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purine-dependent ligand-gated ion channel (hence, X in the P2 subfamily of purine receptors). $P2X_1$ appears to trigger a rapid initial extracellular Ca^{2+} intake by platelets, necessary for $P2Y_1$ and $P2Y_{12}$ to promote platelet aggregation.[1] A second surprise is that $P2X_1$ was shown to bind adenosine triphosphate (ATP) instead of ADP, which is contrary to what was originally thought. The role of ATP in hemostasis is a long-standing controversial issue, but consensus has been reached on the fact that it is an antagonist of ADP for $P2Y_1$ and an agonist for $P2X_1$. However, the issue of ADP versus ATP as a $P2X_1$-specific ligand was recently "reactivated" by the identification of an alternate $P2X_1$ receptor termed $P2X_{1del}$, which is deleted of 17 amino acids within the cytoplasmic tail. $P2X_{1del}$ was found to mediate ADP-evoked inward Ca^{2+} currents and to be present in cell lines of the megakaryocytic lineage, as well as in platelets.[2] Strong controversy was raised by this work,[3] and the issue has remained unsettled. In a new study, Vial and colleagues (page 3646) provide clear and definitive evidence that $P2X_{1del}$ is not surface expressed when transfected alone, but that it can be surface expressed only as an heteromeric $P2X_1/P2X_{1del}$ receptor, which then mediates ATP- and not ADP-evoked inward currents. Finally, these authors show that in platelets the level of total $P2X_{1del}$ is most likely too low to account for a physiologic response, and that ATP but not ADP has potential to evoke the $P2X_1$-specific rapid Ca^{2+} rise in platelets in conditions where $P2Y_1$ response is blunted. These authors therefore conclude that ATP is the sole $P2X_1$ agonist and reinforce the idea that this purine nucleotide is probably an important physiologic platelet activator.

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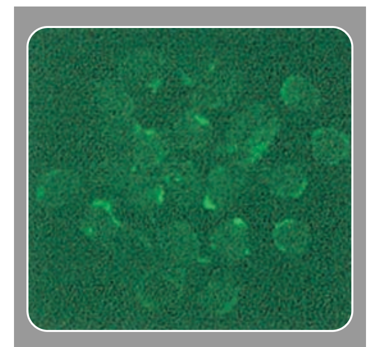
ALG/ATG: illuminating the occult

In the fourth act of Shakespeare's darkest tragedy, the Scottish thane Macbeth—lately elevated to the national throne upon Duncan's betrayal and murder—enters a remote cave in order to consult 3 witches regarding his ultimate fate. To assist their divination, these "weird sisters" brew up a fantastic potion in a seething cauldron, a double-boiled concoction embracing several rather exotic ingredients:

Eye of newt and toe of frog,
Wool of bat and tongue of dog,
Adder's fork and blind-worm's sting,
Lizard's leg and howler's wing,
For a charm of pow'rful trouble,
Like a hell-broth boil and bubble.[1]

After more than a century of research and nearly 4 decades of clinical use, the animal-derived antilymphocyte sera (antilymphocyte globulin [ALG] and antithymocyte globulin [ATG]) are still viewed by some as retaining traces of the baffling aura of a witch's stew. The great Russian immunologist Élie Metchnikoff is credited with being first (in 1899) to have had the idea to grind up rat spleens and inject fragments into guinea pigs in order to produce a hyperimmune serum.[2] Metchnikoff found that this serum was able to agglutinate and destroy rat leukocytes—first the mononuclear cells, followed by the polymorphonuclear cells—and he used this evidence to support his long-standing contention about the primacy of phagocytes in the immune response.[3] Manufacturing practices have advanced considerably since the late Victorian era, and the antilymphocyte/antithymocyte immunoglobulin preparations now available for clinical use in the US (Pfizer's equine ATGAM [New York, NY] and Sangstat-Genzyme's rabbit-derived Thymoglobulin [Cambridge, MA]) are, of course, sterile and purified of contaminants, with quality carefully controlled. Yet just how these agents actually work remains nearly as opaque as the uncanny supernatural aptitude of those 11th-century Scottish witches.

There can be no argument about the fact that ALG and ATG do work. ALG was a key element underpinning the early success of solid organ transplantation in the 1960s and 1970s, and just as it began to yield ground to cyclosporin A and monoclonal anti–T-cell antibodies in the early 1980s, it found new roles combating graft-versus-host disease (GVHD) in the bone marrow transplant unit and treating aplastic anemia. Recently, there have been reports that ATG also benefits some patients with myelodysplastic syndrome,[4] although work continues toward defining just who among that needy group are most likely to enjoy a drug response[5]; unfortunately, our predictions there



are not yet as eerily accurate as the soothsaying of Macbeth's witches.

In this issue of *Blood*, Michallet and colleagues (page 3719) extend previous observations concerning ATG-associated T-cell apoptosis and report new evidence for the release of cathepsin B into the lymphocyte cytoplasm after ATG exposure. The latter finding is novel and interesting, and may open a new line of investigation into the drug's mechanism. To a lymphocyte, having active cathepsin B spill into the cytoplasm is as lethal as Lady Macbeth's ambitions—though the ultimate outcome in this case is cellular suicide instead of homicide.

Some might despair of ever precisely defining the mechanism of ATG—one group of investigators has reported that rabbit ATG

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has 23 different major antibody specificities[6]—and batch-to-batch variability in preparation potency and product properties continue to be problematic. But the report by Michallet and colleagues is certainly a strong step toward achieving a better molecular understanding of these strange sera—and banishing any lingering airs of witchcraft.

—David P. Steensma
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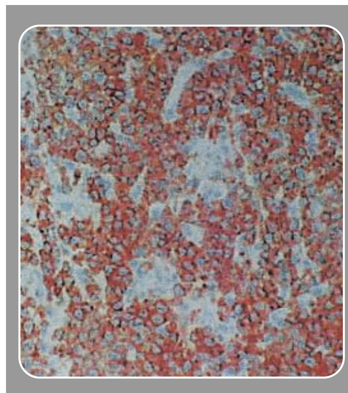
Extracutaneous origin of lymphomatoid papulosis

Lymphomatoid papulosis (LyP) is a cutaneous clonal T-cell lymphoproliferative disorder that manifests as papulonodular lesions that regress spontaneously, only to reappear at the same or other sites. Despite the usual benign clinical course, 10% to 20% of LyP patients develop a systemic malignant lymphoma, usually mycosis fungoides, Hodgkin lymphoma, or anaplastic large-cell lymphoma. In most cases analyzed, the malignant lymphoma is clonally related to the regressing LyP lesions.[1] Although the malignant lymphoma usually follows LyP, the lymphoma may occur simultaneously or precede LyP in 10% of cases.[2] These observations raise the following questions: (1) Why do LyP patients have a high frequency of lymphomas? (2) Why do these lymphomas develop prior to clinical evidence of LyP? (3) Why does LyP persist when the systemic lymphoma is in clinical remission? The study of Gniadecki and colleagues (page 3797) provides important clues to answer these questions. They found that bone marrow from 2 patients who developed lymphoma prior to LyP harbored cells with the unique monoclonal T-cell receptor (TCR) gene rearrangements that characterized the subsequent LyP cells. Their observation is consistent with our hypothesis that a genetic event in an early lymphocyte precursor can explain the clonal relationship between LyP and the lymphomas that LyP patients develop.[3] Gniadecki et al also propose a genetic defect in a multipotent hematopoietic progenitor as a possible explanation for the high frequency of lymphoid and nonlymphoid malignancies in LyP patients. Accordingly, we detected genetic instability as an early event in LyP and mycosis fungoides (A. Ruebben et al, manuscript submitted).

The frequent recurrence of LyP in the skin may be explained by our recent finding



that LyP cells display on their surface cutaneous lymphocyte antigen (CLA), an adhesion molecule that mediates initial tethering of T lymphocytes to the endothelium of cutaneous postcapillary venules, thus causing LyP cells to home to the skin.[4]

It is intriguing that LyP precursor cells in the bone marrow could not be recognized morphologically. Further studies are needed to determine the phenotypic characteristics of these precursor cells. Do they display CLA, the lymphocyte activation antigen CD30, or cytotoxic proteins T-cell intracellular antigen-1 (TIA-1) and granzyme B that characterize LyP cells in the skin?[5] Although the study of Gniadecki et al focuses on LyP, the authors suggest that this model may apply to other types of peripheral T-cell lymphoma. Indeed, bone marrow and cutaneous involvement are frequent in peripheral T-cell lymphomas, unspecified; angioimmunoblastic T-cell lymphoma; and anaplastic large-cell lymphoma, as revealed by immunohistochemical stains for CD30, epithelial membrane antigen (EMA), and anaplastic lymphoma kinase (ALK).[6] The findings of Gniadecki et al suggest that it may be useful to apply immunohistochemical stains and molecular analysis of TCR genes to evaluate the histologically uninvolved bone marrow of patients with peripheral T-cell lymphomas.

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