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In This Issue

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CNS drug development in the blink of an eye The development of drugs for CNS indications is not an efficient process; only 8% of candidate drugs that enter clinical trials gain FDA approval. A key reason for this low success rate is a paucity of preclinical tests that accurately predict drug efficacy and detect unwanted side effects. In this issue (3528–3541), Cahill and colleagues report a new preclinical approach that they hope can be used alongside current strategies to guide more efficient drug development for CNS indications. Specifically, they show that a wide variety of psychoactive compounds — sedatives; antipsychotic, antidepressant, and antiseizure drugs; and drugs of abuse, such as cocaine, morphine, and phencyclidine — induce characteristic alterations in visual stimulus–induced and/or spontaneous eye movements in mice and that monitoring these changes can be used to rapidly and quantitatively assess the response of mice to these compounds. The broad utility of this approach was highlighted by the use of eye-movement analysis to assess the pharmacokinetics of CNS-active drugs, the blood-brain barrier penetration of CNS-active compounds, and the efficacy of a pharmacological treatment in a mouse model of schizophrenia. Eye-movement analysis was also used to monitor disease progression in a mouse model of the neurodegenerative condition Huntington disease (HD) and could therefore be used to assess the effectiveness of candidate […]

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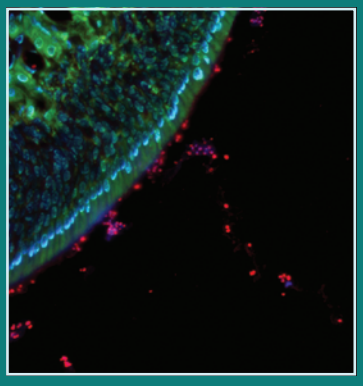
Location, location, location: keeping *S. pneumoniae* in the upper respiratory tract



Streptococcus pneumoniae serially colonizes the mucosal surface of the human upper respiratory tract (URT). Each colonization event lasts several weeks to months before it is cleared by monocytes/macrophages that are recruited to the airway lumen. Under certain conditions (e.g., during influenza virus infection), *S. pneumoniae* can overwhelm the host defense system of the URT and colonize the lower airways, causing secondary pneumococcal pneumonia, which accounts for much of the increased morbidity and mortality during seasonal and pandemic flu. In this issue (3657–3665 and 3666–3676), two reports from the laboratory of Jeffrey Weiser provide new insight in mice into the mechanisms by which an *S. pneumoniae* colonization event is cleared and into those underlying the fact that concurrent infection with influenza virus and *S. pneumoniae* leads to increased bacterial colonization. In the first report, Davis, Nakamura, and Weiser show that in mice, recruitment of the monocytes/macrophages that clear an *S. pneumoniae* colonization event requires their expression of the chemokine receptor CCR2 and is driven by production of the CCR2 ligand CCL2 by professional phagocytes at the site of colonization. CCL2 production was triggered by Nod2 sensing of the products of lysozyme-mediated digestion of *S. pneumoniae*–derived peptidoglycan after uptake of bacteria. In the second report, Nakamura, Davis, and Weiser show that coinfection of the mouse URT with influenza virus and *S. pneumoniae* leads to synergistic stimulation of type I IFNs and that this results in increased density of colonizing bacteria and increased susceptibility to invasive infection. Mechanistically, the enhanced type I IFN response impaired the recruitment of the monocytes/macrophages required for clearing *S. pneumoniae* colonization, as a result of decreased CCL2 production. These complementary reports provide new insight into the mechanisms of host defense in the airway and how concurrent infection with influenza virus and *S. pneumoniae* can dysregulate this system. These data could help explain the higher rates of disease associated with influenza virus and *S. pneumoniae* coinfection in humans.

Decoding infidelity linked to type 2 diabetes

A combination of genetic and environmental factors causes an individual to develop type 2 diabetes (T2D). Among the most reproducible genetic variations associated with T2D in different ethnic populations are those in the CDK5 regulatory associated protein 1–like 1 (*CDKAL1*) gene. However, the relevance of the molecular function of the protein encoded by this gene to T2D has not been elucidated. In this issue (3598–3608), Wei and colleagues generate evidence in mice that could potentially explain the molecular pathogenesis of T2D in individuals carrying *CDKAL1* risk alleles. Initial analysis indicated that Cdkal1 is a methylthiotransferase that biosynthesizes 2-methylthio-N^6-threonylcarbamoyladenosine (ms^2t^6A) in mammalian $tRNA^{Lys}(UUU)$ and that this is required for the accurate translation of AAA and AAG codons. Further analysis indicated that mice lacking Cdkal1 only in pancreatic β cells exhibited impaired glucose-stimulated insulin secretion and glucose tolerance. This was a result of a reduction in glucose-stimulated proinsulin translation caused by misreading of the lysine codon (decoding infidelity) because of insufficient ms^2t^6A modification of $tRNA^{Lys}(UUU)$. One of the lysine residues in proinsulin is located at the cleavage site between the C-peptide and A-chain of insulin, and misreading of the lysine codon also led to the accumulation and aggregation of proinsulin, triggering the ER stress response in β cells. These data provide a potential explanation for the association of *CDKAL1* genetic variations with T2D.