

IMMUNOLOGY

When F-actin Becomes Too Much of a Good Thing

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T lymphocytes are highly mobile and long-lived cells that alternate between circulating in the blood and migrating rapidly in tissue in search of antigens. The actin cytoskeleton, the cell's diverse and dynamic infrastructure, plays a key role in this process, and much attention has been focused on branched networks of filamentous actin (F-actin). These fibrous networks are generated through the activity of the actin-related protein 2/3 (Arp2/3) complex. This complex forms F-actin structures that enable T cells to migrate (see the figure) and to forge a signaling synapse at the interface of an activated T cell and an antigen-presenting cell. Thus, F-actin has been viewed as a “good thing” that is necessary for cell motility and sustained cell signaling. On page 839 of this issue, Föger *et al.* (1) suggest that there can be too much of a good thing. Deficiency in the protein coronin-1, a natural antagonist of Arp2/3, increases F-actin content in a T cell, but in so doing it inhibits chemotactic responses and decreases mitochondrial membrane potential, leading to cell death. Surprisingly, loss of coronin-1 has no consequences for immunological synapse formation or T cell activation.

F-actin is a building block of different cytoskeletal structures. Activation of the Arp2/3 complex leads to the formation of branched F-actin filament networks that generate protrusive force and retrograde F-actin flow in the lamellipodium, the extended region at the front end of a migrating cell. This form of F-actin also lends structural support at the periphery of the immunological synapse and moves organelles like mitochondria within the cytoplasm. Arp2/3's preferred substrate is short F-actin filaments that are produced by cofilin, a protein that severs F-actin. A second form of F-actin is found in the lamella, the region of the cell that is firmly adhered to the substrate and that extends lamellipodia.

F-actin filaments in the lamella are stabilized by tropomyosin (2), a protein that inhibits both cofilin and Arp2/3. Nonmuscle myosin works with these filaments to generate force for cell movement (3). A third type of actin network is based on F-actin anchored to the plasma membrane—for example, the spectrin cytoskeleton in a red blood cell (4). Although coronin-1 concentrates in dynamic actin protrusions, it inhibits the Arp2/3 complex and may bridge F-actin with membranes. This unique mix of potential actin-regulatory characteristics has led to speculation about coronin-1 function in lymphocyte homeostasis and activation (5, 6).

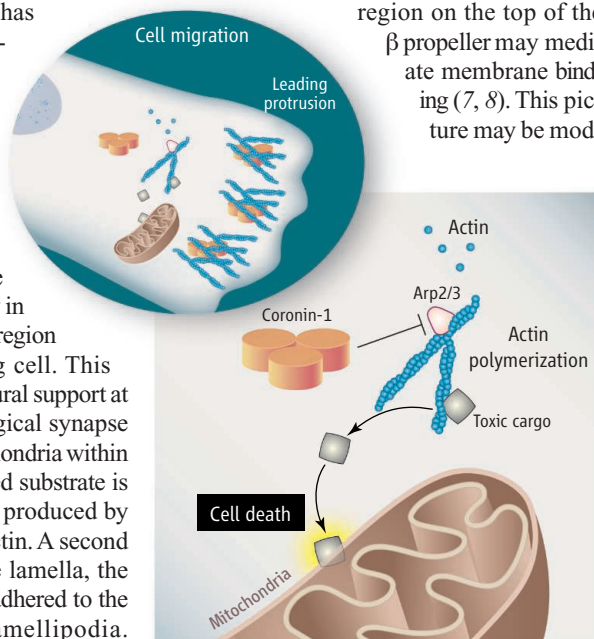
Coronin-1 is a homotrimeric cytoplasmic protein with a single amino-terminal β -propeller domain, a linker peptide that appears to be an integral component of the β -propeller domain, and a carboxyl-terminal coiled-coil domain (7, 8). The coiled-coil domain inhibits Arp2/3 (7). The F-actin binding site appears to be a conserved basic motif on the underside of the β propeller, whereas a less conserved acidic region on the top of the β propeller may mediate membrane binding (7, 8). This picture may be mod-

An excess of a protein that regulates actin assembly in white blood cells unexpectedly kills the cell by altering mitochondrial function.

ified as the recently determined structure allows more precise mutation studies.

Föger *et al.* show that coronin-1-deficient T cells develop normally, but migration and survival defects lead to T lymphopenia. The migration defects are consistent with earlier studies linking coronin-1 to processes like motility and phagocytosis in macrophages. The importance of Arp2/3 inhibition by coronin-1 in motility may be understood in terms of the dominant role of less dynamic F-actin that is in complex with tropomyosin in cell motility (2). It is possible that coronin-1 may play an important role in the transition from high Arp2/3 activity in the lamellipodium to the more stable actin structures in the lamella. Because coronin-1 bridges F-actin to the membrane, it may also play a role in shaping protrusions. This, in combination with inhibiting Arp2/3 activation, may establish an appropriate cortical actin scaffold in cellular protrusions that allow effective migration in the three-dimensional setting of a lymph node, which differs substantially from the two-dimensional settings often studied *in vitro*. In three-dimensional settings, motility may depend more on the shape of the protrusions and the use of mechanical anchoring than on adhesion to couple contractile force to movement.

The relation between F-actin and mitochondrial membrane potential has been noted in studies with yeast and mammalian cells. Mutations that lead to increased F-actin accumulation in yeast decrease mitochondrial membrane potential and abrogate growth on carbon sources that require oxidative phosphorylation. Opening of voltage-dependent anion channels (VDACs) is one mechanism that reduces mitochondrial membrane potential. F-actin can modulate VDACs by controlling the pool of gelsolin, an actin-severing protein that binds and closes VDACs (9, 10). However, this effect was not observed with mouse gelsolin, so it likely is not the specific mechanism of action in coronin-1-deficient T cells. However, the general principle that large amounts of F-actin could work by sequestering a soluble binding protein that has a dual role in controlling VDAC and F-actin may apply. This sequestration idea is also supported by the observations of Föger



Does F-actin deliver toxic cargo to mitochondria? In a migrating cell, coronin-1 inhibits Arp2/3 at the leading edge. It may also prevent the delivery of toxic cargo to mitochondria, such as the apoptotic protein Bax.

et al. and others that simple manipulation of F-actin—including treatment with latrunculin A to decrease F-actin or treatment with jasplakinolide to increase F-actin—either increases or decreases mitochondrial membrane potential, respectively.

Alternatively, F-actin may be critical for delivering proapoptotic molecules to mitochondria (11). F-actin has a role in delivery of other “cargo” to mitochondria. For example, dynamin-related protein 1 is delivered by F-actin in order for mitochondria to undergo fission (12). In yeasts, the F-actin anchoring complex on mitochondria has been defined by genetic studies (13, 14). On this basis, a simple model can be conceived in which coronin-1 reduces the efficiency with which proapoptotic complexes are delivered to the mitochondrial outer membrane (see the figure).

A surprise in this study is that coronin-1 has no role in forming the immunological synapse. Knowledge in this area is explod-

ing, with recent demonstrations that the WAVE2 complex and HS-1 protein are essential activators of Arp2/3 for immunological synapse formation (15, 16). The physiological role of coronin-1 appears to end when the T cell receptor is engaged with antigen, although coronin-1 accumulates in actin-rich projections in the periphery of the immunological synapse (6). It is possible that the role of coronin-1 is redundant with that of other factors that are recruited to the immunological synapse. These studies predict that distinct negative regulators of Arp2/3 will likely play an important role in T cell homeostasis after engagement of the T cell receptor. Negative regulators of Arp2/3 that control F-actin accumulation in the immunological synapse will likely play an important role in postactivation migration, energetics, and survival. The control of survival after activation is fundamental to immunological tolerance for prevention of autoimmunity and the for-

mation of immunological memory—areas in which F-actin is likely to have a new role.

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GEOPHYSICS

Toward “Supervolcano” Technology

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In addition to depicting the ultimate volcano-eruption horror story, the recent Discovery Channel/BBC coproduction “Supervolcano” speculates about what technology will be available to the geophysicist in 2025 to monitor active volcanoes. The result is a fictional Virtual Geophysical Laboratory that, when fed the right data, predicts eruption scenarios, thereby providing information to help guide civil emergency-response decisions. On page 821 of this issue, Patané *et al.* (1) report a key step toward realizing such an advanced volcano-monitoring technology.

The authors have used time-dependent seismic tomography to study Mount Etna during its pre-eruptive and eruptive phases between August 2001 and January 2003 (see the figure). This method is analogous to CAT (computerized axial tomography) scanning in medical technology, except that earthquakes are used as energy sources and that regions of

Earth are the target. In the present case, the region of interest is Mount Etna, a basaltic volcano in Sicily that is ~30 km in diameter and rises to ~3000 m above sea level.

The greatest challenge in this type of work is to obtain a sufficiently good earthquake data set. Patané *et al.* combine data from multiple seismic networks to overcome this difficulty. They observe major changes in the ratio of seismic compressional to shear-wave speed (V_P/V_S) during the buildup to an eruption and during the eruption itself; these changes correlate closely with observed magma movements (2). Most notably, the authors map regions where V_P/V_S decreases, and attribute this decrease to the influx of magma that is rich in volatiles (SO_2 , CO_2 , and water vapor).

Time-lapse seismic tomography can provide detailed insights into magma movements in an active volcano and may help to predict volcanic hazards in the future.



Toward predicting volcanic hazard. Mount Etna emits plumes of ash on 29 October 2002. Patané *et al.* have used time-dependent seismic tomography to gain detailed insights into magma movements within this volcano. Further development of this method should help to predict volcanic hazards at Mount Etna and elsewhere in the future.

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