Significance: These findings are the first to reveal a single gated ion channel in open and closed configurations. When the findings of these two studies are compared with the closed state of the structure, which has been previously described, and combined with functional data or the computational analysis, it is possible to model the movements of the transmembrane helices that cause channel opening. Thus the MscS channel is now one of a select few that has structural and biophysical data for multiple states.

Regulation of CFTR trafficking by its R domain. Lewarchik CM, Peters KW, Qi J, Frizzell RA. *J Biol Chem* 283: 28401–28412, 2008.

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Question: Is the trafficking of the cystic fibrosis transmembrane conductance regulator (CFTR) regulated by an internal structural feature of the protein?

Background: The CFTR is an ABC transporter-class anion channel that transports chloride and bicarbonate ions across epithelial cell membranes. Unlike other ABC transporters, CFTR has a regulatory (R) domain with multiple phosphorylation sites, which mediate cAMP-dependent channel activation via protein kinase A. cAMP agonists function to regulate channel activity and modulate CFTR channel density in the plasma membrane. However, the protein interactions and trafficking pathways that underlie CFTR trafficking are not well defined.

Observations: Lewarchik et al. determined the structural basis of CFTR trafficking regulation by inducing agonist-evoked increases in plasma membrane capacitance in CFTR deletion mutants expressed in *Xenopus* oocytes. When the R domain was deleted, the channel had an elevated basal current and did not undergo trafficking when stimulated. Similarly, when an amino acid sequence known as NEG2 was deleted, the channel could not undergo agonist-induced trafficking. Other data supported the idea that NEG2 is essential for the trafficking of CFTR.

Significance: These findings suggest that a structural feature of CFTR, NEG2, permits CFTR to enter a regulated intracellular compartment from which it traffics to the plasma membrane in response to agonist stimulation. The identification of the CFTR component necessary for regulated trafficking could lead to the identification of targets to modulate the density of CFTR mutants. Although there is still much work to be done, the prospect of being able to modulate the density of CFTR mutants holds promise ultimately for treating cystic fibrosis.

Nicotine administration and withdrawal affect survival in systemic inflammation models. Steiner AA, Oliveira DL, Roberts JL, Petersen SR, Romanovsky AA. *J Appl Physiol* 105: 1028–1034, 2008.

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Question: How do acute exposure, chronic exposure, and withdrawal from nicotine affect systemic inflammatory response syndrome (SIRS) and survival rates in mice?

Background: A leading cause of death in hospitalized patients, SIRS is defined as a clinical response to an inflammatory insult of either infectious or noninfectious origin. If it is determined that the SIRS was caused by an infection, it is sepsis. Whatever the cause of SIRS may be, shock, multiple organ failure, and eventually death can occur, which is due, in large part, to the production of pro-inflammatory mediators. Activation of nicotinic acetylcholine receptors is known to inhibit pro-inflammatory cytokine production and inhibit some of the symptoms of SIRS. Hence, the group of researchers at St. Joseph's Hospital (Phoenix, AZ) led by Andrej Romanovsky sought to determine the effect of nicotine on SIRS.

Observations: To mimic a number of human conditions concerning nicotine exposure, Steiner et al. determined the effect of acute and chronic nicotine administration and acute nicotine withdrawal on aseptic and septic systemic inflammation. They found that chronic nicotine exposure did not affect survival in either inflammatory model. In contrast, acute nicotine administration increased survival rate in aseptic inflammation but decreased survival rate in septic inflammation. Finally, nicotine withdrawal increased survival rates in the sepsis model.

Significance: These complex findings on the effect of nicotine on SIRS are intriguing, but become even more complex when one considers that the constant rate of nicotine infusion in these studies differs from how humans typically consume the drug. Nonetheless, because patients in hospital settings are frequently in the withdrawal group, the astute inclusion of a representative cohort for these patients (or of the corresponding group of animals in an experimental study) is a key piece of data that is often overlooked in other studies that characterize inflammatory factors. A final accolade this research group deserves is for addressing the effect of a factor (nicotine) on inflammation resulting from either a septic or aseptic source, which is not typically addressed in studies of inflammation.

12-Lipoxygenase-knockout mice are resistant to inflammatory effects of a high fat western diet. Nunemaker CS, Chen M, Pei H, Kimble SD, Keller SR, Carter JD, Yang Z, Smith KM, Wu R, Bevard MH, Garmey JC, Nadler JL. *Am J Physiol Endocrinol Metab* (September 9, 2008); doi:10.1152/ajpendo.90371.2008.

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Question: Can the inflammatory effects of a high-fat diet be circumvented?

Background: Numerous studies have provided evidence that visceral fat mass is associated with an increased risk of developing insulin resistance and cardiovascular disease. More recently, a growing body of evidence has identified inflammation in mediating, at least in part, these health concerns. Lipoxygenases (LOs) are a family of iron-containing enzymes that are involved in fatty acid metabolism. 12-LO expression/activity is upregulated by hyperglycemia or cytokine-mediated damage, and the downstream products of 12-LO-induced metabolism are known to activate signaling pathways that lead to increased levels of inflammation.

Observations: Based on the physiological role of 12-LO described above, Nunemaker et al. hypothesized that mice lacking 12-LO would be immune from the inflammatory-mediated damage associated with a high-fat diet. As predicted, they found that 12-LO KO mice were able to maintain glucose and