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In This Issue

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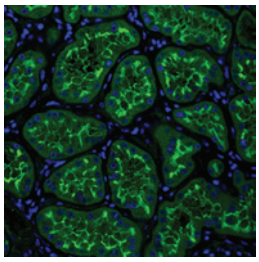
TRPA1 feels the pain of alkaline pH Many biological conditions give rise to alkalinity, some of which (e.g., respiratory alkalosis due to hyperventilation and the high blood pH caused by urinary tract infection) cause pain sensation. However, the mechanisms by which sensory neurons detect alkaline pH are not well defined. Fujita and colleagues have now provided insight into this by using Ca2+ imaging and patch-clamp recording to show that alkaline pH activates transient receptor potential cation channel, subfamily A, member 1 (TRPA1) in human cell lines and mouse neurons (pages 4049–4057). Mechanistically, alkaline pH was found to activate TRPA1 from within the cell in a process that required the two N-terminal cysteine residues of TRPA1. Furthermore, the induction of intracellular alkalization by injection of ammonium chloride into the underside of the hind paws of wild-type and TRPA1-deficient mice caused pain-related behaviors in wild-type mice only. As these results indicate that alkaline pH causes pain sensation in mice through activation of TRPA1, the authors suggest that activation of this ion channel might be the mechanism underlying some of the human alkaline pH–related pain sensations whose mechanisms are currently unknown. Seeing is believing in the lungs of mice with allergic airway inflammation Eosinophils are immune effector cells central to the pathology of asthma. Cortez-Retamozo and colleagues have now used several noninvasive real-time […]

Iminoglycinuria: not a simple Mendelian disorder after all

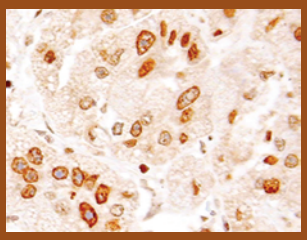


Since its first identification by urinary testing over fifty years ago, about 1 in every 10,000 infants born exhibits iminoglycinuria (IG), which is due to faulty renal reabsorption of glycine and the imino acids proline and hydroxyproline. The identification of individuals with isolated hyperglycinuria without iminoaciduria (HG) led to the suggestion that the autosomal recessive disorder IG results from inheriting two defective alleles of a putative common transporter for glycine, proline, and hydroxyproline, whereas HG occurs when an individual is heterozygous. Using a candidate gene sequencing approach in seven families, Bröer, Bailey, and colleagues have now determined that IG and HG are not simple Mendelian disorders (pages 3881–3892). Inheritance of two nonfunctional alleles of the gene encoding the proton amino acid transporter SLC36A2 was found to be the main cause of IG, whereas inheritance of one nonfunctional *SLC36A2* allele caused HG. However, in some individuals, IG was caused by the combination of a mutated *SLC36A2* allele encoding a protein that retained partial transport activity and an inactivating mutation in the gene encoding the imino acid transporter SLC6A20. As polymorphisms in genes encoding other amino acid transporters were detected in individuals with either IG or HG, the authors conclude that mutations and polymorphisms in a major gene (*SLC36A2*) and accompanying modifier genes are the genetic cause of these disorders.

TRPA1 feels the pain of alkaline pH

Many biological conditions give rise to alkalinity, some of which (e.g., respiratory alkalosis due to hyperventilation and the high blood pH caused by urinary tract infection) cause pain sensation. However, the mechanisms by which sensory neurons detect alkaline pH are not well defined. Fujita and colleagues have now provided insight into this by using Ca^{2+} imaging and patch-clamp recording to show that alkaline pH activates transient receptor potential cation channel, subfamily A, member 1 (TRPA1) in human cell lines and mouse neurons (pages 4049–4057). Mechanistically, alkaline pH was found to activate TRPA1 from within the cell in a process that required the two N-terminal cysteine residues of TRPA1. Furthermore, the induction of intracellular alkalization by injection of ammonium chloride into the underside of the hind paws of wild-type and TRPA1-deficient mice caused pain-related behaviors in wild-type mice only. As these results indicate that alkaline pH causes pain sensation in mice through activation of TRPA1, the authors suggest that activation of this ion channel might be the mechanism underlying some of the human alkaline pH–related pain sensations whose mechanisms are currently unknown.

Getting rid of J(u)NK impairs hepatocellular carcinoma proliferation



Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer in the world. As Hui and colleagues have now identified a critical role for JNK1 but not JNK2 in regulating the proliferation of HCC cells (pages 3943–3953), they suggest that drugs targeting JNK, used either alone or in combination with other drugs, should be considered as a potential therapeutic approach for the treatment of individuals with HCC. Initial analysis indicted that activation of JNK, most probably JNK1, was increased in human primary HCC samples and that JNK1 was required for human HCC cell proliferation in vitro and tumorigenesis after xenotransplantation. This decreased proliferation and tumorigenesis was associated with increased expression of the cell-cycle inhibitor p21 and reduced expression of the c-Myc oncogene. Importantly, treatment with a specific JNK1/2 dual inhibitor markedly decreased the growth of a xenotransplanted human HCC cell line. Similar results indicated that JNK1 also controlled hepatocyte proliferation via p21 and c-Myc in mouse models of liver carcinogenesis and liver regeneration, confirming a mechanistic link between JNK1 and human and mouse hepatocyte proliferation.

Seeing is believing in the lungs of mice with allergic airway inflammation

Eosinophils are immune effector cells central to the pathology of asthma. Cortez-Retamozo and colleagues have now used several noninvasive real-time molecular imaging modalities (specifically, near-infrared fluorescence fiber optic bronchoscopy, intravital microscopy, and fluorescence-mediated tomography) to visualize eosinophil responses in the lung parenchyma and conducting airways of mice with experimental allergic airway inflammation (a model of asthma) (pages 4058–4066). The eosinophils were visualized at single-cell resolution using these imaging techniques following injection of an MMP-targeted optical sensor. Using a combination of the sensitive enzyme-targeted sensor and fluorescence-mediated tomography, the authors observed that dexamethasone (an antiinflammatory glucocorticoid used to treat severe asthma) decreased the number of eosinophils in the lungs of mice with allergic airway inflammation as well as MMP activity on a per-cell basis. Similar effects on eosinophil number and MMP activity were observed following treatment with a viridin-derived prodrug. As fluorescence-mediated tomography and fiber optic bronchoscopy techniques have the potential to be translated into the clinic, the authors suggest that in combination with enzyme-based optical sensors, they might improve our ability to diagnose asthma and to assess treatment efficacy.