dered materials, indicate that the universality associated with thermal phase transitions also emerges for quantum phase transitions in metals. To test this universality with greater rigor, Grigera *et al.* (*9*) have now measured the resistance at the bottom of the funnel, at temperatures an order of magnitude lower than were used before. They find that the metamagnetic transition appears to be split into two transitions, with α rising to an anomalous value of 3 between the two.

At first sight, those seeking simplicity in complex situations will be disappointed. However, classical first-order transitions, characterized by magnetization jumps, often appear split because of coexistence regimes intervening between high and low magnetization states. Metamagnetic transitions, when interpreted as the outcome of a quantum mechanical level crossing (see the bottom panel of the figure), are quintessential first-order transitions. Grigera *et al.*'s experiment verifies another analogy between classical and quantum phase transitions: Coexistence regimes are possible in both cases.

The importance of such coexistence near many quantum critical points in solids is increasingly recognized (*16*). The highly quantum mechanical helium liquids and solids have long been known to coexist in certain pressure ranges near 0 kelvin (*17*). What is new and will require explanation is why the electrical resistance in the two-phase regime for metamagnetic $Sr_3Ru_2O_7$ varies as T^3.

Researchers studying quantum phase transitions now face the same situation as for thermally driven phase transitions 35 years ago: Experiments on ever cleaner materials are revealing increasingly universal behavior independent of the material, even while no quantitative theory can explain the results.

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1. A discussion of factors apart from dimensionality affecting phase transitions, as well as an overview of the entire classical subject, is given in (*18*).
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PERSPECTIVES: STRUCTURE

An Anthropomorphic Integrin

Martin J. Humphries and A. Paul Mould

In multicellular organisms, adhesion receptors organize the molecular complexes that flank the plasma membrane. The extracellular face of the cell apposes extracellular matrix fibrils that are decorated with growth factors, whereas its cytoplasmic face teems with signaling complexes, compartmentalized by cytoskeletal polymers and lipid microdomains. It is the job of specialized plasma membrane adhesion receptors called integrins to bridge and conflate these two dynamic systems, a task that demands a structurally versatile molecule. Despite extensive investigation, it has not been clear exactly how integrins interact with their ligands, how ligand occupancy affects integrin conformation, and how receptor activation is coupled to bidirectional signal propagation. On page 339 of this issue, Xiong *et al.* (*1*) report the first crystal structure of the extracellular portion of an integrin and concomitantly advance the field one enormous stride toward achieving these goals.

The integrin selected by Xiong *et al.* is $\alpha V\beta 3$, a receptor expressed by many cells that recognizes a series of glycoprotein ligands, including vitronectin and fibronectin. This integrin appears to be important for the integrity and function of cardiovascular and bone tissues. The investigators expressed both subunits of the integrin heterodimer as full-length soluble constructs in insect cells, and crystallized this complex in the presence of calcium ions (Ca^{2+}). The overall shape of the crystallized conformer (resolved to 3.1 Å) is that of a large "head" on two "legs" (see the figure), similar to the images seen using electron microscopy (*2*, *3*). The head contains a seven-bladed β-propeller structure contributed by the α subunit (corresponding to its seven amino-terminal repeats) and a von Willebrand factor A domain contributed by the β subunit (termed the βA domain). The β propeller (a toroidal arrangement of seven β sheets) is found in many other proteins, including the β subunit of heterotrimeric GTP-binding proteins (G proteins). The A domain (a central β sheet sandwiched by two sets of α helices) is also a common fold found, for example, in the α subunit of G proteins. In the integrin, the βA domain is positioned cheek-by-jowl with the upper face of the β propeller, with a helical region on top of the βA domain articulated to the β propeller's central shaft. The remainder of the head is a unique hybrid immunoglobulin fold, its two β sheets contributed by the polypeptide regions that flank the amino and carboxyl termini of the βA domain.

The α-subunit leg of the integrin contains three large β-sandwich domains. Between the "thigh" domain and the first of two "calf" domains is a highly flexible "knee" (or "genu"), which exhibits a cramping bend in the crystal structure. The β-subunit leg contains a PSI (plexins, semaphorins, and integrins) domain, four epidermal growth factor (EGF)-like repeats, and a cystatin-like fold. The β-subunit knee region, formed from the conjunction of the hybrid domain, two EGF repeats, and the PSI domain, in agreement with previous biochemical data (*4*), is also capable of extreme flexibility, suggesting that the integrin may pivot at this point.

The binding of an integrin to its ligand is known to be dependent on divalent cations, and six Ca^{2+}-binding sites are seen in the structure. Four of these lie as previously predicted in β-loop-β structures (*5*) on the lower face of the β propeller, and another site is in the knee region of the α subunit. The top face of the βA domain contains a potential cation-binding site, known as the metal ion–dependent adhesion site, or MIDAS (*6*), although this is unoccupied in the crystal structure. However, a new site is seen adjacent to the MIDAS, to which the authors give the name ADMIDAS.

Some features of the integrin structure were widely anticipated from predictive studies [for example, the βA domain and propeller predictions of Tuckwell (*7*) and Springer (*8*)] and from the intense biochemical dissections of the past decade (*9*). Other features, however, were totally unexpected. The Xiong *et al.* structure advances our understanding of how integrins work in at least three ways. First, the means of intersubunit association was previously unknown. Now it can be seen at a glance how the two partners unite, together with the likely mechanism for selecting the α/β pairing. Second, the position of the ligand-binding pocket has been clarified

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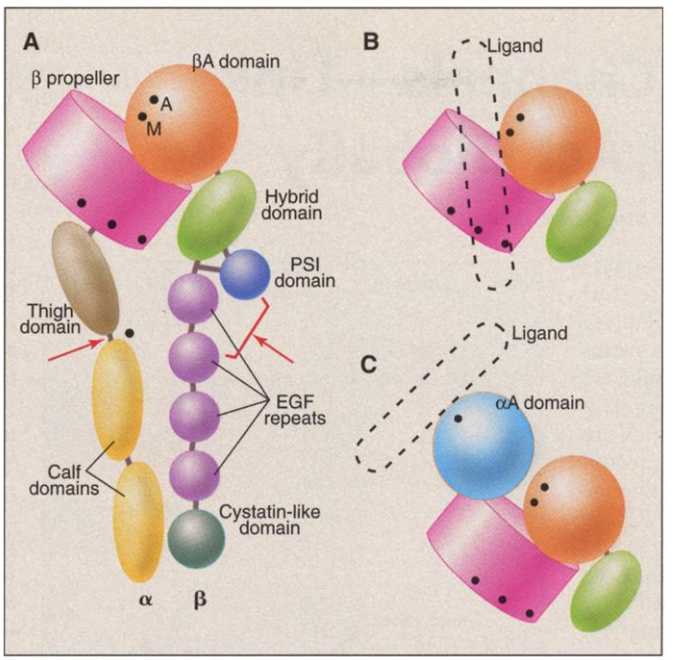
(see the figure). The site of ligand binding on the α subunit was a hotly disputed topic, with locations as far apart as the Ca^{2+}-binding sites on the underneath of the propeller, and loops on the top surface of the propeller having been proposed. In one fell swoop the first theory has been demolished and the second verified (*10*, *11*). The site of ligand binding on the β subunit (the top face of the A domain, which contains the MIDAS site) was correctly predicted (*12*, *13*). The structure also sheds light on the likely mechanism of ligand binding: A divalent cation at the MIDAS site probably coordinates with an acidic residue in integrin ligands (such as Asp in Arg-Gly-Asp and Leu-Asp-Val), and surrounding loops provide specificity to the binding. Third, the striking resemblance between the quaternary structure of the head region of integrins and the nucleotide-binding pocket of heterotrimeric G proteins suggests that the conformational changes involved in integrin activation may be similar to those seen in G proteins (*14*). From the structure it is easy to envisage how a change in the relative orientation of the βA domain and the β propeller could affect the shape and/or exposure of the ligand-binding pocket.



An integrin's MIDAS touch. **(A)** The domain structure of the straightened extracellular segment of integrin αVβ3 (the bends observed in the actual crystal structure are not shown). The molecule is orientated with its ligand-binding head at the top, and the juxtaposed membrane domains of its legs at the bottom. The 12 structural modules comprising the integrin heterodimer are labeled. Cation-binding sites are shown by black dots. M, MIDAS; A, ADMIDAS. Only three of the four cation-binding sites in the β propeller are visible. Arrows indicate regions of extreme flexibility. **(B)** Tentative model of the ligand-binding pocket of αVβ3. Ligand binding probably takes place near the interface between the β propeller and the βA domain, with direct contributions from blades 2 and 3 of the β propeller and the MIDAS site of the βA domain. **(C)** The head of an integrin that contains an αA domain. Ligand binding takes place at the αA domain [as described by Emsley *et al.* (*15*)], which is inserted into the β propeller between blades 2 and 3 and lies next to the βA domain.

Looking ahead, this landmark study now enables previous biochemical work on integrins to be placed in the context of a tertiary structure and will refocus goals in order to elucidate further the structural basis of integrin function. Although higher resolution structures, and structures incorporating the currently untraced domains at the β-subunit knee, are needed, it is the questions relating to integrin activation that are now likely to receive the most attention. If, as seems likely, the current structure is in an active conformation, then a clear priority will be to crystallize an integrin in an inactive conformation. This should then reveal whether activation causes an opening or repositioning of the ligand-binding portion of the two subunits, as suggested by biochemical data and predicted from the G-protein analogy.

It is difficult to draw clear conclusions about the intramolecular events that underlie integrin signaling from this single conformational snapshot, but a number of its intriguing features suggest models that can be tested. Of particular interest is the degree of flexibility in the interdomain interfaces. For example, can the receptor flex its joints in response to ligand binding and/or cytosolic signaling, or is it arthritic? The unexpected finding of severe bends in both knees raises questions about how the ligand-binding pocket is coupled to the interior of the cell; for example, do changes in the angles of the knees affect the interaction of the integrin's cytoplasmic "feet" with the cytoskeleton and signaling molecules, or is the integrin much more compact than previously thought? Solving the structures of other crystal forms of integrins, perhaps with different divalent cations, or integrins complexed with ligands or regulatory antibodies, should help to resolve this issue. The identification of the ADMIDAS motif in the βA domain, the Ca^{2+} ion coordinated at the α-subunit knee, and the coupled β-loop-β Ca^{2+}-binding loops in the β propeller will revitalize studies of how cations regulate integrin activity.

Other joints in the integrin skeleton appear surprisingly inflexible, including the βA domain–hybrid domain linkage in the β subunit. Whether ligand binding triggers conformational changes in the βA domain that in turn alter the positioning of the hybrid domain can now be investigated by targeted mutagenesis. Intriguingly, a subset of integrin α subunits, but not αV, contain an additional A domain inserted into the β propeller. The αVβ3 structure now reveals how this might be accommodated adjacent to the βA domain on the top of the β propeller (see the figure). Previous crystallographic studies of isolated αA domains have revealed conformational changes in response to ligand binding that might underlie activation (*15*), and in the future it will be instructive to crystallize the entire extracellular region of an αA domain–containing integrin to elucidate how the presence of its αA domain alters signal transduction.

Last, but by no means least, is the promise that integrin crystallography may aid drug design. Now that Xiong *et al.* have set a precedent, there will be great interest in determining the structures of the many integrins that are therapeutic targets for inflammatory, infectious, and neoplastic diseases. Hopefully these structures will aid the development of anti-adhesives that block the ligand-binding site—the ultimate jewel in the MIDAS crown of the integrin.

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