**Vitamin D₃ boosts innate immunity in the skin**

Wounding of the skin breaches the physical barrier that protects the body from pathogens in the environment. To counter this breach, wounding triggers an innate immune response that includes the production of antimicrobial peptides and the upregulation of receptors that recognize microbial components. In this issue (pages 803–811), Schaub and colleagues show that wounding of the skin of humans triggers keratinocyte production of the active form of vitamin D₃ (1,25D₃) and that this induces increased expression of the antimicrobial peptide cathelicidin and the microbial pattern-recognition receptors TLR2 and CD14. Further analysis showed that wounding induced keratinocyte expression of CYP27B1 (the enzyme responsible for converting inactive vitamin D₃ to 1,25D₃) and that this could be recapitulated in vitro by culturing keratinocytes in the presence of TGF-β₁. Indeed, both upregulation of CYP27B1 expression and the presence of inactive vitamin D₃ were required for TGF-β₁ to induce keratinocyte expression of cathelicidin, TLR2, and CD14. The authors therefore suggest that soluble factors present in wounds, such as TGF-β₁, induce the expression of CYP27B1, which enables keratinocytes to produce 1,25D₃, which in turn induces the upregulation of some components of the innate immune response.

**Proteases cause pain in irritable bowel syndrome**

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder in the developed world that is characterized by altered bowel function, abdominal discomfort, and pain. However, there are few effective treatments for IBS, in part because the molecular mechanisms underlying the disease symptoms have not been well defined. In this issue (pages 636–647), Cenac and colleagues show that colonic biopsies from individuals with IBS release increased amounts of serine proteases when cultured in vitro compared with colonic biopsies from healthy individuals. Likewise, colonic washes from individuals with IBS contained higher levels of serine proteases than did colonic washes from healthy individuals. The supernatant from cultured colonic biopsies from individuals with IBS activated mouse sensory neurons in vitro and caused mice to exhibit increased visceral responsiveness to pain when administered into the colon. These effects were dependent on the serine proteases in the supernatant and were mediated through activation of protease-activated receptor-2 (PAR₂) on the sensory neurons. This study suggests that serine proteases and PAR₂ might provide new therapeutic targets for the treatment of individuals with IBS.

**PKCε links fat to insulin resistance**

The accumulation of fat in the liver (hepatic steatosis) can result in nonalcoholic fatty liver disease, which is associated with hepatic insulin resistance and type 2 diabetes mellitus. However, the mechanisms by which fat accumulation leads to hepatic insulin resistance have not been well characterized. In this issue (pages 739–745), Samuel and colleagues set out to determine whether PKCε has a role in the development of fat-induced hepatic insulin resistance in rats. Antisense oligonucleotides specific for PKCε were shown to specifically decrease PKCε expression in the liver and white adipose tissue of treated rats. Although this treatment did not decrease fat accumulation following 3 days on a high-fat diet, it did protect the rats from developing hepatic insulin resistance. Further analysis showed that PKCε interacts with the insulin receptor and inhibits signaling downstream of the insulin receptor, providing a molecular mechanism for the lack of hepatic insulin resistance in the rats treated with antisense oligonucleotides specific for PKCε. This identification of PKCε as a mediator of hepatic steatosis–induced hepatic insulin resistance in rats provides a new potential target for the development of therapeutics to treat individuals with nonalcoholic fatty liver disease and type 2 diabetes mellitus.

**Akt makes melanomas grow downward**

Early-stage melanomas grow superficially in a radial manner and can be treated by surgery. By contrast, advanced-stage melanomas grow vertically, gaining the ability to invade other tissues and metastasize to distant organs, and are usually highly resistant to chemotherapy and radiation. Determining the molecular differences between radial and vertical growth melanomas might provide new targets for the development of drugs to treat individuals with advanced-stage melanoma. In this issue (pages 719–729), Govindarajan and colleagues show that overexpression of Akt in a radial growth human melanoma cell line endows the tumor cells with the ability to grow when transplanted into immunocompromised mice. This ability to grow invasively was associated with increased production of ROS, probably because of the increased number of cells with defective mitochondria and increased expression of the ROS-producing enzyme NOX4. This study therefore indicates that overexpression of Akt alone can convert a radial growth melanoma cell line into a highly invasive tumor cell line, leading the authors to suggest that Akt and the pathways that generate ROS might be good targets for the development of drugs to treat individuals with advanced-stage melanoma.