NAD+

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Boosting astrocytic NAD+ against tauopathy

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Nicotinamide adenine dinucleotide (NAD^+) decline is a molecular characteristic of aging and age-associated neurodegenerative diseases. Lee and colleagues uncover an astrocyte-specific regulatory axis directed by the circadian clock component REV-ERBα, and provide proof-of-concept evidence that targeting this pathway alleviates tauopathy in mouse models.

NAD^+ is well recognized to have a major role in aging physiology and various age-associated diseases[1]. NAD^+ serves as a redox carrier and co-enzyme for multiple enzymatic reactions, which are critically involved in brain function, energy homeostasis, DNA and RNA metabolism, inflammation and stress responses throughout the lifespan. There has been a sustained interest in understanding NAD^+ biology and exploring NAD^+ augmentation as an interventional strategy to decelerate aging. Many NAD^+ precursor supplements are commercially available; however, they display marked interindividual variations in efficacy and side effects[2]. Therefore, in-depth mechanistic understanding of NAD^+ regulation and function is still needed to fully exploit its translational potential. In a new study, Lee et al.[3] reveal a pathway directed by the circadian clock protein REV-ERBα to modulate NAD^+ in astrocytes, and provide evidence that deletion or inhibition of REV-ERBα leads to marked pathological and behavioral improvements in tauopathy mice. These results illuminate a cell-type-specific mechanism by which boosting NAD^+ can protect against brain aging and neurodegenerative diseases.

NAD^+ homeostasis is maintained through a complex interplay of enzymes and regulatory factors that function in biosynthesis, consumption and recycling pathways[1]. One of the key cellular mechanisms that bidirectionally intersect with NAD^+ metabolism is the circadian clock, a network of ubiquitous molecular oscillators in which positive (CLOCK, BMAL1 and RORs) and negative (CRYs, PERs and REV-ERBs) factors are organized into intertwined feedback loops[4] (Fig. 1). For example, several NAD^+-requiring enzymes, such as sirtuins and PARPs, have been shown to regulate the clock via post-translational modifications of clock proteins[5]. Furthermore, it has previously been shown that cellular NAD^+ levels display circadian oscillations and that the *Nampt* gene (which encodes the rate-limiting enzyme in the NAD^+ salvage pathway) is transcriptionally controlled in the liver by CLOCK–BMAL1 via their E-box consensus site[6,7]. These studies provide a tantalizing clue that the clock — and especially REV-ERBα — may function to fine-tune NAD^+ metabolism and downstream physiological processes.

Previous studies from Musiek and colleagues have shed important light on a regulatory role of REV-ERBs in the pathological hallmarks of Alzheimer's disease. First, they showed that constitutive global knockout of *Nr1d1* (which encodes REV-ERBα) attenuated Aβ plaque formation and suppressed disease-associated microglial markers in an amyloid mouse model of Alzheimer's disease[8], which suggested a role for REV-ERBα in disease pathogenesis. Somewhat surprisingly however, they later reported that a microglia-specific *Nr1d1* disruption aggravated tau pathology and neuroinflammation in male PS19 tauopathy mice, which was in part attributable to microglial lipid accumulation[9]. These results — coupled with the tissue-specific nature of circadian clock function[4] — prompted them to further explore the specific role of REV-ERBs in brain aging and tauopathy.

In the current study[3], the authors first globally disrupted *Nr1d1* in mice (referred to as RKO mice) via a conditional tamoxifen–Cre driver, and performed bulk RNA sequencing using hippocampus tissues. Interestingly, they observed upregulation of *Nfil3* (also known as *E4bp4*), which encodes a circadian transcription repressor that is known to be directly regulated by REV-ERBα, and marked downregulation of *Cd38*, which encodes a critical enzyme that is involved in NAD^+ consumption. These results raised the intriguing possibility of an

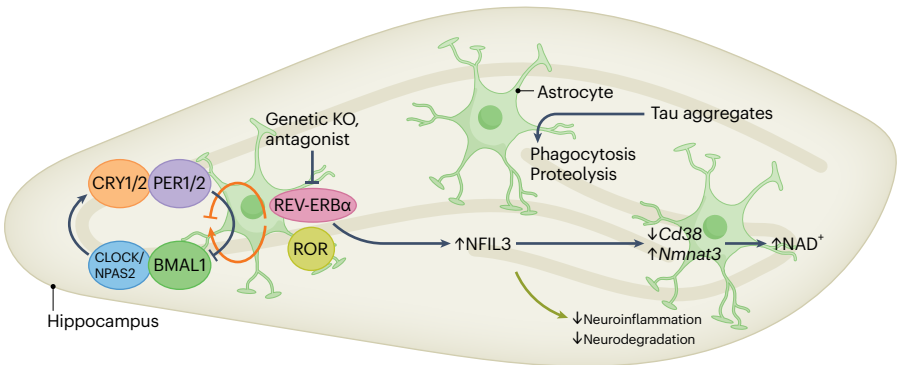

Fig. 1 | The REV-ERBα–NFIL3–CD38 axis regulates astrocytic NAD^+ in tauopathy. REV-ERBα is a nuclear receptor in the circadian oscillator. Lee et al. demonstrate that deletion or inhibition of REV-ERBα leads to upregulation of NFIL3, another circadian repressor protein, followed by a reduced expression of CD38, an NAD^+-consuming protein that is enriched in astrocytes. As a result, astrocytes display increased NAD^+ levels as well as enhanced tau uptake and proteolysis, which blunts tauopathy and neurodegeneration. KO, knockout.

astrocyte-specific mechanism that is distinct from those in other cell types or tissues. First, as *Cd38* is primarily expressed in astrocytes, REV-ERBα could drive an additional cell-type-specific axis, beyond its previously identified role in microglia[9]. Second, the downregulation of *Cd38* by REV-ERBα contrasted with the role of REV-ERBα to enhance NAMPT levels and NAD^+ homeostasis in the heart, which confers protection against cardiomyopathy[7]. Indeed, Lee et al. identified that *Nampt*, which is clock-regulated in the liver and heart[6,7], was not altered in the hippocampus of RKO mice.

To explore a possible astrocyte-specific and CD38-mediated mechanism that is downstream of REV-ERB circadian control, they performed *Nfil3* knockdown in primary cultured astrocytes, which was found to suppress CD38 expression. This result, coupled with bioinformatic identification of putative D-box consensus sites in the *Cd38* locus, strongly suggests a direct regulatory axis of REV-ERBα–NFIL3–CD38. Interestingly, they further discovered that the transcript expression of *Nmnat3*, another gene in the NAD^+ salvage pathway in the mitochondria, was induced in RKO hippocampus, which suggests a multifaceted control by REV-ERBα of cellular and subcellular NAD^+ homeostasis. Accordingly, NAD^+ and several NAD^+ metabolites were found to be enriched in the hippocampus of RKO mice.

Next, the authors generated compound mice that harbor the conditional *Nr1d1* knockout allele in the PS19 tauopathy mouse background (termed PS19;RKO mice). *Nr1d1* deletion was found to increase the level of NAD^+ in the brain in the tauopathy background, and to normalize protective gene signatures in synaptic signaling and neuroinflammation. Consistently, the tau pathological hallmarks were alleviated, as evidenced by reductions in the levels of hyperphosphorylated and misfolded tau. Astrocyte and microglial activation was concomitantly reduced. Although neuronal activity as measured by FOS staining was unchanged in PS19;RKO mice, greater hippocampal volume and CA1 thickness were observed, which indicates a neuroprotective role of REV-ERBα abrogation in tauopathy.

To specifically assess the role of the REV-ERBα–CD38 axis in astrocytes, the authors subsequently produced astrocyte-specific *Nr1d1* deletion (ARKO) mice, and observed *Cd38* downregulation and hippocampal NAD^+ induction in the ARKO mice, reminiscent of the changes in RKO mice. In the compound PS19;ARKO mice, levels of phosphorylated tau were reduced and there was a trend of increased NAD^+ levels. These results together pinpoint the astrocyte-resident REV-ERBα–CD38 axis as a key player in modulating NAD^+ homeostasis and tau pathology. To determine how the astrocytic pathway functions to mitigate tauopathy, they established an in vitro system and demonstrated that knockdown of *Nr1d1* or *Cd38* in primary cultured astrocytes recapitulated the in vivo effects of NAD^+ induction. Importantly, they found that *Cd38* knockdown in the cultured astrocytes enhanced the uptake of tau aggregates and lysosomal proteolysis. Finally, complementary to the above genetic approaches, the authors subjected PS19 mice to an acute treatment of a REV-ERB antagonist, SR8278, via intraperitoneal injection for 2 weeks. Although NAD^+ levels only showed a trend of induction, significant improvements of tau pathology were observed in 9-month-old PS19 mice.

This work has several important implications (Fig. 1). First, this study underscores REV-ERBα as a molecular target against brain aging and tauopathy-related neurogenerative diseases. REV-ERBα is a nuclear receptor that is embedded in the core oscillator of the circadian clock, and many published studies have characterized various compounds that bind to and modulate REV-ERBs[10,11]. More specifically, REV-ERB is strategically located in the secondary loop of the oscillator along with ROR receptors, functioning to fine-tune the primary loop that drives circadian periodicity and modulate downstream gene regulatory networks[4,12]. Therefore, tissue-specific, tonic manipulation of REV-ERBα, as shown by Lee et al., can selectively reprogram circadian gene networks, which leads to desired beneficial effects against age-related pathologies. Furthermore, the study highlights an important role of manipulating astrocytic NAD^+ to mitigate tau pathology, potentially via phagocytosis and proteolysis by astrocytes. In addition, although REV-ERB disruptions in microglia[9] and astrocytes[3] showed distinct effects in tauopathy, the global knockout studies suggested that the astrocyte REV-ERBα deletion predominates over the microglial counterpart to render protective outcomes. This may be explained, at least in part, by the enriched transcript expression of REV-ERBα in astrocytes relative to microglia[13], which suggests a functional importance of astrocytes and the astrocyte clock in tauopathy. Finally, whereas NAMPT and sirtuins are well-known circadian targets in peripheral organs such as the liver and heart, the identification of CD38 as the key NAD^+-consuming factor regulated by REV-ERBα in astrocytes is an important finding. CD38 constitutes a cell-type-specific effector for circadian regulation of NAD^+ homeostasis, which has strong translational potential in Alzheimer's disease-related tauopathy.

Future studies should be conducted to address some key follow-up questions. Extending the acute treatment results, a more refined regimen (for example, compounds with a favorable dose and pharmacokinetic profiles) over a chronic timescale is required to further optimize the interventional efficacy against tauopathy, ideally in multiple disease models. The mechanism by which REV-ERBs regulate NAD^+ in cell-type- and subcellular-specific manners, and how this NAD^+ axis is connected to tau uptake and proteolysis, can be further explored. For example, expression of both *Cd38* and *Nmnat3* were altered in the RKO mice. The contribution of the latter remains to be defined. It is also worth noting that despite *Nr1d1* being among the most oscillatory genes in the whole genome[14], CD38 levels remained constantly downregulated in the absence of REV-ERBα, which suggests a mechanistic complexity that may involve other regulatory proteins. Relatedly, whether and how REV-ERB deletion in astrocytes may perturb local and systemic circadian rhythms can be further characterized, including metabolic pathways and sleep–wake cycles that are known to be involved in tauopathy and/or Alzheimer's disease pathology[15].

In conclusion, the study by Lee et al. highlights REV-ERBα as a cell-type-specific regulator of NAD^+ homeostasis that can be leveraged to decelerate brain aging and tauopathy-related neurodegenerative diseases. Future studies should aim to both refine the interventional strategies that target REV-ERBα and its effectors such as CD38 and to define the mechanistic links among REV-ERBα, circadian rhythms, NAD^+, astrocytes and tauopathy in vivo.

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Z.C. and S.-H.Y. jointly conceptualized the outline. Z.C. drafted the initial text. S.-H.Y. provided key conceptual input and drafted the figure. Z.C. and S.-H.Y. revised the complete draft and approved the submission.

Competing interests
The authors declare no competing interests.