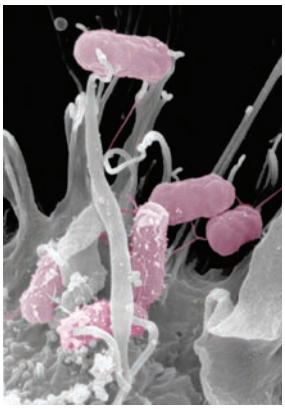
JCI The Journal of Clinical Investigation

# In This Issue

*J Clin Invest.* 2004;113(9):1243-1243. https://doi.org/10.1172/JCI119998.

**In this issue**

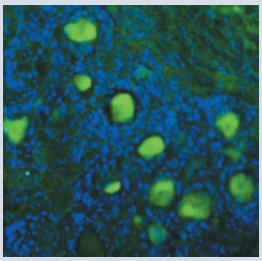
Flagellation in Crohn disease The intestinal mucosa is challenged with more bacterial antigens than any other tissue in the body. Previous work has indicated that inflammatory bowel disease (IBD) results from maladaptive immune responses to intestinal microbiota. However, identification of microbial antigens underlying such intestinal disorders remains difficult due to the diversity of microflora present in these tissues. Through serological cloning of antigens, Robert Hershberg and colleagues determined that the dominant antigens that instigate pathogenesis in Crohn disease (CD) are from a family of related novel flagellins (pages 1296–1306). They examined sera from colitic C3H/HeJBir mice and found reactivity to 15 flagellin clones. Using recombinant flagellin fragments and ELISA assays, they showed that the amino terminus was the immunoreactive domain. Serological studies confirmed that sera from CD patients had high reactivity against particular flagellins, whereas sera from controls and from patients suffering from another IBD, ulcerative colitis, were nonreactive. These findings underscore the link between the innate immune response and the pathogenesis of IBD and offer leads to the identification of other causal antigens in CD. See figure Painstaking work targeting TRPV1 Pain management is important for a variety of disorders including inflammatory hyperalgesia, osteoarthritis, and terminal cancer. Pain treatment requires balancing the elimination of sensory pain with the maintenance of effective proprioceptive, motor, and cognitive neuronal function. In this […]



## Flagellation in Crohn disease

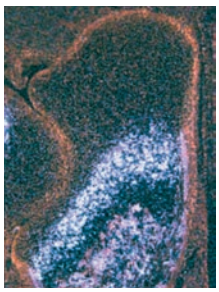
The intestinal mucosa is challenged with more bacterial antigens than any other tissue in the body. Previous work has indicated that inflammatory bowel disease (IBD) results from maladaptive immune responses to intestinal microbiota. However, identification of microbial antigens underlying such intestinal disorders remains difficult due to the diversity of microflora present in these tissues. Through serological cloning of antigens, Robert Hershberg and colleagues determined that the dominant antigens that instigate pathogenesis in Crohn disease (CD) are from a family of related novel flagellins (pages 1296–1306). They examined sera from colitic C3H/HeJBir mice and found reactivity to 15 flagellin clones. Using recombinant flagellin fragments and ELISA assays, they showed that the amino terminus was the immunoreactive domain. Serological studies confirmed that sera from CD patients had high reactivity against particular flagellins, whereas sera from controls and from patients suffering from another IBD, ulcerative colitis, were nonreactive. These findings underscore the link between the innate immune response and the pathogenesis of IBD and offer leads to the identification of other causal antigens in CD.

## Painstaking work targeting TRPV1



Pain management is important for a variety of disorders including inflammatory hyperalgesia, osteoarthritis, and terminal cancer. Pain treatment requires balancing the elimination of sensory pain with the maintenance of effective proprioceptive, motor, and cognitive neuronal function. In this issue, Michael Iadarola and colleagues targeted vanilloid receptors, which are enriched in pain-sensing primary afferent neurons, by using resiniferatoxin (RTX) (pages 1344–1352). RTX is a potent vanilloid receptor 1 (TRPV1) agonist that leads to cellular cytotoxicity through excessive calcium influx. The researchers demonstrated, immunohistochemically, that local administration of RTX selectively deleted TRPV1-positive neurons. They then showed, using assays for analgesic activity in rat and dog models, that pain sensation decreased without a concomitant motor impairment or induction of other sensory neuropathies. Finally, the potential for this form of pain treatment in humans was emphasized by live cell–imaging of human dorsal root ganglia (DRG) in culture using Fluo-4. As previously shown in rats, only a portion of the human DRG neurons were found to be activated by RTX, indicating the likelihood for similar mechanisms and alleviation of pain when used clinically.

## Which switch signals bone development?



Parathyroid hormone-related peptide (PTHrP) plays a key role in bone formation by signaling the switch from chondrocyte proliferation to differentiation. Thus, it is likely that PTHrP regulates the cell cycle machinery either directly or indirectly. Mice lacking *PTHrP* show premature cessation of chondrocyte proliferation and accelerated chondrocyte differentiation. Conversely, cyclin-dependent kinase inhibitor p57–knockout mice have the opposite phenotype. Henry Kronenberg and colleagues theorized that PTHrP may regulate chondrocyte proliferative potential during bone development through suppression of *p57*. To test this, they generated double-knockout *p57/PTHrP* mice and found that bone abnormalities seen in the *PTHrP* knockout were partially rescued by the additional ablation of *p57* (pages 1334–1343). They went on to show that PTHrP downregulates *p57* mRNA in metatarsal cultures treated with parathyroid hormone. While this provides excellent insight into the molecular pathways underlying bone development, not all the defects seen in the *PTHrP*-null mice are completely restored in the double mutant, thus indicating PTHrP likely also mediates its activity through additional factors.

## The c-kit and caboodle of brain injury

Injuries in the brain, such as those caused by blunt trauma or tumor growth or during ischemia, initiate neural stem/progenitor cell (NSPC) migration to the site of the insult. The role NSPCs play in damage repair and the molecular mechanisms underlying NSPC migration in response to injury are unknown. Howard Fine and colleagues present findings that demonstrate stem cell migration into damaged sites in the brain involves stem cell factor (SCF) activation of the c-kit pathway (pages 1364–1374). Using subtraction suppression hybridization, they found higher *SCF* expression in mouse neurons from freeze-brain injury sites than from uninjured sites. The SCF receptor, *c-kit*, is also highly expressed in adult neuronal progenitors. Migration assays using brain lysates revealed that injured brains induced significantly more migration than noninjured tissues. Furthermore, this migration was blocked by c-kit antibody inhibition, supporting the SCF–c-kit chemoattractant system as a homing mechanism for NSPCs. These findings raise the potential for using this system in order to devise cell-based strategies for gene delivery or cellular repair in the brain.