interwound tubes forming a double-helical structure (Fig. 1c). As noted by Pieranski, for this problem there is a critical pitch-to-radius ratio ($p/r = 2\pi = 6.28$) above which the line of contact between the tubes is straight, and below which it is helical. The crystallographic diameter of the classic DNA double helix is 23.7 ångstroms (Å), which would correspond to a radius for each of the two idealized helical tubes of 23.7/4 = 5.92 Å (here the sugar-phosphate backbones lie on the outside of the helical tubes). The generally accepted value for the pitch is 10.5 base pairs or 35.7 Å, so $p/r = 35.7/5.92 = 6.03$, which is within 4% of 2π. Is this an insight or just a coincidence? We suspect it is the former. ■

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Cell biology

A protein accumulator

Jennifer C. Pinder and Anthony J. Baines

We thought we knew what spectrin does. Is it not the elastic, membrane-bound protein that prevents red blood cells from rupturing as they circulate in the bloodstream? And does it not have the same supporting function in other cells? The second assumption has seldom been questioned over the past two decades, but has just been overturned by the power of experimental genetics, as described in three reports[1–3] in the *Journal of Cell Biology*. The results may bear on human diseases such as muscular dystrophy.

Red blood cells with deleterious mutations or deficiencies in spectrin have weakened outer membranes, are misshapen and lack resilience[4], so it is not surprising that spectrin has long been assumed to be necessary for membrane integrity. Over the years, other functions have been ascribed to spectrin as well. For example, it is thought to be involved in generating the polarized morphology of epithelial cells, and to have roles in the functioning of the Golgi complex — an organelle involved in protein secretion from cells — and the organization of synaptic vesicles (see, for example, refs 5–7).

To probe spectrin's function, Hammarlund *et al.*[1] and Moorthy *et al.*[2] have taken advantage of the simplicity of the genome of the nematode worm *Caenorhabditis elegans*. This genome, like that of the fruitfly *Drosophila melanogaster*, has only three spectrin genes, encoding α, β and β_H forms of the protein (Fig. 1). Hammarlund *et al.*[1] looked at worms with a mutation called *unc-70*, which they discovered to lie in the β-spectrin gene. Moorthy *et al.*[2] used a now common technique for blocking protein expression: they injected double-stranded RNA into the worm's gonad to block the expression of one or more spectrin subunits individually and in combination. They then analysed the resulting embryos.

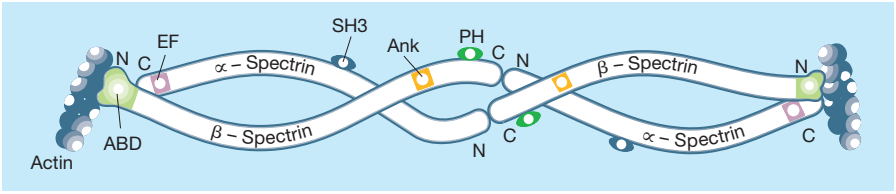

Figure 1 **The structure of spectrin[12,13]. Spectrin is a giant molecule comprising α and β subunits, of which there are different types. For example, *Drosophila* and *C. elegans* have α, β and β_H forms of spectrin. (β_H-Spectrin is a 'heavy' form of β-spectrin.) The α and β subunits associate to form an elongated $(\alpha\beta)_2$ tetramer. Lying near to the interior surface of the plasma membrane, spectrin forms a hexagonal lattice, the nodes of which are crosslinked by the cytoskeletal protein actin. This network is attached to the membrane in several ways, for example through the connecting protein ankyrin. β-Spectrins have binding sites for α-spectrin, actin and ankyrin (Ank). The pleckstrin-homology (PH) domain binds to certain membrane lipids. The Src-homology-3 (SH3) domain of α-spectrin probably accumulates signalling molecules close to the membrane. EF-hands are calcium-binding sites. ABD, actin-binding domain; C, carboxy terminus; N, amino terminus.**

Surprisingly, both groups find that β-spectrin is not essential for many of the processes suggested from previous investigations. Their worms do not lose general membrane integrity, and synaptic vesicles in nerve endings are clustered normally. The cellular secretory pathways appear unimpaired: the worms deposit cuticle and secrete collagen and components of the basement membrane as usual. The cells that should be polarized are polarized, suggesting that β-spectrin has no primary function in this process. Ankyrin is a connecting protein that is known to link spectrin to a variety of transmembrane proteins, including cell-adhesion molecules of the L1 family. Moorthy *et al.*[2] find that, in their worms, ankyrin apparently binds to L1 adhesion molecules normally.

However, the worms are paralysed and have a 'dumpy' appearance[1]. The main defects lie in the organization of muscle and nerve cells. The number of neurons is normal, but the patterns of axon outgrowth are altered[1,2], with few axons finding their targets. The muscle cells have disrupted sarcomeres (contractile units)[1,2], and the sarcoplasmic reticulum — an intracellular calcium store — is generally missing. It seems that the dumpy appearance is caused by a failure of the muscles to spring back after contracting. The muscle defects may arise during the course of contraction, as worms with both the *unc-70* mutation and the *unc-54* mutation, which results in a failure in muscle contraction, show less severe characteristics than the *unc-70* mutants[1].

What, then, has become of the anticipated functions of spectrin? Dubreuil *et al.*[3] have looked at fruitflies that lack β-spectrin, and provide some clues to the role of this protein in cell polarization. These flies live just long enough for 'copper' cells in the intestine to be analysed. In the mutant flies, the copper cells are polarized and ankyrin associates with the membrane of these cells as normal. So spectrin is not the main driver of cell polarization. It has been suggested[8] that what drives cell polarization is the contact of transmembrane cell-adhesion molecules with either their extracellular matrix ligands or their counterparts on other cells. So, in this case, a transmembrane L1-type adhesion molecule binds to its ligand and recruits ankyrin. But a transmembrane ion pump, the Na^+/K^+ ATPase, does not accumulate as normal in the plasma membrane of the mutant copper cells. Why is this?

Spectrin has been described as a 'protein-sorting machine'[9]. The new data[1–3] show that this model can be taken a step further: spectrin not only sorts, but also collects, proteins at the plasma membrane. Genetic evidence indicates that spectrin functions as a tetramer (Fig. 1). Each tetramer has two

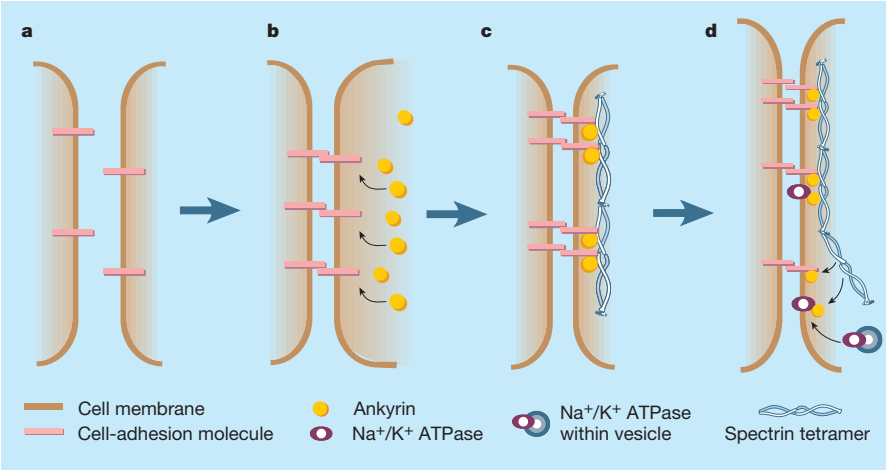

Figure 2 **Model for the accumulation of membrane proteins at points on the cell surface specified by cell-adhesion molecules. The new work[1–3] is consistent with the following model.** a, **Two cells interact through adhesion molecules.** b, **Ankyrin is recruited to ligand-bound cell-adhesion molecules. Other ankyrin-binding molecules, such as Na^+/K^+ ATPase, do not accumulate in the absence of spectrin.** c, **Spectrin tetramers are recruited to membrane-bound ankyrin/cell-adhesion-molecule complexes, crosslinking these complexes and stabilizing the regions of cell–cell contact.** d, **Further spectrin molecules are recruited into a submembrane skeleton crosslinked by the cytoskeletal protein actin. Binding sites on spectrin trap ankyrin bound to other molecules such as Na^+/K^+ ATPase, and promote their stable incorporation into the membrane domain.**

ankyrin-binding sites. One ankyrin molecule, recruited to a cell-adhesion molecule, binds to a spectrin tetramer (Fig. 2). This tetramer then has another ankyrin-binding site free to connect to other ankyrin-containing complexes, such as that consisting of ankyrin and Na^+/K^+ ATPase. If spectrin is missing, this ion pump cannot be captured at the membrane. So spectrin traps and stabilizes proteins at specific points on cell surfaces first specified by ligand-bound cell-adhesion molecules (Fig. 2). The results of Dubreuil *et al.*[3] support this theory as far as the Na^+/K^+ ATPase goes. And the results of Hammarlund *et al.*[1] and Moorthy *et al.*[2] indicate that spectrin may also trap and stabilize key muscle or nerve proteins at specific points on cell membranes as specified by cell-adhesion molecules.

There are more human genes encoding spectrins than there are worm or fruitfly spectrin genes. So, different spectrin isoforms may have evolved other tasks in vertebrates — for example, in Golgi function. This might account for some of the discrepancy between past and present results. But the new results[1–3] may also bear on human biology. It is interesting that, in *C. elegans*, a mutation that causes a loss of muscle contraction suppresses the problems that arise from a lack of β-spectrin. This result hints at the idea that any muscle that is in continual use (for example, the heart or diaphragm) might be the most vulnerable to the effects of spectrin mutations, and some unexplained human muscle and heart disorders may have their origins in mutated spectrin genes.

The new work might apply even more generally. Dystrophin is a protein that is mutated in Duchenne and Becker muscular dystrophies in humans and is a member of the protein superfamily to which spectrin belongs. *C. elegans* with the *dys-1* mutation lack a functional form of dystrophin, but do not show any obvious muscular degeneration. Instead, they lose the enzyme acetyl-cholinesterase, presumably from its anchoring points in muscle-cell membranes[10]. Dystrophic *mdx* mice, which also lack functional dystrophin, lose nitric oxide synthase from the plasma membrane of muscle cells[11]. Perhaps dystrophin and other members of this superfamily emulate spectrin's protein-accumulating activity. ■

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Daedalus

Pulses of the mind

The human brain, which works by processing discrete nerve impulses, is often regarded as a digital computer. Daedalus wants to measure its processing power in operations per second. Modern magnetic-resonance imaging can detect a region of high brain activity by its increased metabolic rate, but cannot deduce the corresponding digit rate. Daedalus now has an improvement.

He points out that the basic processing unit of the whole nervous system is the nerve pulse. At each point it involves a radial movement of sodium ions lasting about a millisecond. Sodium nuclei have spin and magnetic moment. In a suitable magnetic field, a resonating radio-frequency can elevate them to an excited state, from which they will later relax back to the ground state. Suppose that radio-frequency is 1 kilohertz, corresponding to a time constant of a millisecond. Then relaxation should be decidedly stimulated if the nuclei are being vibrated with the same time constant — as by being in a nerve along which a pulse is passing.

The magnetic field for which sodium ions resonate at 1 kHz is a modest 0.9 microtesla. Daedalus's nuclear magnetic psychometer places the subject's head in such a field and irradiates it at 1 kHz. It measures the relaxation times of the sodium ions in the various regions of his brain. The greater his mental activity, the faster the ions will relax; or more exactly, the stronger the peak of their relaxation-time spectrum within the 1 ms region. Once properly calibrated, the instrument will give the total rate of working for the subject's brain, in pulses per second.

Psychology will at last have a sound numerical basis. Daedalus expects that subjects with a high IQ will show a greater processing rate than those of low IQ. But asked to solve a problem, their rate of working will rise less — their algorithms will be more efficient. Yet intuitive types with an unexceptional IQ may still show high firing rates, from their active imaginations. As the subject learns a new skill, the firing rate in the relevant brain region will rise, and then decline as he automates his new ability. Skilled meditators may be able to drive their brain activity right down; but even a sleeping or drugged subject will still show the processing needed for the brain's steady 'housekeeping' — maintaining heart rate, temperature, peristalsis and so on. All the values should exceed a billion pulses per second, showing up modern computers for the primitive devices they are. **David Jones**