REGENERATION

Reversing MS

Nature **502**, 327–332 (2013)

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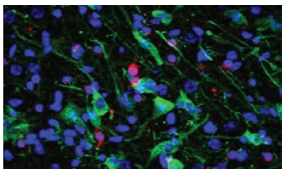


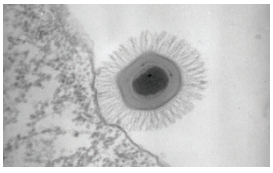
Multiple sclerosis (MS) is an autoimmune disorder in which a T cell–mediated immune response in the central nervous system results in the loss of myelin, the protective sheath that insulates nerve fibers. Current MS treatments have managed to tame the early inflammatory responses, limiting myelin losses, but have been less successful in replenishing myelin. To address this gap, Deshmukh *et al.* performed a high-throughput screen by treating oligodendrocyte precursor cells (OPCs), a myelin progenitor population, with over 100,000 different compounds to search for increases in OPC differentiation into myelin-producing cells. One hit found in the screen was benztropine, which is currently being used to treat Parkinson's disease. Benztropine stimulated the differentiation of OPC cells into myelin-producing cells upon coculture with neurons. Although benztropine has been known to antagonize histamine and dopamine activity, pharmacological experiments suggested that remyelination activity was instead based on the blockade of M1 and M3 muscarinic receptors. The authors tested the therapeutic effects of benztropine on two mouse models with MS-like features. In both cases, benztropine promoted remyelination and alleviated clinical symptoms without altering the overall immune response. As these mouse models recapitulate the major features of human MS, it remains to be seen whether benztropine and/or other analogs can be used in human clinical trials to treat MS. *GM*

GLYCOBIOLOGY

Mimi mimicry

Glycobiology, doi:10.1093/glycob/cwt089

IGS-UMR 7256 CNRS-AMU



The exterior of Mimivirus, a member of the nucleocytoplasmic large DNA virus group, is modified with rhamnose, viosamine, glucose and *N*-acetylglucosamine (GlcNAc) sugars. Recent results have shown that Mimivirus contains the biosynthetic pathways for UDP-L-rhamnose and UDP-D-viosamine. However, as these sugars are produced in small amounts—if at all—by host cells, it was unclear whether Mimivirus would be able to synthesize GlcNAc, which is prevalent in eukaryotes. Piacente *et al.* now identify and characterize three Mimivirus enzymes that together mimic the eukaryotic biosynthetic pathway to UDP-GlcNAc but incorporate prokaryotic elements. The first enzyme, encoded by gene *L619*, is more homologous to the eukaryotic glutamine:fructose-6-phosphate aminotransferase (GFAT) than the bacterial GlmS. However, like its bacterial counterparts, the enzyme is missing an insertion between two domains and is not feedback regulated by UDP-GlcNAc, which may provide an advantage to the quickly replicating virus. *L316* encodes the second enzyme, which, by converting *L619*'s product glucosamine 6-phosphate to the eukaryotic intermediate acetylglucosamine 6-phosphate rather than the bacterial intermediate glucosamine 1-phosphate, defines the pathway as eukaryotic-like. The final enzyme, encoded by *R689*, performs a reaction in the eukaryotic pathway but is most homologous to a bacterial enzyme. These functions, along with additional phylogenetic analysis, suggest that the pathway was not acquired by horizontal gene transfer but may represent an ancient pathway for a now-universal process. *CG*

EPIGENETICS

RNA takes control

Nat. Struct. Mol. Biol., doi:10.1038/nsmb.2679; *Nat. Struct. Mol. Biol.*, doi:10.1038/nsmb.2700

Pervasive genomic transcription produces abundant coding and noncoding RNAs, the functional roles of which remain largely uncharacterized. Two recent studies suggest a new link between transcriptional and epigenetic regulation that is mediated by direct binding of RNA transcripts to a histone methyltransferase complex. In the first study, Davidovich *et al.* showed that the polycomb repressive complex 2 (PRC2), which installs repressive methyl marks on Lys27 of histone 3 (H3K27), binds diverse RNAs *in vitro* and in cells, with a preference for longer transcripts. The authors' analysis of transcriptomic data suggests that PRC2 is localized to repressed genes, but it is also surprisingly associated with active genes that are not typically repressed by PRC2. On this basis, the authors suggest that promiscuous binding of RNA transcripts by PRC2 recruits PRC2 to maintain repressed chromatin. In the second study, Kaneko *et al.* also observe that PRC2 is associated with active chromatin by applying a cross-linking approach to identify RNA-protein interactions within embryonic stem cells. They show that EZH2, the methyltransferase component of PRC2, interacts preferentially with 5′-terminal regions of numerous transcripts. These ezRNAs arise from genes that are not regulated by PRC2 and that are depleted in H3K27me3 marks. Their model suggests that ezRNA-PRC2 interactions sense transcriptional status and that changes in ezRNA expression during differentiation may restore PRC2 repressive activity. Taken together, these two studies provide further evidence that broad-based transcription is harnessed for subtle gene regulatory pathways. *TLS*

PROKARYOTIC IMMUNOLOGY

A measure of RNA

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The CRISPR-Cas systems make up an adaptive immune response used by bacteria and archaea to fend off invaders such as phage and foreign plasmid DNA. CRISPRs are clustered regularly interspaced short palindromic repeats harboring sequences acquired from past invaders that encode small antisense RNAs (crRNAs). To form the crRNAs, long precursor RNAs are first cleaved to intermediate lengths by a Cas endonuclease and undergo maturation, leaving a variable 3′ end that matches the foreign genome target that directs antisense-targeting mechanism. To understand this final step better in *Staphylococcus epidermidis*, Hatoum-Aslan *et al.* identified, by affinity chromatography, a five-protein complex containing known components of the *S. epidermidis* CRISPR-Cas system, which they named Cas10–Csm, as being involved in crRNA maturation. The purified complex contained a 71-nucleotide (nt) intermediate crRNA and a series of six mature crRNAs differing by 6 nt and could generate mature crRNAs from intermediate ones. Using a mutational analysis, the authors found that the Csm3 component of the complex was responsible for the observed crRNA size distribution in the ribonucleoprotein complex. *In vitro*, each Csm3 protein bound 6 nt of substrate and protected it from the cleavage involved in maturation. These results suggest that Csm3 acts as a ruler that measures the extent of crRNA maturation within the Cas10–Csm complex. *MB*