from the polymer to the monomer form. The dramatic P_i-dependent conformational change in actin induced by binding of regulatory proteins enables P_i release to act as the timer that sets the tempo of filament turnover in cells. Some of the same signals that promote the formation of new actin filaments also suppress filament disassembly by inhibiting the ability of cofilin to promote P_i release. With the structure of ADP-actin in hand, the way is now clear to finally elucidate the intricate dynamics of actin filaments.

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PERSPECTIVES: IMMUNOLOGY

The Push-Me Pull-You of T Cell Activation

Monica J. Carson and David Lo

Explanations for an autoimmune response directed against a single tissue seem simple. Immune cells activated in response to a pathogen protein could aberrantly attack a healthy tissue that expresses a structurally similar protein (molecular mimicry) (*1*). Alternatively, dysregulation of immunoregulatory molecules could lead to recruitment and activation of self-reactive T cells within the healthy tissue (*2*). Yet it is difficult to understand how either of these processes could explain chronic intermittent multiorgan autoimmunity, typified by the disease systemic lupus erythematosus (SLE). The puzzle about the molecular events initiating multiorgan autoimmunity may be partly solved by Kabarowski and colleagues (*3*). In their report on page 702 of this issue, they identify lysophospholipids as ligands for the lymphocyte G protein–coupled orphan receptor G2A. By linking lysophospholipids to G2A, these authors bring together two independent lines of research that cumulatively suggest what neither could alone. Lysophospholipids may be potent super-regulators of T cell activation inflammation at sites of tissue damage and in the early stages of atherosclerosis. Defects in the lysophospholipid-G2A pathway may lead to chronic intermittent multiorgan inflammation by lowering the threshold for T cell activation.

Realizing the similarity of G2A to OGR1—the high-affinity receptor for the lysophospholipid sphingosylphosphorylcholine (SPC)—Kabarowski *et al.* tested SPC and the structurally similar lysophosphatidylcholine (LPC) to see whether they would bind to G2A. LPC, and to a lesser extent SPC, turn out to be high-affinity ligands for G2A capable of inducing G2A-dependent calcium fluxes, chemotaxis of immune cells, ERK protein kinase activation, and the internalization of G2A receptors. The fact that G2A overexpression blocks oncogene-induced expansion of pre-B cells and transformation of fibroblasts in vitro hints that the interaction of G2A with its ligand inhibits the proliferation of immune cells (*4*).

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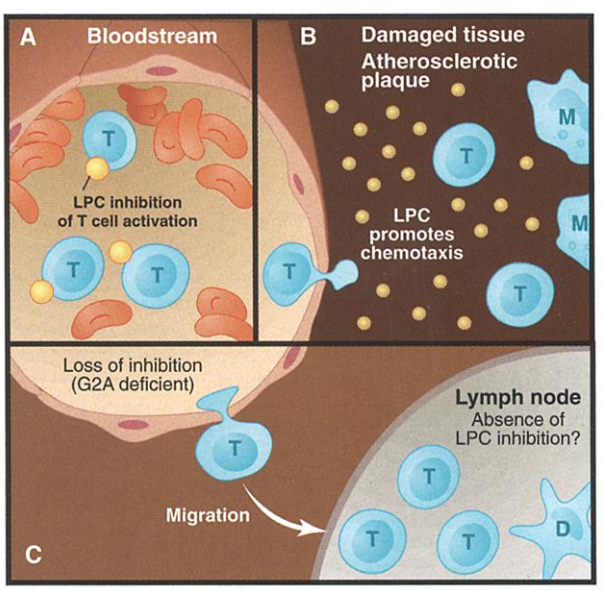

Don't leave it to the professionals. The effects of LPC on T cell activation and migration. (**A**) Physiological concentrations of LPC may inhibit T cell activation in the bloodstream. (**B**) Production of LPC in oxidized LDLs promotes chemotaxis of T cells into damaged tissues and into atherosclerotic plaques in blood vessels. Chronic accumulation and activation of macrophages (M) results in release of large quantities of inflammatory mediators that overcome the inhibitory effects of LPC within atherosclerotic plaques. (**C**) Lymphoid tissues may be exposed to less LPC and so their T cells may be inhibited less strongly, permitting potent T cell activation by dendritic cells (D). In G2A-deficient mice, loss of LPC inhibition in the bloodstream allows a lower stimulation threshold, predisposing the animals to tissue infiltration by lymphocytes, lymphoproliferative disease, and an SLE-like syndrome.

The extent to which G2A, and perhaps LPC, regulate T cell activation and the progression of inflammation is dramatically revealed by the phenotype of mice lacking this receptor (*5*). G2A-deficient mice develop a late-onset multiorgan inflammation that is strikingly similar to SLE. But unlike other murine SLE models, young G2A-deficient mice appear healthy: lymphoid tissues seem normal, and T and B cell lineages display the usual patterns of differentiation. As they age, however, G2A-deficient animals develop progressive enlargement of lymph nodes due to polyclonal (nonmalignant) expansion of lymphocytes. After 1 year, mice develop a wasting disease similar to SLE that is characterized by lymphocytic infiltration of multiple organs, including lung and liver, coupled with immunoglobulin deposition in kidney glomeruli. In vitro analysis reveals that in the absence of G2A, T cells are hyperresponsive to activating stimuli even when they are isolated from young, apparently normal G2A-deficient animals.

When considered together, these data suggest a tantalizingly simple way to integrate two opposing requirements: The need to generate sensitive and rapid antigen-specific responses to pathogens, and the need to avoid unwanted activation of large-scale immune responses caused by transient exposure of lymphocytes to self antigens, molecular mimics, or weak antigenic stimuli (see the figure). In the presence of G2A, physiological concentrations of serum LPC (100 μM) would be expected to increase the threshold for antigen-driven activation of circulating T cells. Conversely, in G2A-deficient mice, the activation threshold would be lower, and thus antigen presentation to T cells would be more effective

even with a shorter exposure to antigen or in the presence of low antigen concentrations. This global increase in T cell responsiveness to antigenic stimuli is mimicked within the local LPC-deficient sites of wild-type mice. Conceivably, T cells found within lymph nodes would be exposed to lower amounts of LPC than T cells in the circulation (see the figure). Thus, differential exposure to LPC or differential activation of G2A may contribute to the highly efficient and effective antigen-driven activation of lymph node T cells compared with T cells in almost any other site of the body (*2*).

LPC may promote the initiation of an immune response while also limiting the extent of that response. This lysophospholipid is generated by hydrolysis of phosphatidylcholine—which is present in low density lipoproteins (LDLs) and the plasma membrane of cells—by phospholipase A_2 (*6, 7*). LPC produced from the disintegrating plasma membranes of necrotic and apoptotic cells may nonspecifically recruit T cells to sites of tissue damage (*6*), but then, high levels of LPC may serve to put the brakes on further T cell activation. Establishing a higher threshold for antigen-specific responses driven by LPC would promote immune responses with greater antigenic specificity or selectivity, even in the presence of a wide spectrum of inflammatory mediators.

Atherosclerosis may represent the most extreme demonstration of this immune regulation pathway (*8*). The accumulation of oxidized LDLs on arterial walls serves to recruit monocytes and T cells—the LPC in oxidized LDLs is a prominent chemoattractant (*6, 7*)—and to promote the growth of atherosclerotic plaques. Oxidized LDLs also convert recruited monocytes into lipid-filled "foamy" macrophages, which produce large quantities of inflammatory factors (*8*). With time these foamy macrophages die in situ, contributing to the formation of atherosclerotic plaques that block blood flow through the blood vessel. Although most studies examine how monocytes are implicated in plaque formation, mice deficient in a variety of immune regulatory molecules hint that activated T cells and interferon γ may also be involved (*8*). Inhibition of T cell activation by G2A and LPC could be overcome by strong and persistent inflammatory signals emitted by the developing plaque.

The notion that the interaction of LPC with G2A regulates T cell responses is attractive, but several elements still require testing. First, the effects of LPC are merely implied by the phenotype of G2A-deficient mice. Does direct application of LPC decrease the extent or kinetics of antigen-driven T cell proliferation or cytokine production? Second, G2A can be detected in both CD4 and CD8 T cell populations, but the prevalence of expression within these populations during development or activation is unknown (*5*). Third, LPC is a known chemoattractant for monocytes and macrophages, but G2A expression in these and other antigen-presenting cells has not been examined (*6, 7*). This must be done because T cell responses are shaped by their interactions with antigen-presenting cells. Failure to detect G2A expression in antigen-presenting cells might indicate the existence of other LPC receptors. Finally, exposure of B cells to DNA-damaging agents or strong mitogenic stimuli induces them to express G2A (they are normally G2A-negative) (*4*). This pattern of induction suggests that LPC may inhibit B cell activation, although this remains to be demonstrated.

Despite these gaps in our knowledge, the key findings of Kabarowski *et al.* underscore the growing realization that the immune system does not operate independently of the tissues that it defends (*2*). Specifically, identification of LPC as a high-affinity ligand for a T cell G protein–coupled receptor implies that regulation of T cell responses is too important to be left solely to the "professional" cells of the immune system. Rather, lymphocyte responses recognizing a vast array of antigens are regulated by more than antigen-presenting cells, antigen, or the limited production of chemokines and rare immunoregulatory peptides. They are likely to be shaped by common and abundant products of hydrolysis, such as LPC produced by tissue macrophages, stromal cells and other "nonprofessional" cells

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PERSPECTIVES: GEOLOGY

The Smile of the Cheshire Cat

Jan Kramers

The interval between the formation of the planets, about 4500 million years ago (Ma) ago and the age of the oldest known rocks on Earth [4000 million years (Myr)] has been termed the Hadean era. This term conjures up a profoundly disagreeable environment. Yet among the oldest known rocks on Earth are water-deposited sediments that contain evidence of life and photosynthetic activity before 3700 Ma (*1*). Earth thus appears to have emerged from the Hadean with liquid water and possibly even life already established on its surface.

At this time, Venus probably already had its greenhouse atmosphere, which became irreversible by loss of water (*2*). The environmental switches that helped Earth escape this fate were thus set in the Hadean. But apart from the knowledge, by analogy with dated lunar structures (*3*), that impacts were frequent (terminating in a "cataclysm" around 3800 to 4000 Ma), we know little about tectonics and geodynamics during the Hadean. How prevalent was continental crust during the Hadean, and since when? The precise calibration of the decay constant of ^{176}Lu reported by Scherer *et al.* on page 683 of this issue (*4*) is an important step toward answering these questions.

Continental crust is unique in the solar system. It is mainly produced by complex partial melting processes of mantle rocks rendered water-rich by subduction of hydrated oceanic crust. Relatively enriched in Al, Si, Ca, and Na, it has a lower density than oceanic crust and therefore stays at Earth's surface, where it can persist for billions of years. Continental crust is also enriched in elements such as P, K, and Mo, which do not fit well into the lattice of the main mantle minerals. Through weathering, these become available to biota. Furthermore, silicate weathering converts CO_2 to HCO_3^-, which is sequestered in sedimentary carbonate rocks. Over geological time, this has been the main mechanism for removing CO_2 from the atmosphere (*5*) and averting a strong greenhouse. Continental crust has thus changed Earth itself.

Today, the oldest rock units, at 3700 to 4000 Myr, are found in West Greenland, Canada, and West Australia. An intensive search for even older crust has yielded nothing, suggesting that if it ever existed, it must have since been destroyed by erosion, large impacts, or melting processes.

Yet where the Cheshire cat has gone, its smile may linger (see the second figure, next page). Detrital grains of zircon (a resistant mineral rich in uranium) in ancient metamorphosed sediments from Jack Hills,

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