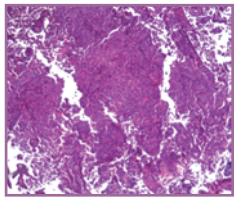
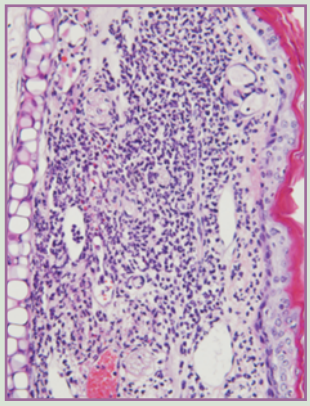
Pik3ca mutations need help to initiate tumors



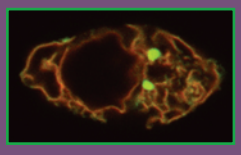
In a substantial number of human cancers, including 8%–12% of ovarian cancers, the *PIK3CA* gene, which encodes the p110α subunit of PI3K, is mutated in such a way that PI3K activity is enhanced. Despite the frequency of such mutations, their precise contribution to tumor initiation and progression has not been determined. Kinross and colleagues have now investigated this issue by generating and analyzing mice in which the $PIK3CA^{H1047R}$ mutation commonly detected in human cancers can be conditionally knocked into the endogenous *Pik3ca* locus (553–557). Induction of $Pik3ca^{H1047R}$ in the mouse ovary failed to induce tumor initiation. However, induction of $Pik3ca^{H1047R}$ together with deletion of *Pten*, which encodes a negative regulator of PI3K activity, led to the development of ovarian tumors. These data indicate that a second genetic hit that enhances PI3K pathway activity is needed for $Pik3ca^{H1047R}$ to initiate tumorigenesis in the mouse ovary. Evidence that this is also the case in humans was provided by the observation that *PIK3CA* mutations commonly coexist with *KRAS* and/or *PTEN* mutations in ovarian cancer samples.

Zinc-deficient individuals irritated by ATP



Zinc (Zn) is an essential trace element. Zn deficiency can be inherited or acquired, for example, as a result of low dietary Zn intake. It has many clinical manifestations, including secondary bacterial and fungal infection of skin lesions due to impaired immune function. Despite their impaired immune function, Zn-deficient individuals develop skin inflammation through an unknown mechanism. Kawamura and colleagues have now determined that mice fed a Zn-deficient diet (ZD mice) develop a severe irritant contact dermatitis (ICD) that has the histological features of the skin inflammation seen in Zn-deficient individuals (722–732). Detailed analysis revealed that irritant-injured keratinocytes released ATP, causing ICD in ZD mice. The ZD mice had decreased numbers of epidermal Langerhans cells (LCs), which are known to hydrolyze ATP and thereby provide protection against ATP-mediated inflammatory conditions such as ICD. The clinical significance of these mouse data was highlighted by the observation that Zn-deficient individuals lacked epidermal LCs. Thus, Kawamura and colleagues suggest that ATP released from injured keratinocytes, which accumulates because there are insufficient epidermal LCs to hydrolyze it, causes the skin inflammation observed in Zn-deficient individuals.

Errant ER morphogenesis causes hereditary spastic paraplegias



Hereditary spastic paraplegias (HSPs) are a group of inherited neurodegenerative disorders characterized by progressive weakness and spasticity of the legs. Mutations in more than 20 genes and over 40 chromosomal loci have been linked to HSPs. In patients with HSP in Northern Europe and America, the most commonly affected genes are receptor accessory protein 1 (*REEP1*), atlastin-1 (*ATL1*), and spastin (*SPG4*). As these genes encode proteins that cooperate to shape the ER into sheets and tubules, it has been suggested that abnormal ER morphogenesis can cause HSP. Montenegro and colleagues have now provided further support for this hypothesis, as they have identified mutations in the gene reticulon 2 (*RTN2*), which encodes a member of the reticulon family of prototypic ER-shaping proteins, in individuals with the HSP spastic paraplegia type 12 (538–544). Analysis of the function of wild-type reticulon 2 and a truncated form of the protein predicted to be encoded by one of the *RTN2* mutations indicated that only the wild-type protein localized to the ER and that it interacted with spastin. These data directly link a new gene to HSPs and uncover the likely underlying mechanism.

Immune system contribution to CML progression

Chronic myelogenous leukemia (CML) arises as a result of a chromosomal translocation in a hematopoietic stem or early progenitor cell that leads to the generation of the oncogenic fusion protein BCR/ABL. CML is characterized by a chronic phase that can last for years — during this phase, patients have few symptoms of disease — but it inevitably progresses via an accelerated stage to blast crisis, a fatal acute leukemia. Schürch and colleagues have now generated data that suggest that the immune system can contribute to CML progression (624–638). Specifically, they found that CML stem/progenitor cells in the bone marrow of patients with CML and in mice with a condition that models CML expressed CD27; and that CD27 signaling promoted the proliferation of both human and mouse BCR/ABL^+ leukemia cells via activation of the Wnt pathway. Moreover, blocking CD27 signaling delayed disease progression and prolonged survival in the mouse model of CML. Schürch and colleagues therefore suggest that blocking the CD27 signaling pathway they have uncovered could provide a new approach for treating CML. This approach would specifically target CML stem/progenitor cells, which seem largely resistant to current therapeutic interventions.