Chetty *et al.* went on to provide evidence that economic connectedness might underlie and explain many social phenomena. For instance, a landmark 1997 study showed that Black people living in predominantly Black neighbourhoods have poorer educational and economic outcomes than do those living in neighbourhoods with low proportions of Black people[7]. Chetty and colleagues demonstrated that this relationship can be largely accounted for (in a statistical sense) by the presence or absence of economic connectedness to higher-income individuals. They also show that, across counties, economic connectedness is much more highly correlated with economic mobility than are median incomes, racial segregation or income inequality.

In the second of the papers (page 122), the authors consider the factors that foster connections between people with high and people with low SES. Many policy efforts focus on integrating people of different SES through increased exposure; for example, by bussing children from different neighbourhoods to the same school. The researchers found that half the difference in the rate at which high-SES individuals befriended low-SES individuals could be attributed to differences in exposure to economically diverse peers. The other half was due to differences in 'friending bias' — the likelihood that a person will interact with a high-SES individual, given the opportunity.

That both these factors play an equal part is surprising, given how much attention is focused on exposure policies rather than on those aimed at reducing friending bias. Chetty and colleagues' analysis suggests that both types of policy should be addressed. Moreover, the authors show that increasing the level to which high- and low-SES students are exposed to each other in schools increases economic connectedness only in schools in which friending bias is low. In future, policymakers could use data from the current studies to maximize the effectiveness of their interventions. For example, if bussing is used as an exposure policy, it is most likely to result in economic connectedness in schools in which friending bias is low. In schools where this bias is high, policy should focus on fostering interactions — for example, through smaller classes or curriculum reform.

In addition to Chetty and colleagues' analyses, anonymized and aggregated subsets of the data have been publicly released (www.socialcapital.org). In particular, the data release includes privacy-protected measures of social capital for most zip codes, counties, colleges and secondary schools in the United States. This is an important contribution to research that will enable a deeper understanding of social capital. The resource will also help policymakers to target particular zip codes or counties with policies and interventions that enhance social capital, and to monitor their effects.

Much of the work on social capital up to now has centred on establishing its relevance, rather than on identifying approaches to create it[2]. Chetty *et al.* have taken steps to do both, by building a large-scale database, exploring links to long-term outcomes and investigating the effects of policies on fostering social capital. In the past two years, a wave of experimental work has also begun to explore approaches to fostering social capital[8–10] — an exciting direction for further research.

A sensible next step is to extend Chetty and colleagues' monumental data creation and analysis to countries beyond the United States. With global data, questions can be explored such as whether economic connectedness is more or less crucial to mobility in more-equal societies. Moreover, time-series data would be valuable for tracking the formation or depreciation of social capital and economic connectedness over time. And data similar to those collected by Chetty *et al.* could be used to explore how specific changes to the availability of high-income peers (such as school-integration orders, housing-mobility programmes or natural disasters) alter friendship networks and ultimately economic outcomes. These types of analysis are natural extensions of the road map laid out by Chetty and colleagues.

Finally, the current studies highlight the value of collecting large-scale data on social capital. Although some forms of capital, such as gross domestic product, are now routinely collected by governments and reported annually, measurement of other forms of capital — such as human[11] and social capital — is still much too infrequent. As Chetty and colleagues' work makes clear, it is worth making the same effort for social capital.

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Biochemistry

Escort proteins for cellular zinc ions

Wolfgang Maret

A metallochaperone protein that ensures that zinc ions are delivered to a crucial cellular enzyme has now been discovered. The finding underscores the subtleties of controlling cellular zinc allocation when the metal is scarce.

Metal ions such as zinc are essential for proper cell function. At least 10% of human proteins contain zinc as a cofactor[1], and zinc(II) ions need to be correctly allocated to these proteins to prevent mismetallation of other proteins. However, the identity of proteins that could allocate zinc ions to the appropriate targets has been a mystery. Two groups — one writing in *Cell*[2] and the other in *Cell Reports*[3] — now identify one such protein.

Zinc is ingested as a key micronutrient in human diets. Given that about 20% of people globally are at risk of not receiving enough zinc[4], a key question in the field of metallobiology has been how zinc ions are allocated when the micronutrient is scarce. Are the proteins that most need zinc ions served first — and, if so, do zinc-chaperone molecules exist for the purpose of prioritizing these proteins? Levels of copper(I) ions are generally low in cells, and metallochaperones have been shown[5] to acquire enough copper ions to

safeguard them for transfer to client proteins. But although this process is feasible for a limited number of copper proteins, the large number of zinc proteins makes it unlikely that zinc ions could be transferred to all of these proteins in the same way.

Yet, in the current investigations, Weiss *et al.*[2] and Pasquini *et al.*[3] identify COG0253 proteins as putative zinc chaperones. These evolutionarily conserved proteins make up a poorly understood subset of a broader enzyme family known as P-loop G3E GTPases, which use energy generated by hydrolysis of the molecule GTP for the transfer of metal ions (including iron, cobalt and nickel)[6]. Some evidence has indicated that expression of the genes encoding the COG0253 proteins is induced when zinc is limited[7] – could they therefore be the missing zinc metallochaperones?

The two groups searched for evolutionarily conserved proteins that could interact physically with COG0253 – Weiss *et al.* using the human, mouse and zebrafish versions of the protein, and Pasquini *et al.* the human and yeast proteins. Both sets of screens identified the enzyme methionine aminopeptidase 1 (METAP1; known as Map1 in yeast) as the only interacting enzyme found in all species. METAP1 uses two metal ions to catalyse the removal of a methionine amino-acid residue from the amino terminus of proteins, thereby affecting the proteins' turnover and other functions[8]. The groups showed that these metal ions can be zinc.

Weiss and colleagues examined the interaction between COG0253 and METAP1 in vertebrates in more detail. They found that recognition between the two proteins involves a specific amino-acid sequence (dubbed CPELVPI) on COG0253, and a 'zinc-finger' domain in METAP1 that already contains two zinc ions (Fig. 1). Both groups showed that, once the proteins associate, COG0253 catalyses GTP hydrolysis; this generates the energy to power a conformational change that is thought to enable zinc transfer from COG0253 to METAP1, activating the latter. The groups therefore renamed COG0253 as Zn-regulated GTPase metalloprotein activator 1 (ZNG1).

They went on to show (Weiss *et al.* in mice and zebrafish, Pasquini *et al.* in yeast) that genetic deletion of the *Zng1* gene exacerbates the growth defects caused by zinc deficiency. Thus, ZNG1 maintains the function of METAP1 in low-zinc conditions. By contrast, Pasquini *et al.* report that, when zinc ions are replete, they can reach their destination in METAP1 without the assistance of ZNG1 (expression of which is repressed when zinc levels are high[7]).

Together, the studies suggest a hierarchy in zinc-ion distribution, with a metallochaperone acting as a safeguard to ensure that METAP1 receives the zinc it needs to perform its crucial role as a 'checkpoint' protein that regulates

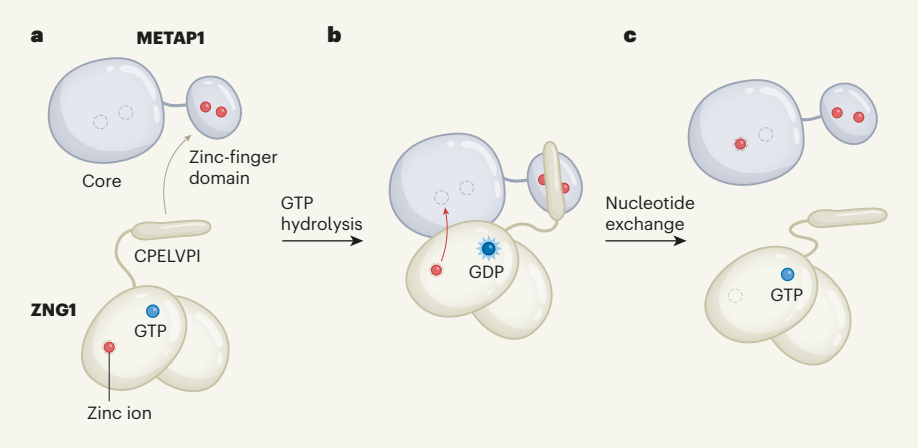

Figure 1 | A chaperone for zinc ions. Two groups[2,3] report that, when levels of zinc(II) ions in the body are low, they are preferentially allocated to the enzyme methionine aminopeptidase 1 (METAP1), through an interaction with the chaperone protein ZNG1. **a**, METAP1 has a zinc-finger domain, with two zinc ions that can interact with a specific amino-acid sequence in ZNG1 (CPELVPI), and a core that can receive metal ions. ZNG1 carries a zinc ion and a molecule of the nucleotide GTP. **b**, Binding between the two proteins triggers hydrolysis of GTP to GDP. This reaction is thought to provide the energy for a conformational change in ZNG1 that drives transfer of its zinc ion to the core of METAP1. **c**, The proteins undock as nucleotide exchange replaces GDP with GTP once more. METAP1 – activated by the zinc ion – can be released to perform crucial cell functions. (Adapted from Fig. 4G of ref. 2.)

proper cell division[9]. Indeed, Weiss *et al.* showed that deleting *Zng1* has the same effects as inhibiting METAP1 in mouse cells; namely, reduced proliferation and functioning of mitochondria, the cellular organelles that serve as power stations. Pasquini and colleagues, by contrast, focused on analysing the changes of proteins in *Zng1*-deficient yeast, and found that the abundance of proteins in the ribosome, the cell's protein-producing factory, is affected.

The discoveries mark an important step forward in our understanding of how some proteins – probably a limited number of zinc-requiring enzymes – receive their zinc ions. Chaperone-mediated zinc-ion transfer

"The zinc-chaperone protein could be useful as a direly needed biomarker for cellular zinc deficiency."

now becomes the third known mechanism for allocating zinc ions. The first depends on a pool of available zinc ions, and the second on metallothionein proteins. These proteins serve as zinc buffers; they can also transfer zinc ions or copper ions directly to client proteins *in vitro* in the same way as do copper metallochaperones, but without using energy from GTP hydrolysis[10].

Both groups are candid in discussing the limitations of their work. As they highlight, many aspects of ZNG1 biology remain to be explored. For instance, is zinc indeed the metal accepted by METAP1 under zinc deficiency? Some methionine aminopeptidases, including the yeast enzyme, can use cobalt, and Pasquini *et al.* demonstrate that yeast ZNG1 can transfer cobalt as well as zinc. The promiscuity in metal usage is also evident from the fact that the 3D crystal structure of human METAP1 was determined with cobalt rather than zinc[8]. Details of the mechanisms by which ZNG1 acquires, binds to and transfers zinc ions are yet to be elucidated. Five versions of the ZNG1 protein exist in humans – do they target different proteins and, if so, how do recognition codes vary? Finally, the exact roles of ZNG1 and its interaction with METAP1 in ribosome function remain to be investigated.

The discovery of a zinc-dependent process crucial for growth under zinc limitation has implications in a range of fields. For example, it indicates that ZNG1 could be useful as a direly needed biomarker for cellular zinc deficiency. In addition, it provides roads for investigating the effects of targeting ZNG1, METAP1 and zinc in proliferative diseases such as cancer.

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