

these two isoforms not mix, through diffusion, during their residence time in the cytoplasm? After all, their sites of synthesis are, on average, only 1 to 10 μm away from one another, and their turnover time is several days. Besides, even with disparate localizations of β - and γ -actin mRNA synthesis, the conundrum remained: Could the slight differences in their sequences imbue them with differences in function?

The fact that antibodies were generated that specifically recognize the amino-terminal differences between β - and γ -actin (4) raised the possibility that cellular proteins could also exhibit isoform-specific recognition. A few glimmers of suggestive evidence were tantalizing. These two isoforms of actin can form biochemically distinct complexes with the actin-binding protein profilin (6). The actin-binding protein betaCap73 discriminates between nonmuscle β -actin and muscle α -actin, which are more divergent in amino acid sequence than β - and γ -actin (7). However, no binding proteins specific for β - or γ -actin emerged.

That is, until now. Karakozova *et al.* demonstrate recognition of β -actin, but not γ -actin, by the enzyme Ate1 (Arg-tRNA protein transferase 1). Ate1 catalyzes the addition of an arginine residue to the amino terminus of target proteins (8), a modification thought to mark proteins for prompt ubiquitination and proteasome-mediated degradation. As a result, the two actin isoforms are not only chemically different, but the authors further demonstrate that the two isoforms take on wholly different organizations of the filamentous actin (f-actin) in which they are enriched. Arginylated β -actin forms single f-actin filaments, whereas γ -actin forms dense parallel bundles of filaments. The authors also reveal that each isoform's filament organization provides a possible mechanism for maintaining the two actins as separate pools. The leading edge can accommodate a fibrous meshwork of actin filaments, such as that generated by individual filaments of β -actin. More interior to the cell, thick filament bundles of γ -actin prevail, as they are too large to invade the leading edge. Strikingly, at least one of the elusive isoform-specific actin-binding proteins turns out to be actin itself. Actin filaments containing arginylated β -actin appear to repel one another instead of forming bundles.

The mystery of the two isoforms was solved, as is often the case, by investigators seemingly unconcerned by the arcane and long-standing question of actin's molecular evolution. Karakozova *et al.* were sleuthing a mystery of their own: Investigating the N-end rule of protein modification, which relates the half-life of a protein to the identity of its amino-terminal residue (9), led the authors to engineer mice lacking Ate1. The Ate1-deficient mice died during embryogenesis as a result of cardiovascular defects, suggesting that the enzyme plays a vital role in turnover of its substrate proteins.

Surprisingly, although β -actin was identified as a major substrate of Ate1, its isoform-specific arginylation seems to have nothing to do with shortening its half-life. Instead, arginylation of β -actin at its amino terminus—a domain that projects from β -actin filaments (10)—restricts the organization of β -actin filaments, and apparently prolongs the restricted subcellular localization of the β -actin isoform to the lamellipodial region where it was synthesized. The authors demonstrate that preventing arginylation of β -actin in fibroblasts causes inappropriate bundling of β -actin filaments within the cortical actin network (the cytoskeleton that lies just beneath the plasma membrane) at the leading edge, thus contributing to the defects in cell motility.

It is clear from the work of Karakozova *et al.* that posttranslational arginylation of a single protein target can induce global changes on the cellular level. Ate1 is evolutionarily conserved, and there are undoubtedly other substrates whose modification similarly results in altered properties that affect their cellular functions (or their degradation). Does this modification affect

the cardiac muscle α -actin isoform, given that the similarity of its amino terminus to β -actin (2) makes it a possible substrate for Ate1? Is the modification reversible? The answer to one conundrum has, not surprisingly, given rise to many more questions.

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APPLIED PHYSICS

Tunneling Across a Ferroelectric

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Spontaneously polarized materials through which electrons pass by tunneling may be used in novel electronic devices and may reveal new basic physics at the nanometer scale.

The phenomenon of electron tunneling has been known since the advent of quantum mechanics, but it continues to enrich our understanding of many fields of physics, as well as offering a route toward useful devices. A tunnel junction consists of two metal electrodes separated by a nanometer-thick insulating barrier layer, as was first discussed by Frenkel in 1930 (1). Although forbidden by classical physics, an electron is allowed to traverse a potential barrier that exceeds the electron's energy. The electron therefore has a finite probability of being found on the opposite side of the barrier. A famous example is electron tunneling in superconducting tunnel junctions, discovered by Giaever, that allowed measurement of important properties of superconductors (2, 3). In the 1970s, spin-dependent electron tunneling from ferromag-

netic metal electrodes across an amorphous Al_2O_3 film was observed by Tedrow and Meservey (4, 5). The latter discovery led Jullière to propose and demonstrate a magnetic tunnel junction in which the tunneling current depends on the relative magnetization orientation of the two ferromagnetic electrodes (6), the phenomenon nowadays known as tunneling (or junction) magnetoresistance (7). New kinds of tunnel junctions may be very useful for various technological applications. For example, magnetic tunnel junctions have recently attracted considerable interest due to their potential application in spin-electronic devices such as magnetic field sensors and magnetic random access memories.

The range of insulators for tunnel barriers is not limited to Al_2O_3 , however. For example, De Teresa *et al.* studied tunnel junctions with epitaxial perovskite SrTiO_3 barriers to demonstrate the decisive role of interfaces in spin-dependent tunneling (8). Parkin *et al.* (9) and Yuasa *et al.* (10) found large magnetoresistance in crystalline tunnel junctions with MgO barriers. Despite the diversity of materials used in tunnel junctions, the common feature of almost all the existing tunnel junctions is that

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