In the end, Wallace is interesting not so much because his scientific work overlapped with that of Darwin but because these two naturalists approached the species question from significantly different intellectual and ideological backgrounds. Their research programs overlapped and led them to ideas that were similar if not identical, and Wallace certainly deserves recognition for his work on topics such as biogeography as well as evolution theory. But his opposition to scientific naturalism and materialism meant that his views on both human nature and its position in the wider world rested on a view of society that Darwin and Huxley were gradually (and in Huxley's case deliberately) seeking to undermine.

Wallace's views were not completely out of kilter with the time, because they were shared by many who distrusted both science's rejection of natural theology and the trend towards a managerial approach in politics. Nevertheless, his activities left him isolated from communities that might otherwise have been more appreciative of his scientific work and have led to him being seen as someone who was being pulled in two directions at once. Costa's biography helps us to see that Wallace was not, in fact, a case of split personality: he was engaged in a lifelong effort to find a moral agenda underlying the activities of nature and the forces that drive human interactions. The enthusiasts who are seeking to gain him wider recognition today are fascinated not just by his scientific achievement but also by his willingness to speak out against the ideological forces he distrusted. James Costa's new account of his life and work may help to show that as far as Wallace was concerned the two areas were actually part of a coherent program, but whether it can do more than its many predecessors to improve Wallace's standing in the modern world remains to be seen.

DECLARATION OF INTERESTS

The author declares no competing interests.

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Quick guide

LIM domain proteins

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What is a LIM domain? The LIM domain is an evolutionarily conserved protein module that was discovered in the late 1980s in the transcription factors Lin-11, Isl-1 and Mec-3, from which the acronym is derived. LIM domains are typically 50–65 amino acids in size and composed of two zinc-finger motifs. Each zinc finger contains four conserved residues (mostly cysteines and histidines) that coordinate a zinc ion (Figure 1, top left). The rest of the LIM sequence is highly variable. While zinc-finger motifs are found in many transcription factors, there is little evidence that LIM domains themselves bind DNA. They instead act as protein–protein interaction motifs and bind a diverse array of cellular proteins, including many cytoskeletal proteins.

How many different LIM domain proteins are there? In humans, there are ~70 genes encoding LIM proteins that contain anywhere from one to five LIM domains and have been broken down into ~14 different classes. LIM domains can be at the amino terminus, carboxyl terminus or in the middle of the protein. Most LIM proteins contain additional domains such as PDZ or kinase domains (Figure 1, top left), although some (e.g. FHL and PINCH) contain just LIM domains. This multimodular nature enables these proteins to act as scaffolds controlling the assembly of diverse protein complexes in several subcellular compartments and as signaling molecules triggering diverse biochemical pathways. The number of LIM proteins significantly expanded throughout evolution, with only a few (e.g. CRP and paxillin) found in some single-celled organisms. It has even been hypothesized that their expansion contributed to multicellular life.

Where are LIM proteins found in the cell? Pretty much everywhere! LIM proteins can be found in the nucleus, cytoplasm, bound to the actin cytoskeleton, and in adhesions (Figure 1). While many can shuttle between the cytoskeleton and the nucleus, the microenvironmental conditions that trigger their translocation are still largely unknown. The ubiquitous presence of LIM proteins underlies their involvement in a wide range of cellular functions, including transcription, cytokinesis, adhesion, and motility. More recently they have also been implicated in both mechanosensing and mechanotransduction.

What do LIM proteins do in the nucleus? The LHX and LMO classes of LIM proteins reside in the nucleus and function as *bona fide* transcription factors (LHX) or cofactors (LMO). The LIM domains in the LHX transcription factors regulate protein activity, while their homeodomains bind DNA. By mediating tissue-specific gene expression, nuclear LIM proteins regulate several developmental processes, particularly within the nervous system. Conversely, the nuclear functions of LIM proteins that undergo nuclear-cytoplasmic shuttling (e.g. zyxin, paxillin and FHL) are largely unknown. Emerging evidence, however, indicates their involvement in gene expression regulation as co-activators or corepressors by interacting with the transcription machinery, including nuclear receptors.

What role do LIM proteins play in the cytoskeleton? Many LIM proteins are found in focal adhesions and adherens junctions where they act as molecular scaffolds mediating cell adhesion. They can also trigger specific cellular pathways from these cytoskeletal structures by affecting the localization, expression or activity of signaling molecules (e.g. focal adhesion kinase, Rho, and MAP kinase) that promote cell migration, proliferation and apoptosis. A subset of LIM proteins also localize to stress fibers and regulate actin filament organization and dynamics by affecting actin (de)polymerization or stabilizing actin filaments through crosslinking or bundling. These LIM proteins can bind stress fibers either directly via their specific actin-binding domains/motifs (e.g. Eplin and Ablim) or indirectly through interactions with other actin-binding proteins (e.g. RIL). Recent research has also revealed a role for LIM proteins in responding to mechanical cues.

What do you mean by mechanical cues? The LIM protein zyxin relocates to actin stress fibers when cells are cyclically stretched and also localizes to tears within stress fibers that are under

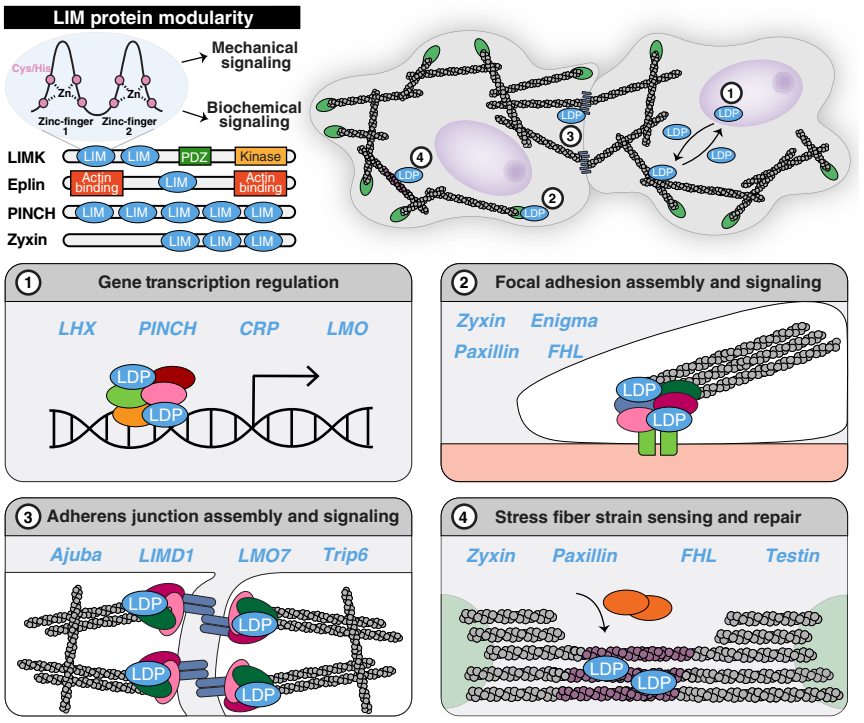

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Figure 1. LIM protein structure, cellular localization and function.
LIM domains, composed of two zinc fingers, can be found in many different arrangements in a variety of proteins (not drawn to scale). Their multimodular nature underlies their involvement in both biochemical and mechanical signaling. LIM domain proteins (LDPs) localize to the nucleus where they are mainly involved in transcription (1). They also localize to the cytoskeleton where they contribute to focal adhesion/adherens junction assembly and signaling (2 and 3) or recognize sites of strain within stress fibers to facilitate repair (4). Representative examples of LIM proteins at each site are shown in blue text.

tension. These findings have led to the hypothesis that zyxin is strain sensitive, where strain refers to a component that is stretched or compressed compared to its original length. Zyxin has been proposed to recognize strained actin filaments.

Is zyxin the only LIM protein that responds to mechanical signals? Although zyxin was the first identified mechanosensitive LIM protein, many other LIM proteins behave similarly, including paxillin, Hic-5, and FHL. Interestingly, some LIM proteins, such as testin, do not readily exhibit mechanosensitivity as full-length proteins, but contain LIM domains that independently recognize mechanical signals. In the case of testin, its mechanosensitivity is additionally regulated by RhoA, a key mediator of cytoskeletal function. It is thus likely that the mechanosensitivity of other LIM proteins is also regulated.

How do LIM proteins sense mechanical signals? We do not know exactly! A truncation consisting only of zyxin's three LIM domains was found to be sufficient to recognize strain sites. As many other mechanosensitive LIM proteins also contain multiple LIM domains in series, it has been hypothesized that this is a requirement for strain sensing. The first LIM domain of testin, however, recognizes these strain sites on its own, suggesting that the requirement for multiple LIM domains is not universal. By comparing sequences of both mechanosensitive and non-mechanosensitive LIM domains, a conserved phenylalanine was identified that could be important for determining mechanosensitivity. This residue is not conserved in all mechanosensitive LIM proteins, however, suggesting again that multiple mechanisms could, and likely do, exist.

How do LIM domains recognize strained actin? The exact molecular mechanism remains elusive. We know, however, that LIM domains only recognize strained actin filaments, not fully severed ones. The current thought is that, under increased tension, actin filaments undergo a conformational change that could expose cryptic or novel binding sites for LIM domains. Experiments *in vitro* suggest that LIM domains directly bind strained actin, but the magnitude of accumulation is significantly less than is typically seen in cells, making it impossible to rule out the involvement of additional interaction partners. Dissecting the various mechanisms and kinetics of these mechanosensitive interactions are all exciting and active research areas.

Why is LIM protein mechanosensitivity important? LIM proteins are thought to act as cellular mechanosensors that serve to translate mechanical signals into biochemical signals, a process known as mechanotransduction. Their multimodular construction makes them perfect candidates for this role. In zyxin, for example, the carboxy-terminal LIM domains recognize strained actin (the mechanical signal), while the amino-terminal domains recruit the actin crosslinker α-actinin and the actin polymerization factor VASP (the biochemical signals) to facilitate stress fiber repair. As LIM proteins localize to a number of other actin-based sites, it is likely that other LIM proteins similarly behave as mechanotransducers, recognizing actin strain in these structures via their LIM domains and promoting additional protein interactions and downstream signaling via their other domains. This would be consistent with reports that LIM proteins in adherens junctions (e.g. Ajuba and LIMD1) have tension-dependent roles in Hippo signaling. Mechanosensitive LIM domains could also serve to sequester proteins in the cytoskeleton, with changes in tension freeing these proteins to localize to other compartments, such as the nucleus in the case of FHL2 and MLP. The multifunctional nature and ubiquitous presence of LIM proteins in cells suggest that the mechanotransduction pathways they trigger are likely specific to each protein, providing both excitement and a challenge to the field.

Are LIM proteins involved in disease? Altered LIM protein function has been associated with certain pathologies,

mostly heart and muscle diseases, as well as cancer. This is not too surprising, as the pathogenesis of these disorders is often characterized by the impairment of certain mechanical processes (e.g. altered contractility or abnormal motility). A key question, however, is how these LIM proteins directly contribute. Since their role as cellular mechanosensors is hypothesized to maintain mechanical homeostasis in cells and tissues, it begs the question of whether impaired mechanosensing underlies their role in these diseases.

Where can I find out more?

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Quick guide

Siamese fighting fish

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What is a Siamese fighting fish?
Siamese fighting fish (*Betta splendens*; Figure 1) belong to the Anabantoidei group, native to the freshwaters of southeast Asia. Often living in oxygen-poor water, they are small (*c*. 7 cm) carnivorous fish that have a long history with humans, with their domestication dating back at least 1,000 years. Today Siamese fighting fish remain one of the most popular species worldwide in the tropical fish aquarium trade, and decades of domestic breeding have created many elaborate colors and fin shapes (Figure 2). Wild male Siamese fighting fish are typically not as brightly colored or long-finned as the selectively bred domestic breeds, with the most common colours being dark red and blue. Females are typically smaller than males, with shorter less-elaborate fins and more subdued coloration. Siamese fighting fish thrive in shallow water with dense vegetation. This vegetation provides cover from predators while also supporting the invertebrate communities upon which they feed. It is likely the predominance of paddy fields in Southeast Asia contributed to our long history with this species, as Siamese fighting fish thrive in the conditions under which rice is grown. An unusual feature of all members of the Anabantoidei is the presence of an air-breathing labyrinth organ, akin to a lung, that allows them to obtain oxygen by taking gulps of air at the surface of the water. Siamese fighting fish are facultative air breathers, and if access to the water surface is restricted, they will drown. Their Latin name, *Betta splendens*, indicates what has made this species so famous around the world: *bettah* in Malay refers to an ancient warrior tribe. Male Siamese fighting fish are extremely territorial and engage in a series of aggressive displays when in combat with another male. These displays are intense and result in a substantial increase in metabolic rate, and unusually, can in some instances involve fights to the death of one opponent. It is this interaction between physiology and behavior, and the reliability of their aggressive responses, that has made Siamese fighting fish such a popular study species.

What happens when they fight?
One of the most frequent displays of aggression in male Siamese fighting fish is the flaring of the opercula (Figure 2), whereby the fish spread out their gill covers. This flaring creates an illusion of greater size, while also being an honest signal about the condition of the male. While flaring the opercula, ventilation of the gills is reduced, akin to the fish holding its breath. The duration of opercular flare displays largely determines who wins an aggressive encounter, with the victor being the individual who flared for the longest. If Siamese fighting fish are kept in water with extremely low oxygen concentrations, opercular flaring is significantly reduced, suggesting a link between the duration of breath holding and body condition. Oxygen demands increase significantly during these energetic displays, yet the fish are unable to extract any more oxygen from the water than they can when they are at rest, due to their reduced gill surface area. This means the fish can only meet their increased oxygen requirements during combat via more air-breathing from the surface of the water. To make matters more complicated for the fish, they are unable to increase oxygen uptake per breath — they can't just take deeper breaths — thus the only solution is to take more breaths at the surface, at each visit. This creates a problem when two fish are dueling underwater; how do you ensure enough trips to the surface, without being attacked by your rival? Siamese fighting fish have evolved an unusual system of stereotyped synchronous surface breathing, whereby one of the fish will lead the other to the surface and will take a breath of air.

Why is their behavior and physiology so extreme? Their extreme behavior is linked to their reproduction. Male