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JAK-STAT signaling keeps leukemia cells alive (See article on pages 351– 362.) Large granular lymphocyte (LGL) leukemia is characterized by the clonal expansion of a T-cell population sharing many similarities with antigen-activated cytotoxic T lymphocytes (CTLs). Unlike normal CTLs, which are readily targeted for destruction by Fas ligand (FasL) binding to the Fas receptor, leukemic LGLs resist Fas-mediated apoptosis. Here, Epling-Burnette and coworkers present data on abnormalities underlying LGL leukemia. Because constitutive activation of STAT transcription factors had been shown to promote resistance to apoptosis in other systems, these authors have assessed the role of STAT proteins in LGL leukemia. They show here that leukemic LGLs from all patients studied showed constitutive activation of STAT3 and/or STAT1, which are normally held latent in the cytoplasm until they are activated by tyrosine kinases of the JAK family. Epling-Burnette et al. show that AG-490, an inhibitor of JAKs, blocks STAT3 function and promotes apoptosis of LGL leukemic cells. While prior studies of other types of leukemia and solid tumors had suggested that STAT activation might promote resistance to apoptosis via induction of the Bcl-xL protein, the authors found no evidence that Bcl-xL was highly expressed in leukemic LGLs; rather, the authors found increased expression of Mcl-1, an antiapoptotic factor in the Bcl-2 family whose expression is regulated by STAT3. The work reinforces […]

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By John Ashkenas, Science Editor

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Large granular lymphocyte (LGL) leukemia is characterized by the clonal expansion of a T-cell population sharing many similarities with antigen-activated cytotoxic T lymphocytes (CTLs). Unlike normal CTLs, which are readily targeted for destruction by Fas ligand (FasL) binding to the Fas receptor, leukemic LGLs resist Fas-mediated apoptosis. Here, Epling-Burnette and coworkers present data on abnormalities underlying LGL leukemia. Because constitutive activation of STAT transcription factors had been shown to promote resistance to apoptosis in other systems, these authors have assessed the role of STAT proteins in LGL leukemia. They show here that leukemic LGLs from all patients studied showed constitutive activation of STAT3 and/or STAT1, which are normally held latent in the cytoplasm until they are activated by tyrosine kinases of the JAK family. Epling-Burnette et al. show that AG-490, an inhibitor of JAKs, blocks STAT3 function and promotes apoptosis of LGL leukemic cells. While prior studies of other types of leukemia and solid tumors had suggested that STAT activation might promote resistance to apoptosis via induction of the Bcl-x_L protein, the authors found no evidence that Bcl-x_L was highly expressed in leukemic LGLs; rather, the authors found increased expression of Mcl-1, an anti-apoptotic factor in the Bcl-2 family whose expression is regulated by STAT3. The work reinforces the view that chemotherapeutic agents inhibiting the JAK-STAT pathway might prove of considerable utility in treating LGL leukemia and perhaps other neoplasms.

Untangling prostaglandin signaling

(See article on pages 325–331)

Prostaglandin E2 (PGE_2) signaling contributes to each of the manifestations that classically define inflammation — redness, heat, and pain. Although nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin are well known to inhibit this pathway by blocking prostaglandin biosynthesis, more specific agents would be useful, given the disparate biological responses that prostaglandins mediate. Stock et al. now report that the genetic disruption of the PGE_2 receptor EP1, one of four such receptors, is responsible for pain perception and the regulation of blood pressure, two of the cardinal physiological responses to PGE_2 signaling. The authors find that pained behavior by animals treated to provoke inflammation of the gut is decreased by half in the *EP1*$^{-/-}$ strain. Remarkably, NSAID treatment causes a similar 50% diminution of such responses in wild-type mice and has little or no additional benefit in mutant animals, suggesting that most of the analgesic effect of these drugs can be explained by their inhibition of signaling through this single receptor type. Stock and colleagues also observe a drop in systolic blood pressure in male mutants, which they attribute to impaired maintenance of the extracellular fluid volume. They also note that other aspects of blood pressure regulation have been found to occur differently in males and females, both in humans and in experimental animals. Thus, although pure EP1 antagonists might prove to be powerful and relatively specific analgesics, such drugs might also be expected to diminish blood pressure in men.

Normal salt levels in the lung of the cystic fibrosis mouse

(See article on pages 317–324)

The physical and chemical properties of the airway-surface liquid (ASL) of the lung are believed to be perturbed in cystic fibrosis, but precisely how they differ from conditions in the healthy lung, and why such a disturbance should render the lung sensitive to infections, are hotly disputed. High salt levels in the ASL might allow for bacterial growth by blocking the antibiotic activity of endogenous defense peptides; alternatively, a dehydrated and relatively viscous ASL, even at isotonic saline, might provide a hospitable climate for bacteria. Unfortunately, these models are not easily tested. Fluid flow across the delicate pulmonary epithelium could be readily disturbed by any probes introduced to sample the ASL, raising serious doubts about the accuracy of in vivo measurements. Jayaraman and colleagues have now provided a set of tools that may resolve this difficulty. Their approach employs fluorescent indicators that can be introduced into the ASL and observed in several settings, including within the living trachea. Using confocal fluorescence microscopy, Jayaraman et al. measure the depth and the concentrations of various ions of the ASL layer produced by normal human and mouse pulmonary tissue, and they show that there is no significant difference in ASL salinity between normal and *CFTR*$^{-/-}$ mice. The authors note that this noninvasive approach may be of use in the study of other lung diseases where the properties of the ASL have not been adequately studied.