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EPIGENETICS

Legionella makes its mark on histones

Post-translational modification of histones has a key role in the epigenetic regulation of eukaryotic gene expression, which can be manipulated by pathogens to promote their own survival. Rolando *et al.* now report that a newly identified *Legionella pneumophila* methyltransferase generates a unique histone modification that represses host gene expression and enhances intracellular replication of the bacterium.

L. pneumophila exploits a range of processes in its human and protozoan hosts through the secretion of effector proteins by the Dot/Icm type IV secretion system (T4SS). The authors discovered that the T4SS substrate Lpp1683 has a eukaryotic SET domain, which is known to catalyse histone lysine methylation. Using *in vitro* histone methyltransferase assays, the authors established that Lpp1683 catalyses trimethylation of histone H3 lysine 14 (H3K14), and the protein was subsequently renamed regulator of methylation A (RomA). RomA was also found to be functional *in vivo*: infection of both human macrophages (that is, THP-1 cells) and protozoan cells with either a wild-type or a RomA-deficient *L. pneumophila* strain (*Δlpp1683*) showed that only the wild-type strain induced strong methylation of H3K14.

H3K14 is usually acetylated, and together with S10 phosphorylation and K9 acetylation, these H3 modifications are associated with transcriptional activation. Because methylation of H3K14 could potentially inhibit its acetylation, the authors hypothesized that RomA could exert transcriptional repression. To investigate this, a model cell line was constructed that contained artificial RomA-tethering sites upstream of the luciferase reporter gene. Transfection with wild-type RomA or a catalytically inactive mutant allowed assessment of the transcriptional effect of RomA and its effect on chromatin modifications.

Wild-type RomA strongly repressed luciferase activity, whereas the inactive variant did not. Chromatin immunoprecipitation (ChIP) experiments also showed that recruitment of RomA to the luciferase promoter led to an increase in H3K14 methylation and a consequent decrease in acetylation. Moreover, ChIP followed by high-throughput sequencing (ChIP–seq) analyses of *L. pneumophila*-infected THP-1 cells identified 4,870 promoters that were enriched for methylated H3K14, suggesting that RomA activity occurs on a genome-wide scale. Interestingly, H3K14 methylation was particularly pronounced at the promoters of some immune genes, and it was confirmed that RomA represses transcription of these genes.

Although chromatin remodelling by bacterial pathogens has previously been observed, this is the first demonstration of a bacterial effector that directly modifies host chromatin.

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