

on versatility

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Diversity is one of Nature's fortes. See how she has spread life and let it flow into Earth's every nook and cranny: into oceans and seas, rivers and lakes, woodland, forests and jungles, mountains, valleys, deserts, marshland and glaciers, and even stifled cities where weeds push their way through bricks and where flies, rats and pigeons feed on our waste. Though humans seem set on diminishing diversity, there is still a great variety of living organisms on most of the planet's surfaces. It continues on a smaller scale too. Consider a cell and the myriads of different molecules inside it all working together in relative harmony, to keep the cell alive and healthy. It may seem a paradox but the principle of economy is one of diversity's driving forces, and the world of proteins illustrates this beautifully. Imagine a basic sequence, a template if you like, then add a methyl group here or remove a phosphate group there, and you have a protein that behaves in two different ways. This is the realm of post-translational modifications, or PTMs. In cells, special enzymes – of which there are many – have the task of adding or removing molecules onto or from proteins to this end. One of these is SET domain protein 3, or SETD3 which shifts the behaviour of a certain kind of actin.



"Früchte auf rot", by Paul Klee (1879-1940)

Source: wikimedia

Widely used by cells across all kingdoms, PTMs are used to regulate all sorts of biological processes and enhance a protein's, or indeed a cell's, versatility. Different enzymes carry out different kinds of PTMs such as acetylation, SUMOylation, ubiquitination or methylation. As an example, methylation is carried out by methyltransferases, which are particularly widespread enzymes able to transfer a methyl group onto another molecule such as a protein. Once

methylated, the protein's behaviour is affected one way or another. On this subject, in 1967, a team of scientists discovered a methyltransferase they had never encountered before. This particular methyltransferase hooked its methyl group onto a histidine residue rather than onto a lysine residue in a protein known as β -actin. As the years rolled on, actin-specific histidine methylation actually turned out to be a relatively frequent phenomenon but no one could understand how it was happening nor what was doing it. Until very recently. The culprit is a histidine methyltransferase that belongs to the SET domain protein superfamily, and has been coined SETD3. SETD3 is special in that, unlike other members of the SET superfamily, it methylates histidine residues as opposed to lysine residues and specifically on β -actins.

Actin is one of the most abundant proteins in cells. Found in every kingdom, it has changed very little over time, and yeast and human actin are 90% similar. Globular in shape, actin polymerizes into microfilaments to form the cell's cytoskeleton by building highways to transport molecules, and scaffolds as aids in cell division or to prevent a cell from caving in. Actin is also present in large quantities in muscle cells where it works in unison with another protein, known as myosin, to power muscle contraction. All cells harbour pools of actin monomers in their cytoplasm, which polymerize and depolymerize continuously, depleting the cell's energy – ATP – as they do so, while over one hundred proteins are thought to be involved in their turnover. Actin comes in six isoforms in humans,

and SETD3 specifically methylates β -actin which is exclusive to the cell's cytoskeleton.

SETD3 always methylates a histidine residue situated at position 73 (H73) on the β -actin chain that it recognises thanks to flanking sequences. Structurally, SETD3 forms a V-shaped cleft in which are three distinct SET domains (SET, iSET and C-SET) and from which protrudes a methyl group. β -actin monomers fit comfortably inside this cleft and in such a way that their H73 residue turns to the methyltransferase. Consequently, methylation is prompted and both proteins undergo a conformational change. Though it has not yet been observed, there is little doubt that an extensive network of interactions and proteins are needed for β -actin to find its way into SETD3's narrow groove to be clamped into place properly, ready for methylation.

Once β -actin H73 has been methylated, what overall effect does it have on a cell? Remember: β -actin polymerizes into microfilaments to form the cell's cytoskeleton. What scientists discovered is that when SETD3 is present in cells, microfilaments tend to be more stable. In other words, the actin monomers remain linked to one another instead of losing hold of each other thus causing the filament to disintegrate. Actin microfilament depolymerisation requires concomitant ATP hydrolysis. This suggests that SETD3 methylation somehow re-orientates ATP on the β -actin monomer in such a way that hydrolysis is checked – as is microfilament depolymerisation. To cut a long story short, β -actin H73 methylation by SETD3 guarantees cell cytoskeleton stability. On the other hand, if SETD3 is deficient or absent, methylation is faulty and depolymerisation accelerates. Downstream, many things can go wrong: the cytoskeleton will be mal-formed, molecules will have no highways to travel along and cell division

will be affected. In this light, SETD3 was recently found to be associated with cancer.

An intriguing observation: β -actin H73 methylation is involved in primary dystocia. The cause of dystocia – or difficult childbirth – can arise from the mother or the baby, and can be anatomical or due to poor contractions or hormone signalling. Primary dystocia is defined as difficult childbirth whose origin is not anatomical. Scientists discovered that a lack of SETD3 causes the smooth muscle in the uterus to be lazy (atony). Yet β -actin is not part of the actin-myosin muscle system – so why would SETD3 affect uterus contraction? It must have to do with impeded microfilament polymerisation, which in turn impedes muscle contraction. This would imply the presence of actin microfilaments in the uterus that support – and perhaps strengthen – smooth muscle contraction. In their absence, contractions are then poor and childbirth is difficult.

Researchers are gradually sketching the contours of SETD3 and β -actin methylation. Until very recently, SET methyltransferases were thought to methylate only lysines – but this turned out to be inaccurate with β -actins and SETD3. We are now aware that SETD3 helps stabilise microfilaments and that it may well have a role in carcinogenesis and primary dystocia. Consequently, further studies could lead to the design of small molecule inhibitors of SETD3 to counter cancer progression or to small molecules that could enhance the expression or activity of SETD3 in the event of primary dystocia. This said, while SETD3 seems bent on β -actin, researchers think it may have affinity for other actin isoforms too, such as γ - or α -actin. Certainly, SETD3 seems to be able to wave its baton at β -actin as it orchestrates microfilament polymerisation, and in so doing prevents one of life's most essential scaffolds from becoming too frail.

Cross-references to UniProt

Actin-histidine N-methyltransferase SETD3, *Homo sapiens* (Human): Q86TU7

References

1. Guo Q., Liao S., Kwiatkowski S. *et al.*
Structural insights into SETD3-mediated histidine methylation on β -actin
eLife 2019;8:e43676
PMID: 30785395
2. Wilkinson A.W., Diep J., Dai S. *et al.*
SETD3 is an actin histidine methyltransferase that prevents primary dystocia
Nature 565:372-376(2019)
PMID: 30626964

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