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In This Issue

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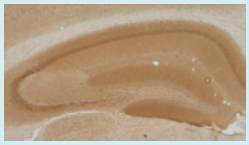
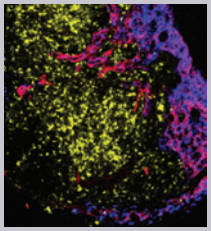
New target for epilepsy treatment Epilepsy is a seizure disorder caused by the generation of aberrant electrical activity within the brain. In animal models of the disease, seizures can be induced by the administration of drugs that activate the muscarinic acetylcholine 1 (M1) receptors; however, how this process is dysregulated in epileptic patients is not completely understood. Pannexin-1 (Panx1) is a membrane channel that allows the passage of ions and other molecules between the cytoplasm and extracellular space. Panx1 can be opened at the resting membrane potential by extracellular ATP via the P2X7 receptor. The opening of Panx1 has been linked to neuronal cell death and aberrant firing, and thus could be a therapeutic target in the treatment of neurological disorders, including epilepsy. Here, Kim and Kang found that mice lacking the P2X7 receptor had increased susceptibility to seizures induced by an M1 receptor agonist, independent of glutamatergic or GABAergic transmission (2037–2047). They also found that this process was mediated by PKC via intracellular Ca2+ release. The researchers believe this suggests that the P2X7-Panx1 complex plays an important role in vivo in negatively regulating M1 receptor–mediated seizures. Pathway that worsens lung cancer severity identified Lung cancer is one of the most common and deadly forms of cancer. Cigarette smoking has been identified as one of the major causes of […]

New target for epilepsy treatment



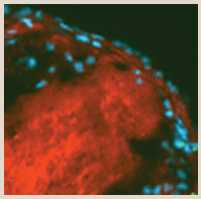
Epilepsy is a seizure disorder caused by the generation of aberrant electrical activity within the brain. In animal models of the disease, seizures can be induced by the administration of drugs that activate the muscarinic acetylcholine 1 (M1) receptors; however, how this process is dysregulated in epileptic patients is not completely understood. Pannexin-1 (Panx1) is a membrane channel that allows the passage of ions and other molecules between the cytoplasm and extracellular space. Panx1 can be opened at the resting membrane potential by extracellular ATP via the P2X7 receptor. The opening of Panx1 has been linked to neuronal cell death and aberrant firing, and thus could be a therapeutic target in the treatment of neurological disorders, including epilepsy. Here, Kim and Kang found that mice lacking the P2X7 receptor had increased susceptibility to seizures induced by an M1 receptor agonist, independent of glutamatergic or GABAergic transmission (2037–2047). They also found that this process was mediated by PKC via intracellular Ca^{2+} release. The researchers believe this suggests that the P2X7-Panx1 complex plays an important role in vivo in negatively regulating M1 receptor–mediated seizures.

Targeting multiple pathways improves vaccine efficacy



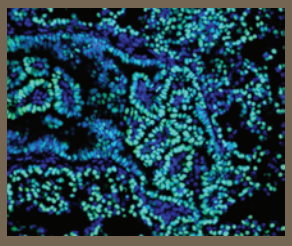
One of the goals of vaccine design is to elicit strong reactions from multiple groups of immune cells specialized for priming a long-lived immune memory that will serve to mediate protection. Accordingly, physically linking molecules that activate immune responses through different innate signaling pathways to the vaccine antigen is a critical step toward optimizing protective immunity. Researchers have previously immunized mice with proteins coupled to nucleic acids (so-called conjugate vaccines) so that they stimulate innate immune responses simultaneously, leading to improved adaptive immunity. However, the mechanisms that explain the improved responses to these conjugate vaccines are not completely understood. New insight into this question has now been provided by Kastenmüller, Wille-Reece, and colleagues, who found that conjugating proteins to small synthetic molecules that trigger through distinct intracellular innate signaling pathways increased the uptake of the vaccine by DCs (1782–1796). In addition, they found that conjugate vaccines worked through engaging multiple specialized subsets of DCs and induced the production of two key cytokines that contributed to the overall response. The authors believe this work helps to define the responses to conjugate vaccines and suggests new methods to enhance vaccine efficacy.

Understanding atherosclerotic plaque regression



Atherosclerosis is a disease marked by the buildup of fatty plaques in the blood vessel walls; recruitment of monocytes into these plaques is thought to contribute to the progression of this chronic inflammatory condition. Medical and dietary strategies that lower plasma lipid content can cause plaques to regress, and this regression is associated with decreased monocyte infiltration. It is not clear how plaques become more stable in patients taking cholesterol-lowering drugs; if the mechanisms were better understood, scientists might be able to identify therapeutics that enhance these natural processes and improve clinical outcome. Potteaux, Gautier, and colleagues examined the action of macrophages in regressing plaques using a mouse model in which they could rapidly reduce cholesterol levels (2025–2036). They found that falling cholesterol led to plaque regression and a reduction in plaque macrophage content. Surprisingly, the decrease in plaque macrophages was related to decreased infiltration, rather than active exit, of these cells. The researchers believe these findings suggest that therapies that prevent macrophage recruitment into plaques could augment the efficacy of lipid-lowering medications.

Pathway that worsens lung cancer severity identified



Lung cancer is one of the most common and deadly forms of cancer. Cigarette smoking has been identified as one of the major causes of the disease, but lung cancers can also arise in nonsmokers, and research suggests that mutations in cell signaling pathways underlie these events. Aberrant signaling of the Wnt/β-catenin pathway has been implicated in the pathogenesis of many malignancies, including colon cancer, but its role in lung cancer has not been established. New insight is now provided by Pacheco-Pinedo and colleagues, who investigated the role of Wnt/β-catenin signaling in the development of lung cancer in mice (1935–1945). They found that activating the pathway did not by itself induce tumor formation, but did increase the frequency and size of tumors induced by mutations in Kras, in part by inducing a very immature lung epithelial phenotype similar to that observed in the developing lung. The researchers believe their findings suggest that Wnt/β-catenin activation is a marker of more aggressive lung cancer and hope this may help clinicians more accurately diagnose and treat the human disease.