EPIGENETICS

Serotonin goes nuclear

The function of histone proteins can be modified through addition or removal of certain chemical groups. The addition of a serotonin molecule is a newly found histone modification that could influence gene expression. SEE LETTER P.535

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Epigenetics has been defined as the study of heritable traits that do not involve changes in the DNA sequence. This view has been broadened by an avalanche of biochemical evidence revealing a complex and versatile array of molecular mechanisms that regulate gene expression without changing DNA sequences. These include chemical modifications of DNA and RNA molecules, as well as post-translational modifications of histones — the proteins around which DNA coils to form chromatin strands. Post-translational modifications of histones include acetylation, phosphorylation and methylation (addition of acetyl, phosphate and methyl groups, respectively) at specific amino-acid residues of these proteins[1]. Farrelly *et al.*[2] report on page 535 that histones can also be modified by the addition of serotonin, a molecule with essential roles in regulating neuron activity.

Serotonin is generated from the metabolism of the amino acid tryptophan. It functions as a neurotransmitter — a molecule that acts as a signal between neurons — and as a trophic factor that helps neurons to grow, survive and differentiate. Psychiatric disorders such as schizophrenia, depression and autism spectrum disorder have been linked to serotonin-dependent signalling during key periods of the development of the nervous system[3].

Signalling through various serotonin receptors leads to chromatin remodelling, whereby the conformation of chromatin changes in a way that permits gene expression[4] (Fig. 1a). Serotonin-receptor-dependent chromatin remodelling is mediated by signals that include histone post-translational modifications[4]. How serotonin-driven signals are integrated with other molecular signals that affect chromatin architecture remains poorly explored.

The study by Farrelly and colleagues reveals that serotonin can act on chromatin in a receptor-independent manner, by directly targeting histones through a post-translational modification called serotonylation. This chemical modification has been known for more than a decade on some non-nuclear proteins. Some small enzymes belonging to the GTPase family are serotonylated at specific glutamine amino-acid residues by other enzymes called calcium-dependent transglutaminases[5–7] (Fig. 1b). This process has a role in the induction of cell division in smooth-muscle cells[5], the regulation of insulin secretion by β-cells in the pancreas[6] and the internalization of the protein that transports serotonin from blood into platelets[7].

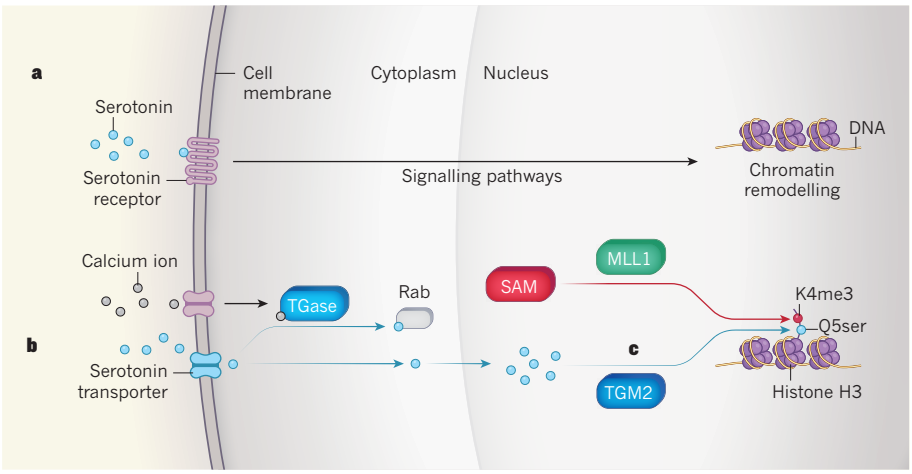

Figure 1 | Serotonylation in cells. a, The molecule serotonin activates specific receptors on the cell membrane, triggering intracellular signalling events that lead to changes in chromatin (DNA plus histone proteins) and gene expression (not shown). **b**, Internalization of serotonin through specialized transporters activates calcium-dependent transglutaminase enzymes (TGases) in the cytoplasm. These add serotonin molecules (a reaction called serotonylation) to certain small GTPase enzymes, such as Rab. **c**, Farrelly *et al.*[2] show that serotonylation also occurs in the nucleus, in a serotonin-receptor-independent manner. A nuclear TGase called transglutaminase 2 (TGM2) adds serotonin to the glutamine amino-acid residue in position 5 of histone H3. This post-translational modification, dubbed Q5ser, occurs predominantly in combination with another modification of histone H3, the trimethylation of the lysine amino-acid residue at position 4 (K4me3). This modification is mediated by methyltransferase enzymes such as MLL1, which transfer a methyl group from *S*-adenosylmethionine (SAM) to histone H3. The presence of K4me3 indicates that chromatin is in a transcriptionally active state, and the double mark K4me/Q5ser might reinforce this state.

Although serotonylation in the nucleus had not previously been described, some intriguing hints supported its existence. A small fraction of the total amount of the enzyme transglutaminase 2 (TGM2) in cells[8], as well as a portion of the cells' serotonin content[9], were found in the nucleus. These observations suggested that serotonylation could target nuclear proteins, and thereby influence gene expression independently of serotonin receptors and their signalling pathways. Farrelly and colleagues detected serotonylation on the glutamine residue at position 5 of histone H3 (the H3Q5 position). As with many other targets of post-translational modifications of histones, this residue is located on the protein's amino-terminal region. No other serotonylation sites seem to exist on histones H3, H2A, H2B or H4, which highlights the remarkable specificity of this modification.

The N-terminal tail of histone H3 is the best-characterized region of all histones. Many modifications that have functional significance (alone or in combination) have been described in this protein region over the past decade[10]. The trimethylation (addition of three methyl groups) of the lysine amino-acid residue at position 4 of histone H3 (H3K4) is considered the most reliable mark for identifying parts of the genome that are in a state that enables transcription. Notably, the enzymes responsible for transferring the first, second and third methyl groups to this lysine residue are unique[11].

Farrelly and colleagues report that TGM2 serotonylates H3Q5 when H3K4 is

trimethylated (Fig. 1c). The combination of these two post-translational modifications is called H3K4me3Q5ser. Given that the modified lysine and glutamine residues are adjacent, the stability (or half-life) of the two modifications might be co-dependent. This proximity might also aid the recruitment of specialized chromatin-remodelling protein complexes. Indeed, the authors' findings suggest that H3K4me3Q5ser might help the function of the transcription factor TFIID, which acts on chromatin to promote transcription.

These findings raise other compelling questions. Does TGM2 have a role in the function of the enzymes that methylate H3K4, such as MLL1? If so, future studies should try to clarify the functional interplay between these enzymes. Does serotonylation of H3Q5 influence other post-translational modifications, in a similar way to how the trimethylation of H3K4 and the acetylation of lysine residues at positions 9 and 14 of histone H3 influence each other[12]? Are the intracellular pools of serotonin replenished in different ways depending on how serotonin is being used in various cellular compartments at any given time? Does extra-nuclear serotonin influence the serotonylation of histones by being transported into the nucleus on demand?

Serotonylation of histones and its potential influence on transcription might be only the tip of the iceberg in an ever-expanding scenario of post-translational modifications associated with chromatin changes. Histaminylation and dopaminylation (addition of histamine, an amino acid, and dopamine, a neurotransmitter, respectively) are likely to join the party, which could complicate the task of deciphering the language of histone modifications. However, an exciting road to discovery seems to lie ahead. ■

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MATERIALS SCIENCE

Improved charge carrying for solar cells

The commercialization of a promising class of solar cell has been hindered by issues associated with the components needed to construct it. A possible solution has now been reported. SEE LETTER P.511

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The most promising technology for the next generation of solar cells is based on a class of material known as perovskites. Perovskite solar cells can convert light into electricity with high efficiency (about 22%)[1], but only when polymers known as polytriarylamine (PTAA) or 2,2′,7,7′-tetrakis(*N*,*N*-di-*p*-methoxyphenylamine)-9,9′-spirobifluorene (spiro-OMeTAD) are used to transport holes — quasiparticles that bear a positive charge and are produced as part of the power-generating mechanism — within the cells. The high cost of these polymers limits their use in commercial solar cells. Another issue is that trace quantities of compounds called dopants need to be added to the polymers to enhance hole transport, but such dopants cause degradation of the perovskite layer in the devices[2,3]. On page 511, Jung *et al.*[4] report an architecture for a perovskite solar cell that uses a cheaper, dopant-free polymer as the hole-transport material, and that has a truly impressive efficiency of 22.7%.

The problems associated with PTAA and spiro-OMeTAD have stimulated the search for alternatives. Cheaper, dopant-free materials for transporting holes have been reported[5–7], as well as new stable dopants[8], but the power-conversion efficiencies of perovskite solar cells made using these materials cannot compete with those of devices that use PTAA or spiro-OMeTAD. Finding low-cost hole-transport materials that provide both high efficiency and stability, and that are compatible with the industrial processes used to make solar cells, remains challenging.

One alternative candidate is poly(3-hexylthiophene) (P3HT; ref. 2). This polymer is cheap, has optoelectronic properties that are perfect for solar cells, and could be used in industrial-scale manufacturing processes. However, no efficiencies higher than 20% have been reported for perovskite solar cells made using P3HT. To understand the problems

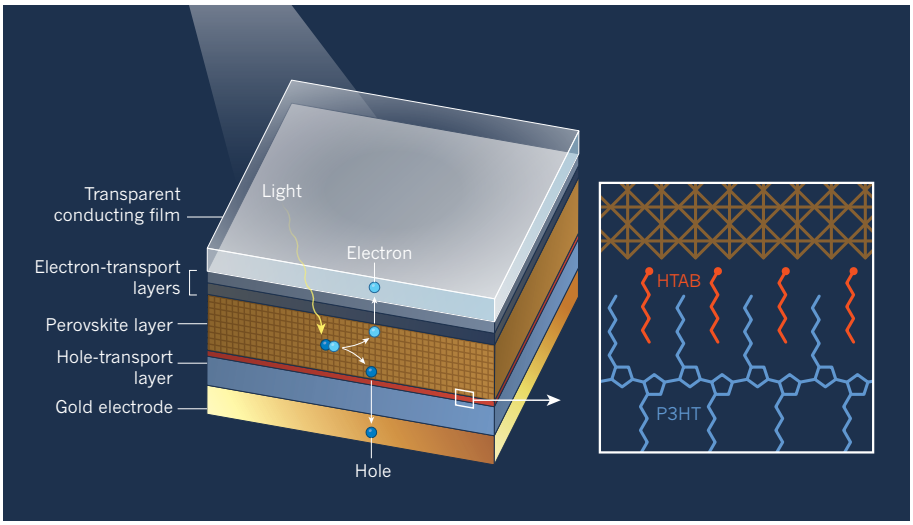

Figure 1 | An extra layer for perovskite solar cells. In solar cells, light absorbed by an active material, such as a perovskite, generates electron–hole pairs; holes are quasiparticles formed by the absence of an electron. The electrons and holes separate and pass through electron- or hole-transport materials, respectively, until they reach an electrode. In this example, the holes pass through to a gold electrode, whereas the electrons travel to a transparent conducting film that acts as an electrode. A current is generated when the electrodes are connected to a circuit. The polymer poly(3-hexylthiophene) (P3HT) is a cheap hole-transport material, but solar cells made using P3HT have had low power-conversion efficiency. Jung *et al.*[4] inserted a material called *n*-hexyl trimethyl ammonium bromide (HTAB) between P3HT and the perovskite layer. Interdigitation of molecular chains in HTAB and P3HT causes the polymer to self-assemble into fibrils that have excellent hole-transport properties, thereby increasing the efficiency of the solar cell. The extra layer also improves the stability of the device.