transgenic model and in HIV-transgenic mice significantly improved the glomerular phenotype and reduced proteinuria. The parallel changes in TERT and β-catenin expression in human biopsies and in