Editorial Commentary

Functions of SETD7 during development, homeostasis and cancer

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A controlled organ homeostasis is essential to sustain the integrity of any living organism. This homeostasis relies on stem cells, which maintain themselves and give rise to the various types of differentiated cells. It is well established that the differentiation of pluripotent embryonic stem cells (ESCs) depends on major changes in transcriptional programs. Covalent modifications of DNA, RNA and proteins are instrumental in setting up the genetic programs associated with cell fates. Another important mechanism for regulation of gene expression is protein localisation and stability. In addition to ubiquitination, SUMOylation and phosphorylation, methylation of proteins is an important determinant of their properties.

Our current understanding of the biological significance of protein methylation comes from studies of histones. Methylation of histones is catalysed by enzymes containing a conserved amino acid motif collectively named the Su(var)3-9, Enhancer of zeste [E(z)], Tritorax (SET) domain (1). First characterized as a novel methyltransferase modifying histone 3 at lysine 4 (2), SETD7 interacts with and methylates a large number of proteins, including transcription factors BRG1 (3), E2F1 (4), SMAD3 (5), SOX2 (6), TATA box-binding protein associated factor 10 (7) and DNMT1 DNA methyltransferase (8). In some instances, SETD7-dependent methylation reduces protein stability, for example of SOX2, DNMT1 and E2F1. In other cases, SETD7-mediated methylation facilitates recruitment of transcription factors to chromatin (9,10). Finally, methylation of proteins by SETD7 affects protein-protein interaction both in the nucleus and cytoplasm (7,11,12).

SETD7 is absent in pluripotent ESCs (11). Its expression is activated once cells transit from pluripotent to multipotent state and further maintained in post-mitotic differentiated cells (11). Interestingly, the expression of SETD7 is lost in epithelial tumours (13,14). The levels of SETD7 expression negatively correlate with the degree of cancer progression. It is not clear whether SETD7 is silenced upon neoplastic transformation or SETD7-negative cells represent the adult somatic stem/progenitor pool, which is expanded in neoplastic tissues. Similar to ESCs, SETD7 is not expressed in quiescent adult muscle stem cells but is rapidly activated once cells enter the cell cycle (12). This suggests that the primary function of SETD7 is to promote differentiation of lineage-committed progenies. Indeed, SETD7 is required for mes-endoderm specification as well as for the differentiation of cardiomyocytes, endothelial cells, hepatocytes and neuron precursor cells *in vitro* (11). Notably, the methyltransferase activity is not required during these processes. How does SETD7 regulate its dynamic sets of target genes during each step of differentiation? It does so by changing its binding partners.

In mesodermal progenitors, SETD7 interacts with components of SWI/SNF chromatin-remodelling complex, including BRG1, and recruits them to the promoters of the mesoderm specific genes (11). Once mesodermal progenitors are committed towards the cardiac lineage, the expression of *BRG1* is downregulated (15). In contrast, the expression of cardiac lineage genes, including *NKX2-5* is upregulated. SETD7 interacts with NKX2-5 (11). Both SETD7, NKX2-5 and other cardiac specific transcription factors co-occupy the promoters of genes promoting differentiation of cardiomyocytes. It remains to be determined whether SETD7 is required for the recruitment of NKX2-5

to its target genes.

In contrast to transcription factors or the members of SWI/SNF complex, SETD7 is associated not only with the promoters but also with the gene body of the target genes, in a pattern reminiscent of H3K36me3 (11). Histone H3K36 is co-transcriptionally tri-methylated by SETD2 methyltransferase during RNA polymerase II (RNA pol II) transcription elongation (16). H3K36me3 serves as a recruitment platform for several chromatin-modifying proteins, including DNA methyltransferase 3a (17) and the member of Rpd3S deacetylase complex Eaf3 (18-20). Using *SETD2* knock-down human ES cells, co-immunoprecipitation and peptide arrays, Lee *et al.*, showed that H3K36me3 directly interacts with SETD7 and is required for the recruitment of the protein to the gene bodies (11). While the loss of *SETD7* does not affect the distribution of H3K36me3, it reduces the occupancy of the elongating form of RNA pol II along the target genes. The biological significance of SETD7 dual distribution, at the promoters and the gene bodies, is not clear. In contrast to *SETD7* mutants, lacking the protein at the both promoters and gene bodies, loss of SETD7 at the gene bodies has little or no effect on the expression of the few tested target genes (11).

Interestingly, *Setd7* mutant mice are viable and do not show any defects in either mesoderm or cardiomyocyte specification (21,22). The different requirement for SETD7 between mouse and human can be attributed to the presence of the species-specific factor(s) acting redundantly with Setd7 in mice. Alternatively, the cell culture conditions used for differentiation of human ESCs towards cardiomyocytes lack paracrine signals present within the developing embryos *in vivo*.

Although *Setd7* is dispensable during mouse embryogenesis, it is required for the differentiation of adult muscle stem cells/satellite cells upon injury (12). In the absence of *Setd7*, quiescent satellite cells enter the cell cycle and give rise to myogenic progenitors. Yet, those progenitors do not differentiate further and do not form muscle fibres. In both satellite cells and myogenic progenitors, Setd7 is localized in the cytoplasm, where it binds and methylates β-catenin. Upon stimulation of myogenic progenitors with Wnt ligands, β-catenin translocates to the nucleus and activates the transcription of its target genes (23). Inhibition of Setd7 methyltransferase activity blocks the translocation of β-catenin to the nucleus and disrupts the myogenic programme. Setd7 regulates Wnt/β-catenin dependent gene expression not only in skeletal muscles but also in intestinal epithelial tumours (24). $Apc^{Min/+}$ mice deficient for *Setd7* develop twice fewer polyps compared to the controls. Yet, in this biological context Setd7 promotes proliferation and inhibits differentiation of neoplastic cells. In summary, the requirement for Setd7 in multiple contexts both during differentiation of adult progenitors and ESCs highlights the importance of understanding how its two functions as methyltransferase in the cytoplasm and chromatin binding factor in the nucleus are integrated and how their impaired activity leads to diseases.

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Footnote

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