that accumulate at a given energy and that are highly confined at the surfaces of these materials.

Surface phonon–polariton resonances give rise to enhanced near-field thermal radiation at almost a single wavelength[8], which greatly increases near-field heat transfer. Using a photodiode with a narrow bandgap that matches the energy of a resonance could lead to optical cooling that has extremely high efficiency. Such cooling would be faster than that of conventional coolers, with the advantage that the two objects would not need to be in contact with each other[4].

The authors' technique could also be improved using infrared plasmonic nanoantennas — devices that produce thermal radiation at well-defined frequencies and with electromagnetic energy that is highly concentrated in a region of space that is much smaller than the thermal wavelength[9]. Work published last year showed that such devices could be implemented in micrometre-sized, semiconductor-based infrared light detectors that can be operated at room temperature[10]. This suggests that, with some modification, Zhu and colleagues' set-up could be reduced in size and fabricated into semiconductor devices to carry out on-chip cooling of electronics. ■

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METABOLISM

Signalling a brake on heart disease

If blood flow from the heart is impeded, the pressure created causes tissue dysfunction. It emerges that different signals converge on the TSC2 and mTOR proteins to fine-tune the response of heart cells to stress. SEE LETTER P.264

BRENDAN D. MANNING

Chronic tissue stress causes the emission of molecular signals that propagate through cellular lines of communication known as signal-transduction pathways. These pathways trigger responses that can either exacerbate tissue damage or alleviate the harmful effects of the stress. Conditions that hinder the outflow of blood from the heart, such as high blood pressure (hypertension), can induce a type of chronic stress known as pressure overload. This can, in turn, cause abnormal overgrowth of the heart muscle (cardiac hypertrophy), which can precede heart failure (Fig. 1a). Ranek *et al.*[1] report on page 264 that, in heart muscle cells (cardiomyocytes) of mice, pressure overload activates two signal-transduction pathways, one involving an enzyme complex known as mTORC1, and the other involving the enzyme PKG1. The authors show that the two pathways converge to influence the adverse consequences of this stress.

The mTORC1 pathway operates in all cells, detecting changes in their local environment and controlling cell and tissue growth accordingly[2]. On activation, mTORC1 promotes protein synthesis and the formation of cellular components, while suppressing autophagy, a process in which cellular constituents are broken down and recycled[3]. Genetic and dietary factors can lead to chronic mTORC1 signalling in various tissues, a feature shared by diverse disease states, including cancer, obesity and immunological and neurological disorders[2]. Studies in mice show that abnormal loss or gain of mTORC1 signalling can both result in cardiac dysfunction[4–6], underscoring the importance of precise regulation of this pathway in the heart.

Ranek *et al.* found that mTORC1 is chronically activated in the hearts of mice subjected to sustained pressure overload, and that treatment with everolimus, a pharmacological inhibitor of mTORC1, can prevent the development of cardiac hypertrophy and dysfunction resulting from this stress. Interestingly, the authors observed that the drug sildenafil (Viagra), which strongly activates the PKG1 pathway, also blocks the development of cardiac hypertrophy resulting from pressure overload. Ranek *et al.* went on to identify a previously unknown mechanism whereby PKG1 inhibits mTORC1 signalling.

The protein TSC2 is a key regulator of mTORC1 activity in all tissues. TSC2 forms a complex with another protein, TSC1, to

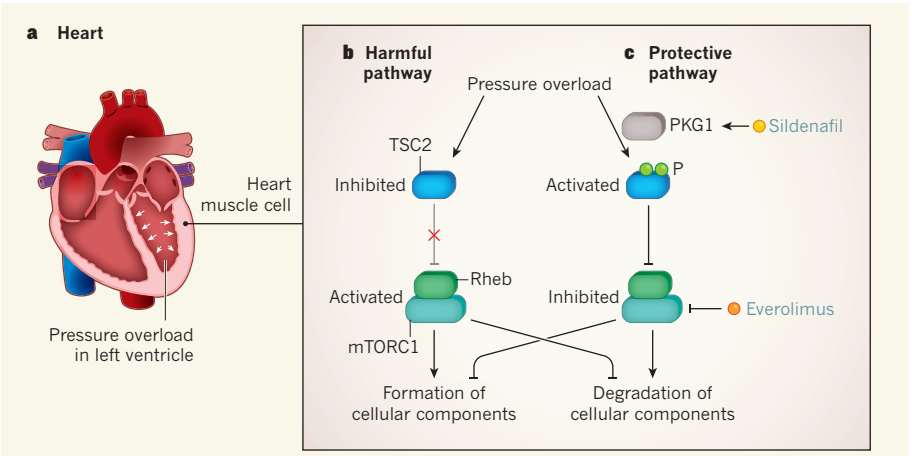

Figure 1 | A key regulatory pathway in the response of heart cells to pressure overload. **a**, Hampered outflow of blood from one of the heart's chambers (left ventricle pictured as an example) leads to sustained pressure on the heart muscle, an effect called pressure overload. **b**, Heart muscle cells sense pressure overload through molecular signalling pathways that regulate the TSC2 protein. Sustained pressure overload inhibits TSC2 (possibly through phosphorylation), preventing the protein from inhibiting the Rheb–mTORC1 protein complex. Chronic mTORC1 activation stimulates the synthesis and inhibits the degradation of cellular components, leading to abnormal tissue growth and heart disease. Ranek *et al.*[1] find that pressure overload also modestly activates the PKG1 protein, which phosphorylates (P indicates a phosphate group) and activates TSC2. This activation attenuates Rheb–mTORC1 signalling and mitigates the harmful effects of stress. Sildenafil strongly activates PKG1, blocking mTORC1 activation and protecting the heart. The mTORC1 inhibitor everolimus also protects the heart by inhibiting the Rheb–mTORC1 complex.

inhibit the protein Rheb, the direct activator of mTORC1 (ref. 7). Growth-promoting signals inhibit TSC2, thereby blocking its inhibition of Rheb and activating mTORC1 (Fig. 1b). Conversely, growth-inhibitory signals promote the TSC2-mediated inhibition of Rheb and mTORC1. Individual signals influence TSC2 through distinct protein kinase enzymes, which phosphorylate specific serine or threonine amino-acid residues to modify the protein's function. Ranek and colleagues found that PKG1 phosphorylates serine residues at positions 1,364 and 1,365 in the human TSC2 protein (Fig. 1c). They further show that the phosphorylation of these two residues by PKG1 enhances the ability of TSC2 to inhibit Rheb and mTORC1, and is responsible for the sildenafil-induced inhibition of mTORC1 signalling seen in the hearts and isolated cardiomyocytes of mice.

Ranek and colleagues investigated how PKG1-mediated phosphorylation of TSC2 modulates the heart's response to pressure overload using two types of genetically modified mice. One type expressed a version of TSC2 in which the serine residue at position 1,365 had been changed to an alanine residue (dubbed the S1365A mutation), which cannot be phosphorylated. The other model expressed a version of TSC2 in which the serine residue at the same position had been changed to a glutamate residue (S1365E), a modification that mimics stable phosphorylation. Mice with the S1365A mutation had enhanced mTORC1 signalling in the heart and dramatically worsened cardiac hypertrophy and dysfunction in response to pressure overload, compared with wild-type mice. Furthermore, they were no longer protected by sildenafil treatment. By contrast, pressure overload did not activate the mTORC1 pathway in the hearts of mice with the S1365E mutation, which were protected from the harmful consequences of this stress.

Curiously, pressure overload had a dual effect. In addition to activating mTORC1 in the heart muscle and causing cardiac dysfunction, it triggered a modest increase in PKG1-mediated phosphorylation of TSC2, which attenuated mTORC1 activity and mitigated the effects of the stress. Increasing PKG1 activity using sildenafil further enhanced TSC2 phosphorylation and mTORC1 suppression, resulting in complete protection from cardiac hypertrophy induced by pressure overload (Fig. 1c).

Several points of clinical relevance arise from these findings. The yet unidentified mTORC1-activating signal that is triggered by pressure overload could be a potential therapeutic target. This signal probably leads to the phosphorylation of other amino-acid residues of TSC2, inhibiting the protein and consequently activating mTORC1 (Fig. 1b). A strong candidate is the peptide hormone endothelin-1, whose levels increase in humans with hypertension and which can induce cardiac hypertrophy in rodent models of the condition[8]. Endothelin-1 can stimulate mTORC1 activity in isolated cardiomyocytes[9], and Ranek *et al.* found that this effect could be blocked by PKG1-mediated phosphorylation of TSC2. Future work should also define the cellular processes downstream of mTORC1 that contribute to the development of cardiac hypertrophy. The findings of the current study suggest that chronic inhibition of autophagy and a failure to properly clear protein aggregates might be involved.

Given that chronic mTORC1 signalling is associated with a variety of disease states, the possibility that PKG1 activators would be useful in suppressing mTORC1 signalling in the heart or other affected tissues should be investigated. Could PKG1 activators, such as sildenafil, be more effective and safer than direct inhibitors of mTORC1, such as rapamycin and everolimus, in alleviating the harmful effects of uncontrolled mTORC1 signalling in specific tissues? The current study shows that TSC2 phosphorylation leading to mTORC1 inhibition is both necessary and sufficient for the protective effects of PKG1 activation in a setting of cardiac hypertrophy caused by pressure overload. However, other signals downstream of PKG1 are also likely to contribute to the protective effects of this pathway's activation[10]. This provides some rationale for the use of PKG1 activators, rather than mTOR inhibitors, for this condition. ■

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CANCER

One rogue agent suffices for genomic chaos

Genetic instability is a hallmark of cancer cells, and occurs when genes required for genomic maintenance are inactivated. It emerges that altering just one of the two copies of certain genes can drive genetic instability in yeast. SEE LETTER P.275

KATHERINE E. LARRIMORE & GIULIA RANCATI

Cancer is a disease of uncontrolled cell division that is fuelled by genetic instability — a state in which cells acquire mutations at an abnormally high rate. When normal cells are transforming into cancer cells, a common early event is the acquisition of mutations in a type of gene called a tumour-suppressor gene. If both of the two copies of a tumour-suppressor gene are inactivated in a cell, this decreases genomic stability and aids the acquisition of other cancer-initiating mutations. On page 275, Coelho *et al.*[1] report their studies in budding yeast (*Saccharomyces cerevisiae*), which indicate that, frequently, the disruption of just one copy of certain genes can be sufficient to trigger genetic instability.

The existence of tumour-suppressor genes was first proposed about 50 years ago to explain why, in some families, there is a puzzling pattern of inheritance of a type of cancer called retinoblastoma[2,3]. Clinical observations suggested that this cancer is caused by a type of mutation, known as a recessive mutation, in the gene *RB*. Such a mutation has an effect only if both copies of the gene are mutated in a cell. The 'two-hit' hypothesis was proposed[2] to explain the inheritance patterns of retinoblastoma. It suggested that if a cell inherits a recessive mutation in one copy of *RB*, it must also acquire a mutation in its other copy for cancer to develop. Subsequent research in mice[4] revealed that, although a two-hit scenario is common, the presence of a mutation in only one of the two copies of some tumour-suppressor genes (a condition termed haploinsufficiency) can suffice to trigger cancer formation.

Many other tumour-suppressor genes have been identified as being haploinsufficient in mice[5]. Moreover, a mutation in one copy of the *BRCA1* gene, which is associated with breast cancer, can cause genetic instability in the epithelial cells of human breast tissue grown *in vitro*[6], suggesting that haploinsufficiency of tumour-suppressor genes can kick-start cancer formation in human cells. But determining