diagnostics when it does not involve a disease-causing variant. Although this might be true to some extent, it is a rather unsatisfactory explanation in this era of deep DNA sequencing. Nevertheless, Luo and colleagues' findings should provoke a reassessment of the extensive global mtDNA sequencing data available, for those wishing to unearth further instances of atypical heteroplasmy. If the paternal contribution to mtDNA is more common than previously realized, this could alter some estimated timings of human evolution, because these are often based on predictions of mtDNA sequence variation under the assumption of exclusive maternal inheritance.

Although biparental inheritance of mtDNA and heteroplasmy coincided with disease symptoms in some of the individuals studied by Luo *et al.*, the authors' data do not demonstrate a causal link with disease. In fact, we cannot be certain that the study participants have mitochondrial disease, because no specific examinations to confirm this diagnosis are reported. Further study is needed to identify more cases of potential paternal mtDNA inheritance, and to determine the functional consequences of such heteroplasmy. Notably, this knowledge is relevant to mitochondrial-donation therapy ("three-parent babies"), which aims to prevent the transmission of disease-causing mtDNA to offspring[14], but which can also potentially generate individuals with two types of mtDNA, one from the donor and another from the mother.

Could the amount of paternal mtDNA in a fertilized egg or developing embryo be deliberately boosted to diminish the adverse effects of mutant maternal mtDNA when this is present? This is an interesting option, but still far from reality. In addition to evading elimination, paternal mtDNA molecules would need to have a considerable replicative advantage over maternal ones to reach meaningful proportions.

Will Luo and colleagues' findings affect the counselling of individuals carrying disease-causing mtDNA mutations who are considering having children? Not greatly, because paternal mitochondrial transmission seems to be exceedingly rare in humans. At present, this discovery represents an interesting conceptual breakthrough, rather than one that will directly influence clinical practice.

Previous work[15] has shown that mitophagy, the process by which cells 'eat' their own mitochondria, has a role in the selective elimination of paternal mitochondria. Given our rapidly expanding knowledge of mammalian mitophagy *in vivo*[16], these rare instances of paternal mtDNA transmission might be attributed to defective mitochondrial turnover. The inheritance pattern of paternal mtDNA in Luo and colleagues' study suggests that a yet unidentified gene on one of the autosomes (non-sex chromosomes) is involved in eliminating paternal mitochondria. The families in whom paternal mtDNA inheritance was observed provide an exciting opportunity to decipher the signalling pathways that modulate paternal mitochondrial elimination and prevent biparental mitochondrial transfer. ■

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CELL BIOLOGY

How to fine-tune the cell's force producers

Identification of the enzyme that catalyses a site-specific modification of the protein actin reveals how this change modulates the function of the cell's force-producing machinery. SEE LETTER P.372

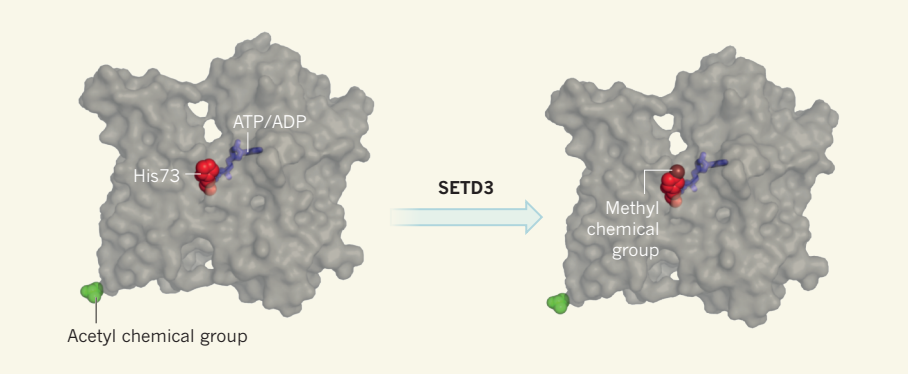
PEKKA LAPPALAINEN

Actin is one of the most abundant proteins in our cells. It assembles into filaments that produce force for many processes that are essential to the life of animals, plants and fungi — including cell migration and division, and muscle contraction[1]. The organization and dynamics of actin filaments in cells are regulated by a large array of actin-binding proteins. Moreover, post-translational modifications of actin — the addition of certain chemical groups to its amino-acid residues, or their removal — is thought to have a role in controlling the cellular functions of actin filaments. However, the proteins that catalyse these changes have been elusive. On page 372, Wilkinson *et al.*[2] report the identification of the long-sought enzyme that catalyses the methylation (addition of a methyl group) of actin, and shed light on the biological role of this post-translational modification in animals.

Some post-translational modifications of actin are present in all isoforms (structural variants) of the protein, whereas others are more specific. The protein's amino-terminal region can be modified by acetylation (addition of an acetyl group) and arginylation (addition of an arginine amino-acid residue)[3]. Recent studies identified the enzyme responsible for amino-terminal acetylation of actin and demonstrated that this modification affects the elongation and depolymerization of actin filaments[4,5].

Most actin isoforms are also methylated at a particular histidine amino-acid residue known as His73, which is close to the site to which one of two nucleotides, ATP or ADP, binds. Hydrolysis of ATP to ADP plus one free phosphate molecule is essential for the turnover of actin filaments, and hence for their ability to produce force in cells. Although methylation of His73 was identified more than five decades ago[6], the enzyme responsible and the biological functions of this modification have remained unknown.

The study by Wilkinson *et al.* and a related study published in *eLife*[7] report that the SETD3 protein is the enzyme that methylates actin at His73 (Fig. 1). This is the first time an actin methyltransferase (an enzyme that catalyses methylation) has been identified, and also the first time a histidine methyltransferase has been identified in animals. Earlier work suggested that SETD3 methylates lysine amino-acid residues in histone H3 (ref. 8), a protein associated with DNA, but Wilkinson *et al.* convincingly demonstrate that SETD3 is not a methyltransferase for histones. The authors provide extensive biochemical and cell-biological evidence showing that, at least



KONSTATIN KOGAN

Figure 1 | Methylation of actin by the SETD3 protein. Wilkinson *et al.*[2] show that SETD3 catalyses the addition of a methyl chemical group (methylation) to a histidine amino-acid residue (His73) of the protein actin, and that this modification fine-tunes the protein's function. His73 is close to a site to which either an ATP or an ADP nucleotide binds. The switch between ATP and ADP is essential to allow actin filaments to produce force in cells. Other evolutionarily conserved post-translational modifications of actin, including the addition of an acetyl chemical group (acetylation) to its amino-terminal region, are distant from the nucleotide-binding pocket of actin.

in mammals, SETD3 is the only enzyme that catalyses the His73 methylation of actin, and that actin is the only substrate of SETD3. They also show that SETD3 and His73 methylation of actin are present in a wide range of organisms, including plants and animals, but that SETD3 is not present in budding yeast, which also lacks His73-methylated actin.

Why does SETD3 methylate actin, but not other proteins? To answer this question, Wilkinson *et al.* determined the atomic structure of SETD3 in complex with a short chain of amino acids (a peptide) that has the same amino-acid sequence as the region of actin around His73. They found that this peptide occupies an extended groove in the domain of SETD3 that is responsible for the enzyme's methyltransferase activity. The interface between SETD3 and the actin peptide has many specific interactions, which explain why SETD3 binds to and methylates only actin.

To examine the biological functions of this post-translational modification, Wilkinson *et al.* generated 'knockout' mice and cell lines in which the gene encoding SETD3 was inactive. They observed that actin is no longer methylated in these models. Surprisingly, the mice lacking SETD3 seemed to be healthy, which demonstrates that methylation of actin at His73 is not essential in mammals. However, female mice lacking SETD3 took longer to give birth than did mice in which this protein was present. The delay resulted from defective contraction of certain muscles of the uterus during labour. Moreover, the migration of SETD3-knockout cells in culture was slower than that of wild-type cells. Finally, non-methylated actin purified from the SETD3-knockout cells polymerized slightly more slowly than did methylated actin, and had a faster rate of exchange of nucleotides on single actin molecules than did actin purified from wild-type cells.

These experiments provide evidence that, despite being evolutionarily conserved across a broad group of organisms, methylation at His73 is not essential for the normal functioning of actin. Instead, this modification seems to fine-tune the protein's biochemical properties and cellular roles.

Future studies should investigate the SETD3-knockout mice in more detail for possible additional differences from wild-type mice, and should examine the effects of SETD3 deletion in other model organisms. Also, the effects of His73 methylation on actin biochemistry should be studied more precisely. Previously, analysing these effects was possible only by mutating the His73 residue in actin or by producing human actin in yeast, in which this protein cannot be methylated[9,10]. The new findings will enable careful side-by-side comparison of wild-type actin and actin that lacks methylation only at His73.

Because His73 is close to the nucleotide-binding site of actin, it will be especially interesting to study how this modification affects the functions of proteins that catalyse nucleotide exchange on actin[11] and that rely on ATP hydrolysis and subsequent release of free phosphate for their interactions with actin filaments[12]. ■

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BIOTECHNOLOGY

Implant aids responsive bladder control

Implants that electrically stimulate nerves continuously to treat disease can cause off-target effects and pain. An implant that uses light to modulate the activity of genetically modified nerve cells might offer a solution. SEE LETTER P.361

ELLEN T. ROCHE

Advances in bioelectronics have enabled progress[1] in the use of implanted electronic devices for treating disease. In the clinic, such approaches to modulating nerve cells that control bladder function[2] can treat a condition called overactive bladder, which is characterized by a frequent urgent need to urinate, sometimes with associated incontinence, and an abnormally high number of bladder-emptying episodes. The conventional approach taken for such nerve modulation is to apply continuous electrical stimulation; this does not affect only the relevant nerve cells, however, and can lead to pain and off-target effects[3]. Mickle *et al.*[4] describe on page 361 a potential way of tackling this problem — a miniature implanted device that can sense and control bladder function in rats.

Rather than modulating nerve activity through the direct use of electrical stimuli, the authors harnessed an established technique called optogenetics, in which nerve cells in the bladder were genetically modified to express a light-sensitive receptor protein that can inhibit nerve-cell activation. Mickle and colleagues implanted a stretchable, high-precision strain sensor around each animal's bladder that measured changes in bladder circumference over time. The bladder sensor was connected