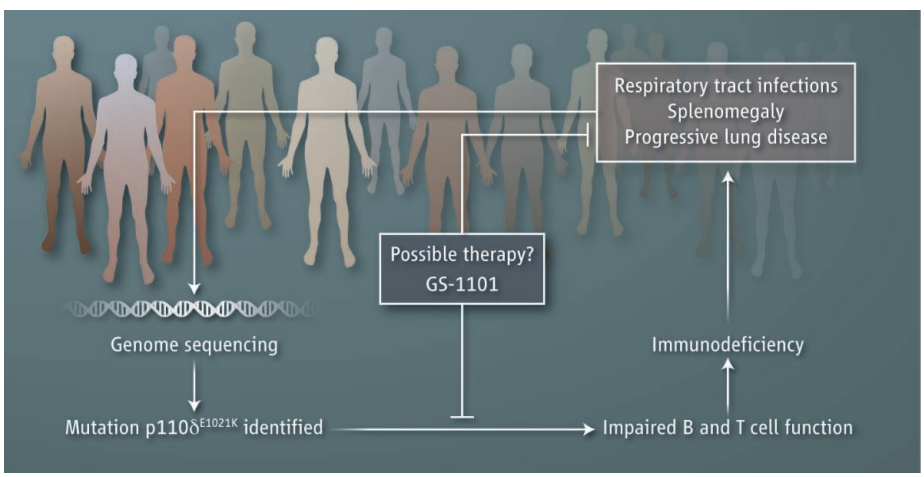
GENETICS

Can Cancer Drugs Treat Immunodeficiency?

Genome sequencing has defined the genetic basis for a primary immunodeficiency disease.

Mary Ellen Conley[1] and David A. Fruman[2]

The usual arduous path to the discovery and implementation of a new medical therapy is to start at the "bench" with the characterization of a molecular aberration in a specific disease (such as a type of cancer), assess its function, design a drug, and eventually bring that intervention to "bedside" through clinical trials. Rarely, if ever, does the path start at bedside with patients who share a profile of symptoms, lead back to the bench where the gathering of mutation data defines a new disease, and then move forward again to bedside. But on page 866 of this issue, Angulo *et al*. (*1*) show that just such a route has led to the discovery of a new genetic immune deficiency disease, with a drug that is potentially at-the-ready for therapy (see the figure). The study emphasizes the power of exome (DNA coding regions) sequencing to identify causative mutations in rare diseases.



Genetic disease discovery. Patients with common symptoms were found to have the same mutation in p110δ. The mutation results in aberrant B cell and T cell function and immunodeficiency, thus revealing a new primary immunodeficiency syndrome (APDS). The p110δ inhibitor GS-1101 has shown encouraging results in clinical trials in patients with chronic lymphocytic leukemia and some non-Hodgkin's lymphomas. p110δ inhibitors are also under development for certain inflammatory diseases (*15*). The new primary immunodeficiency disease may be sensitive to the drug.

Angulo *et al.* examined 17 members of seven unrelated families for whom the clinical phenotype was quite variable, but most affected patients had recurrent respiratory tract infections, splenomegaly (enlarged spleen), and progressive lung disease. The authors identified the exact same heterozygous mutation (Glu^{1021} → Lys, or E1021K) in the gene *PIK3CD* in all 17 individuals. *PIK3CD* encodes the protein p110δ, the catalytic subunit of an enzyme that belongs to the phosphoinositide 3-kinase (PI3K) family. As the E1021K mutation results in inappropriate activation of the kinase, the authors aptly named the condition activated PI3Kδ syndrome (APDS).

The class IA PI3Ks are a highly conserved family of enzymes that phosphorylate the membrane lipid phosphatidylinositol 4,5-bisphosphate (*2*). These heterodimeric enzymes are composed of one of three catalytic p110 subunits (p110α, p110β, and p110δ encoded by *PIK3CA*, *PIK3CB*, and *PIK3CD*, respectively) and a regulatory subunit (encoded by *PIK3R1*, *PIK3R2*, or *PIK3R3*). Whereas p110α and p110β are broadly expressed, p110δ is mainly expressed in cells found in the blood. Activation of PI3K enzymes downstream of cell surface receptors can induce cell growth, proliferation, survival, migration, metabolism, angiogenesis, and differentiation, depending on the cell lineage, the specific PI3K isoform, and cooperating cellular signals (*2*).

Our understanding of how PI3K family members function has been greatly informed by murine models and by patients who have genetic alterations in the components of these kinases. In mice, loss of p110α or p110β is lethal, causing embryonic death, but loss of p110δ results in a more focused phenotype characterized by a partial block in B cell differentiation and impaired function of mature B cells and T cells (*3*–*5*). Mice lacking p110δ have decreased concentrations of serum immunoglobulins and severely reduced antibody responses to T cell–independent and T cell–dependent antigens. Loss of the regulatory subunit encoded by *Pik3r1* causes a similar B cell immunodeficiency in mice (*6*, *7*). A single patient has been reported with a homozygous premature stop codon in the 5′ part of the *PIK3R1* gene (*8*). This patient had agammaglobulinemia (no immunoglobulin production) and a complete failure of B cell development, a phenotype that is similar to but much more severe than that seen in mice with loss of *Pik3r1*.

Genetic studies of human cancer have shown that most tumors have mutations that activate cell signaling pathways that involve PI3Ks (*9*). Frequent gain-of-function mutations in *PIK3CA* or *PIK3R1* are prominent examples. Activating mutations in *PIK3CA* and *PIK3R2* are also seen in affected tissues of patients with megalencephaly (enlargement of the brain) and somatic overgrowth syndromes (*10*–*12*). Of interest, many of the cancer-promoting mutations in *PIK3CA* cluster around the site in the catalytic domain that is mutated in the patients with activated *PIK3CD*. Angulo *et al*. confirmed through biochemical and cellular assays that the E1021K mutation increases p110δ enzyme activity and its association with cellular membranes.

The clinical phenotype in the patients with the E1021K activating mutation in *PIK3CD* has some surprises. The most consistent feature is recurrent infections with encapsulated bacteria, but this is a rather

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common, nonspecific finding. Although the serum concentration of immunoglobulin M (IgM; the first antibody produced in response to infection) was sometimes elevated, the total serum immunoglobulin G (IgG, the high-affinity antibody) was normal. Serum antibody titers to tetanus toxoid, a very strong T cell–dependent antigen, were normal, but titers to the T cell–independent antigens *Streptococcus pneumoniae* and *Haemophilus influenzae* were low despite the use of conjugate vaccines. The mice lacking *Pik3cd* also had poor responses to T cell–dependent and –independent antigens, suggesting that just the right amount of p110δ is needed at just the right time.

Strikingly, the progressive lung disease in these patients appears to be out of proportion to the degree of antibody deficiency. Requirements for normal p110δ activity for neutrophil function have been reported, but Angulo *et al*. did not observe neutrophil dysfunction in their patients. However, in vitro assays do not always reflect in vivo function.

One might expect patients with activated p110δ to have a high incidence of malignancy and autoimmune disease. Although these disorders were seen, they were not predominant. This may be because patient lymphocytes are highly susceptible to activation-induced cell death. Angulo *et al*. also noted that the 17 patients have an increased proportion of transitional B cells, which are newly released from the bone marrow. The authors suggest that this might be due to a late block in B cell development or enhanced death of mature B cells, but there is also the possibility that there is increased production of early B cell precursors in the bone marrow. The early onset of splenomegaly and enlarged lymph nodes before the development of recurrent infections supports this possibility. The fact that multiple patients with this newly recognized activated PI3Kδ syndrome were identified in a relatively small cohort suggests that other physicians have similar patients. Indeed, activating *PIK3CD* mutations in 14 immunodeficiency patients from seven families were recently identified (*13*). A particularly exciting aspect of this work is that a viable treatment for these individuals might soon be available. The selective p110δ inhibitor GS-1101 has shown impressive efficacy and tolerability in patients with certain B cell cancers and is in phase III clinical trials (*14*). GS-1101 and a related compound, IC87114, both blocked the activity of the E1021K mutant; moreover, IC87114 protected T cells from activation-induced cell death. Whether such compounds can restore immune function and forestall organ damage in the patients will be interesting to evaluate. At a broader level, it is remarkable that one enzyme is a potential drug target for indications as diverse as leukemia, immunodeficiency, and inflammation.

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ECOLOGY

Understanding Lakes Near and Far

Satellite and in situ sensor data complement long-term studies of individual lakes to provide insights into the effects of climate change and pollution.

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Scientists have long viewed lakes as microcosms in which to study fundamental ecosystem processes (*1*). A large, heterogeneous body of multidecadal data has been accumulated around the world, documenting historical conditions, capturing temporal dynamics of complex ecological phenomena that could not be observed within shorter time periods. Building on this legacy of long-term data collection, innovations in sensor applications and computing are creating new opportunities for integrating data across different scales in space and time, enriching long-term research and stimulating collaboration.

A shared characteristic of long-term lake studies is that they address questions far beyond those posed at inception. Lake Washington is a famous story of lake restoration (*2*). In 1955, Edmondson and colleagues noted a sudden shift in microalgae suggestive of nutrient pollution, and so began long-term studies that examined algal-nutrient relationships, informed the public process leading to sewage diversion, and documented the restoration of water clarity. The case could have been closed here, but further water clarity increases shifted attention to food web interactions that transpired across decades, providing insights into trophic cascades (*2*) and continuing through the present to reveal subtle responses to climate change, such as temperature controls on the timing of plankton growth that appear to be general across many lakes (*3*).

Meanwhile in Siberia, three generations of a family of Russian scientists and their colleagues were maintaining comparable records on the world's most voluminous freshwater lake—Lake Baikal—to study drivers of plankton dynamics (*4*). From 1945 to the present, the exceptional duration and continuity of the temperature record turned out to be uniquely suited for deciphering seasonal timing shifts attributable to decadal climate oscillations. The detailed data revealed that changes in the timing of seasonal transitions in lake temperature, and potentially throughout the region, are predictably forced by changes in the trajectory and strength of the jet stream and its storm tracks (*5*).

Other examples of long-term lake research have been a result of sustained government support. In England's Lake District, research since the 1930s has produced seminal work from physics to food webs and ultimately documented complex effects of climate change that could not have been discerned in shorter studies. Researchers working with the long-term Lake District data were among the first to recognize and demonstrate the relationship of lake processes with large-scale climate dynamics such as the North Atlantic Oscillation (*6*).

Until 2012, Canada boasted similar strong governmental support for the crown jewel of its environmental science programs, the Experimental Lakes Area (ELA). From elucidating effects of acid rain and nutrient pollution on freshwater to pathways for

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