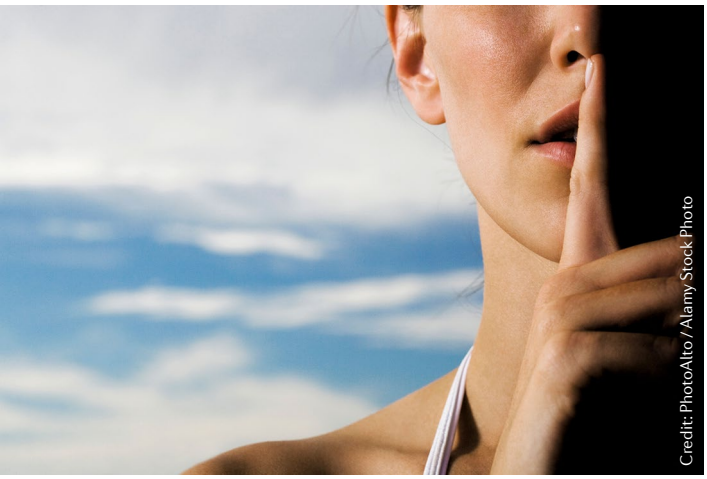
Credit: PhotoAlto / Alamy Stock Photo

dysregulated neurogenesis and implicate elevated Notch signalling in delayed terminal differentiation.

This study demonstrates potential for chromosome therapy by inducing *XIST* expression in differentiated cells. In addition, experimentally controlled *XIST* expression provides a platform to study the neurodevelopmental phenotypes of Down syndrome.

Minju Ha, Associate Editor, Nature Communications

ORIGINAL ARTICLE Czerminski, J. T. & Lawrence, J. B. Silencing trisomy 21 with XIST in neural stem cells promotes neuronal differentiation. *Dev. Cell* https://doi.org/10.1016/j.devcel.2019.12.015 (2020)

> ECM of tendons harbours collagen fibres that are continuously remodelled in a circadian fashion

collagen fibres per cell. In line with these observations, the tendons of mice harbouring tendon-specific deletion of the *Clock* partner, *Bmal1*, were thicker and exhibited aberrant mechanical properties, along with disturbances in collagen fibre distribution and architecture.

Thus, in addition to a lifelong pool of collagen, ECM of tendons harbours collagen fibres that are continuously remodelled in a circadian fashion through rhythmic pro-collagen secretion and collagen degradation, and this remodelling is important to maintain tissue function. It would be interesting to study whether, and if so how, these homeostatic mechanisms are perturbed in genetic disorders, fibrosis, wound-healing deficiencies and ageing.

Paulina Strzyz

ORIGINAL ARTICLE Chang, J. et al. Circadian control of the secretory pathway maintains collagen homeostasis. *Nat. Cell Biol.* **22**, 74–86 (2020)
RELATED ARTICLE Patke, A., Young, M. W. & Axelrod, S. Molecular mechanisms and physiological importance of circadian rhythms. *Nat. Rev. Mol. Cell Biol.* https://doi.org/10.1038/s41580-019-0179-2 (2019)

Journal Club

LIPID TRANSFER AT ER–ISOLATION MEMBRANE CONTACTS

The core step of autophagy involves nucleation of the isolation membrane and its expansion and closure into the double-membrane autophagosome. As the isolation membrane expands into an autophagosome, its outer and inner surfaces are closely apposed to the endoplasmic reticulum (ER). The associated ER also interconnects with the isolation membrane, mainly at its growing edges, via thin tubular membrane extensions. These ER–isolation membrane associations are collectively referred to as ER–isolation membrane contacts. ER–isolation membrane contact formation is mediated by multiple tethering complexes, which may be differentially employed at different locations of the isolation membrane and different stages of autophagosome biogenesis. The main tethering mechanism involves the interaction of the integral ER proteins VAPA and VAPB (VAPs) with the FIP200–ULK1 complex, FIP200–ULK1 with one of the WD40-repeat-containing PI3P-binding proteins (WIPIs), and WIPIs with the core autophagy protein ATG2 (Zhao et al., 2017; 2018).

> ATG2 may directly transfer phospholipids from the ER to the isolation membrane at contact sites

The lipid source for isolation membrane expansion has been a long-standing question. It has been suggested that phospholipids could be supplied by vesicular transport and lateral diffusion from source membranes via membrane continuities. Recent in vitro studies demonstrate that ATG2 acts as a lipid transfer protein (Maeda et al., 2019; Osawa et al., 2019; Valverde et al., 2019). ATG2, together with VPS13 proteins, which are present at multiple membrane contact sites, belong to a family of evolutionarily conserved lipid transfer proteins whose N termini contain a chorein_N domain. Structurally, ATG2 and VPS13 form an elongated groove-shaped hydrophobic cavity and the chorein_N region forms a cap at one tip. The hydrophobic groove is able to solubilize and transport lipids between two tethered membranes (Wong et al., 2019). The cavity of ATG2 and VPS13 accommodates and transfers tens of glycerophospholipids at once. The lipid transfer activity of ATG2 is independent of ATP hydrolysis and is promoted by membrane tethering (a process enhanced by complex formation with ATG18/WIPIs), and also by negatively charged membranes.

Identification of ATG2 as a membrane tethering factor and a bulk lipid transfer protein provides novel insights into the lipid source for isolation membrane expansion. ATG2 may directly transfer phospholipids from the ER to the isolation membrane at contact sites. However, the exact mechanism by which phospholipids are unidirectionally channelled from the ER to the isolation membrane via ATG2 remains to be elucidated. Isolation membranes form contacts with other membrane-bound organelles such as lipid droplets and mitochondria, raising the possibility that other lipid transport proteins may also participate in autophagosome biogenesis.

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RELATED ARTICLE Wong, L. H. et al. Lipid transfer proteins: the lipid commute via shuttles, bridges and tubes. *Nat. Rev. Mol. Cell Biol.* **20**, 85–101 (2019)