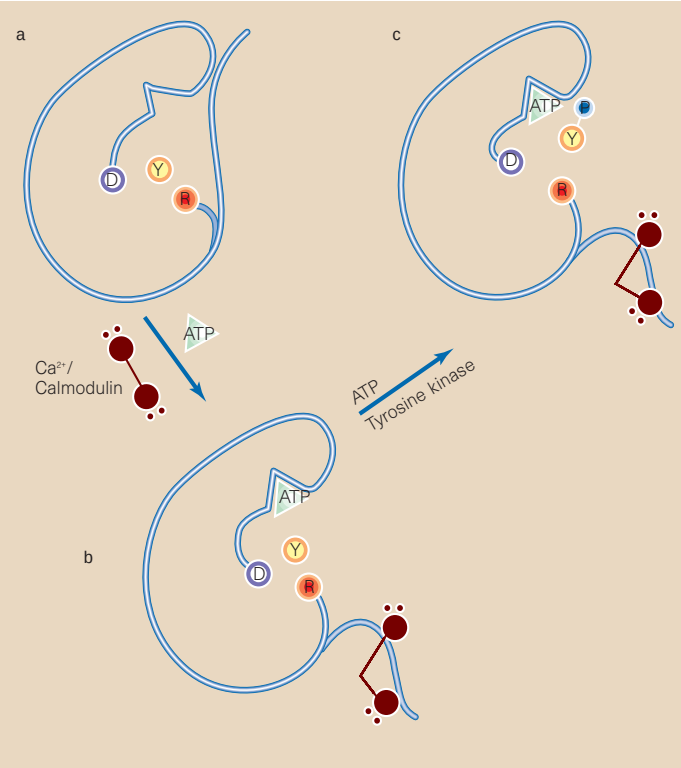

Figure 1 **Model for activation of the protein-kinase domain of titin.** a, **The titin kinase domain is auto-inhibited. Tyrosine (Y170) interacts with the catalytic aspartic acid (D127) and arginine (R129) to prevent binding of the protein substrate. The autoregulatory segment occludes the ATP-binding site.** b, **Calcium/calmodulin displaces the auto-regulatory segment, allowing ATP to bind and exposing Y170.** c, **An unknown tyrosine kinase phosphorylates Y170, which then interacts with the P+1 residue (R), on the protein substrate.**

P+1 loop interacts with the residue immediately carboxy-terminal to the amino acid that will be phosphorylated (P = 0) on the protein substrate. Before phosphorylation, the tyrosine-170 residue in the titin kinase domain interacts with the catalytic aspartic acid, as well as with an arginine that is two amino acids carboxy-terminal of this. This interaction blocks the binding site for the protein substrate. Mayans *et al.*[1] now show that phosphorylation of the tyrosine residue relieves this autoinhibition (Fig. 1). Moreover, they surmised that the phosphorylated tyrosine would interact with the P+1 residue of the substrate, and predicted that this residue would be an arginine. Sure enough, when they identified telethonin (an endogenous muscle protein that is a substrate for titin's kinase domain), they found that it contains arginine at P+1. However, this form of autoinhibition is probably rare, because only one other kinase in sequence databases contains the key features — an arginine in the same location relative to the catalytic aspartic acid, and a tyrosine in the P+1 loop.

With the likelihood that titin exists in many, if not all, mammalian cells, and may be involved in both sarcomere formation and chromosome condensation, the new results raise a number of questions. For example, what is the physiological function of the kinase activity, and is it connected to the structural roles of titin? As the telethonin substrate is muscle specific, are there other, biologically relevant, substrates out there? And given that calmodulin binding seems important for kinase activity, even when the enzyme is phosphorylated at a tyrosine residue, does activation of the kinase depend on a sustained increase in the intracellular concentration of calcium? Will dephosphorylation of tyrosine or a decrease in calcium be enough to inactivate the kinase?

Finally, what about the tyrosine kinase that phosphorylates the titin kinase domain? Titin and calmodulin co-localize to the actin-based cytoskeleton, so is the tyrosine kinase also to be found on the cytoskeleton? A number of the non-receptor tyrosine kinases are localized there[10]. Both calcium and tyrosine-kinase activities are frequently increased or deregulated in transformed cells, so is unscheduled activation of titin kinase a cause or a consequence of transformation? If so, could this lead to rearrangement of the actin-based cytoskeleton, which is characteristic of many transformed cells? The visage of titin kinase revealed by Mayans *et al.* will undoubtedly provide new impetus to understand how regulation of this giant protein kinase creates cellular order from potential chaos. □

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Daedalus

Photocoiffure

Most furry animals look neat, smooth and appealing. Each hair on the animal's surface grows so as to reach the envelope defined by all the others. A tree achieves this effect optically: an overshadowed shoot grows faster. So Daedalus reckons that each hair is an optic fibre, carrying ambient light at its tip down to its growing root. If it is 'overshadowed' by the other fibres, it is stimulated to grow. When its tip reaches daylight, growth is turned off. Most animal fur has a visible colour, so the light used must be infrared or deep red. (Thus, despite its obvious camouflage advantages, no animal has green fur; it would absorb the crucial radiation.)

Now human hair must be just as transparent to near infrared. A ruby-red laser treatment can be used to destroy unwanted hair; presumably the massively intense pulse coming down the shaft disorganizes the photosensitive follicle. So why does our hair not grow as neat and smooth as animal fur? Daedalus blames hair-cutting. An uncut hair has a tapered tip, giving a graded match between the refractive index of air and the much higher index of the hair. Radiation enters with little loss — some moth eyes have a micro-spiky surface for just this reason. But a cut hair terminates in an abrupt planar discontinuity, an optical mismatch which reflects away most of the radiation. The root is left permanently in the dark, and the hair just grows uncontrolled. Hair that is seldom or never cut (such as that of the eyebrows) is usually neat and even.

So in barbering, as in much else, once we start interfering with Mother Nature, we are forced to go on doing it. Most of us need endless hair-cutting to avoid looking shaggy and unkempt. Daedalus's analysis provides a neat way out. His 'Fluorostyle' hair-spray is an aerosol loaded with an infrared fluorescing agent. Sprayed onto the head, it is absorbed into the most prominent, outer hairs. The fluorescer absorbs visible light, and emits infrared inside the hair; this is transmitted down the shaft and inhibits growth. Shorter, overshadowed hairs are shielded from the aerosol, and grow normally.

Soon the user will have a neat and even thatch. Selective, graded applications of Fluorostyle spray will then shape, sculpt and maintain it to any desired envelope. The happy user will be as smart and trim as our primitive ancestors — whose popular image as shambling, shaggy, matted monsters can now be seen as totally undeserved.

David Jones