tions. Above the quantum limit, all the electrons are in the lowest-orbit level but still have a range of kinetic energies owing to their motion along the field direction. The experiments of Behnia *et al*. explore what happens in this case.

They report measurements of the transverse voltage induced across a single crystal of bismuth by a longitudinal temperature gradient as the magnetic field is varied. Such voltages, known as the Nernst signal, have been used as sensitive probes of the motion of electrons in superconductors (*5*). The origin of the Nernst signal in bismuth, which is not a superconductor even in zero magnetic field, is different and at low magnetic field is ascribed to normal electrons. Behnia *et al.* now show that the Nernst signal has well-defined peaks at high fields (well above the quantum limit) indicating the presence of fractional charge behavior in a bulk metal.

Although the detailed behavior of the Hall coefficient at low fields around and below the quantum limit is not yet understood in bismuth, Behnia *et al*. also observe signatures at high field reminiscent of the fractional quantum Hall effect in 2D electron gases. However, the lack of clear plateaus of the Hall resistance makes it very difficult to assign filling factors to these features. Behnia *et al*. tentatively assign a level filling of ½ to the first such feature, based on the magnetic field at which it occurs. Because this filling factor is atypical for 2D electron gases in the archetype fractional quantum Hall system gallium arsenide, understanding why it might be stabilized in bismuth will be one of many challenges for theoreticians.

The main theoretical challenge, however, is to understand the role of dimensionality. A way to construct a 3D quantum Hall state is to start with 2D sheets of electrons stacked along the third dimension. The electron behavior becomes 3D through quantum tunneling of electrons between the layers. Experimental systems of this behave like normal metals in the direction perpendicular to the layers and exhibit fractional quantum Hall states within the plane, as predicted theoretically. The data reported by Behnia *et al*. for bismuth also display these two types of behavior. However, in bismuth the natural starting point is a 3D metal, and a theoretical understanding of how similar states may form from this starting point does not exist.

As well as presenting challenges to theory, the work is also a catalyst for future experimental studies. For example, in the 2D fractional quantum Hall state, many more fractional states appear as purity is increased. It will be interesting to see whether similar phenomena occur in bismuth.

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BIOCHEMISTRY

How Cells Control Zinc Homeostasis

The structure of a transport protein for divalent metal cations sheds light on how metal concentrations in the cell are regulated.

Dietrich H. Nies

Divalent metal cations are essential for all living cells. For example, Mg^{2+} stabilizes the phosphates in adenosine triphosphate (ATP), and Zn^{2+} is required for transcription, immune functions, and neurotransmission. On page 1746 of this issue, Lu and Fu report the structure of a zinc transport protein that elucidates how the zinc concentration of the cell is controlled (*1*).

Tight control of the cellular concentration of divalent metals (a process referred to as metal homeostasis) prevents the formation of metal complexes or the occurrence of redox reactions that are toxic to the cell. Sequestration of transition metals to metal-binding and storage compounds prevents unwanted chemical reactions. However, the key to metal homeostasis is transport. This metal homeostasis can be envisioned as the equilibrium between metal uptake and efflux. Understanding metal homeostasis thus requires knowledge of the structure and function of the transport proteins involved.

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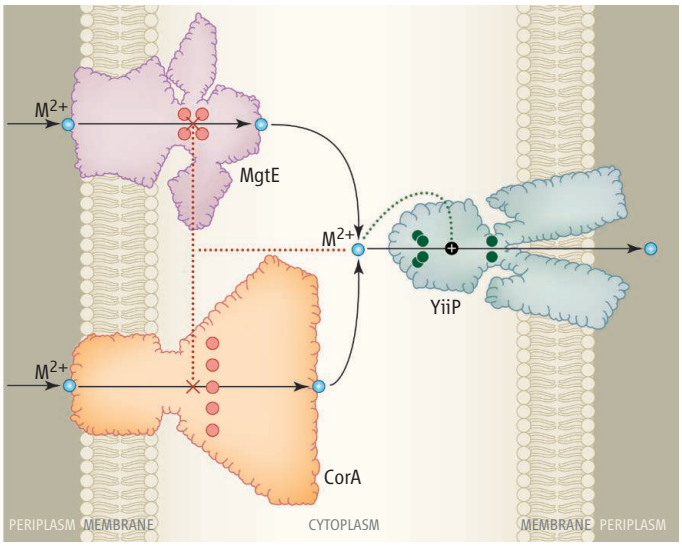
Lu and Fu now reveal the structure of YiiP, a transport protein for transition metal cations, from *Escherichia coli*. Toyoshima reported the structure of the Ca^{2+}-transporting P-type adenosine triphosphatase (ATPase) (*2*); many members of the P-type ATPase protein family transport zinc. Thus, we now have structures for the two known zinc exporter families. Common motifs in these two exporter families and that of uptake systems for divalent metal cations (*3*, *4*) indicate that flux control of transport proteins through the metal concentration may be an important contribution to metal homeostasis. Moreover, the structures demonstrate how such a process may be accomplished.

The YiiP protein belongs to the cation diffusion facilitator (CDF) protein family. CDF proteins (*5*) occur in bacteria, archaea, and eukaryotes (*6*). Their substrates are Zn^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, and Fe^{2+}; the ZnT (zinc transport) proteins from humans mainly transport Zn^{2+}. In addition to efflux, CDF proteins may also be involved in cation uptake when the metal concentration in the cytoplasm is too low (*7*, *8*).

YiiP (*1*) is a dimeric protein, in which the transmembrane domains of the two subunits are clearly separated but the carboxyl-terminal cytoplasmic domains are closely associated (see the figure, right). Fu and Lu identify four bound Zn^{2+} ions per subunit, two in or next to the transmembrane domain and two in the cytoplasmic domain. Three of these ions seem to be required to form and stabilize the YiiP dimer, the active form of the protein. In the Mg^{2+} uptake systems CorA and MgtE (see the figure, left), the magnesium-binding sites are in the cytoplasmic domains, which suggests that Mg^{2+} uptake is controlled by cytoplasmic Mg^{2+} concentrations (*3*, *4*); the divalent metal cation is only taken up when needed. Similarly, the YiiP structure indicates that superfluous Zn^{2+} in the cytoplasm may lead to or stabilize the formation of the active dimer, which exports Zn^{2+} until homeostasis is attained.

Control of zinc efflux via activity (rather than gene expression) might be required for two reasons. First, flux control enables much quicker and finer control of the cytoplasmic zinc concentration than can be achieved by gene expression, which happens in addition to flux control for many known Zn^{2+} efflux sys-



Controlling cellular metal homeostasis. The backbone of cellular metal homeostasis is a flow equilibrium of uptake and efflux reactions. Activity of either transport process seems to be controlled by cytoplasmic concentrations of divalent metal cations (M^{2+}). Solid lines, transport, dashed lines, regulation of transport activity; red, inhibition; green, activation. Uptake (**left**) can be understood from the structures of the Mg^{2+} uptake systems MgtE (*4*) and CorA (*3*), which also transport other divalent metal cations. Binding of Mg^{2+} to sites in cytoplasmic domains of either protein (red circles) closes the gate and prevents cation uptake at sufficient cytoplasmic concentrations (red dashed line with crosses). Similarly, the Zn^{2+} efflux gate (**right**) may be opened through binding of Zn^{2+} to sites Z2, Z3, and Z4 (green circles) in the cytoplasmic domain of YiiP (*1*). Thus, superfluous cytoplasmic Zn^{2+} concentrations may stimulate efflux (green dashed line ending with "+").

tems (*9*). Second, Zn^{2+} is taken up into most cells by highly specific Zn^{2+} uptake systems that are expressed under conditions of zinc starvation. However, other uptake systems (such as Mg^{2+} uptake systems) also transport Zn^{2+} nonspecifically. Because these nonspecific systems are regulated by their specific substrate, but not by Zn^{2+}, this may lead to superfluous zinc concentration in the cytoplasm, necessitating activated Zn^{2+} efflux.

These nonspecific uptake systems import a range of divalent metal cations until the concentration of the main substrate, such as Mg^{2+}, reaches the desired cytoplasmic concentration. Following that, the various efflux systems (for example, CDF proteins and P-type ATPases for Zn^{2+}) select and remove with high specificity all those cations that reach dangerous concentrations. Thus, the controlled flow of metal cations though a cellular compartment regulates not only the ambient concentration of one metal cation but also the composition of the complete set.

The YiiP structure far increases our understanding of CDF proteins and of zinc homeostasis, but many questions remain open. YiiP transports Zn^{2+} in vitro (*10*), but in vivo (*11*), its main substrate is Fe^{2+}. Thus, YiiP is the first model not only for a transition metal transporter but also for a bacterial Fe^{2+} efflux system. However, it is currently not known which metal cation binds to which site in vivo and what consequences these binding events have on stabilization of the structure, regulation, or transport.

Answers may come from an unexpected direction. The cytoplasmic domain of YiiP forms a metallochaperone-like structure (*1*), and interactions between metallochaperones and transport proteins are essential for cellular copper homeostasis mechanisms (*12*). No cytoplasmic zinc chaperone is known. Nevertheless, knowledge of the interaction between transport and binding processes may be the key to unraveling the mechanisms by which the cell controls zinc concentrations.

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DEVELOPMENTAL BIOLOGY

Home for the Precious Few

Live imaging reveals that branching of blood vessels in the mammalian testes may define the location of niches for germline stem cells.

Steve DiNardo and Robert E. Braun

Cells in multicellular organisms rarely escape the influence of other cell types. This is especially true for stem cells, which reside in tissue-specific niches, or homes. Niche cells regulate fundamental stem cell properties, including long-term survival, proliferation, and the balance between cell divisions that are self-renewing or differentiative. Simply identifying a niche can stimulate hypotheses about these properties. For instance, the identification of neural stem cells in a vascular niche (*1*) suggested correctly that co-culture of these stem cells with vascular endothelial cells could affect their potency (*2*). Similarly, in fruit fly gonads, identifying the germline stem cell niche led to the elucidation of locally acting self-renewal signals, and revealed how oriented cell divisions contribute to stem cell fate (*3*–*6*). On page 1722 in this issue, Yoshida *et al.* (*7*) take an exciting step toward identifying stem cell niches in the mammalian testis.

It was initially surmised that testis stem cells must exist because men make sperm for decades. Then, in rodent models, it was observed that spermatogenesis would naturally be reestablished after a severe toxic insult. Spermatogonial stem cells were eventually identified when a preparation of cells from a donor mouse testis was shown to repopulate spermatogenesis when transplanted into the testis of a sterile recipient animal (*8*). As with any tissue maintained by stem cells, only a small fraction of testis cells are spermatogonial stem cells. But where is home for these precious, few cells?

In mice, putative spermatogonial stem cells were initially identified histologically, as type A single (A_s), undifferentiated cells. A_s cells gen-

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