Growth Signaling from Inside
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Science **334**, 611 (2011);
DOI: 10.1126/science.1214355

between single-layer graphene and bilayer graphene (*5*), where the two mechanisms would result in opposite signs of the photovoltage, and the one corresponding to the thermoelectric mechanism was observed. In the doubly gated monolayer graphene of Gabor *et al*., for the field-induced carrier separation the sign of the photovoltage would be simply determined by which of the two regions has the higher electronic density. In contrast, the thermoelectric mechanism would result in a peculiar six-fold photovoltage pattern (*6*), as was observed by Gabor *et al*.

The efficient design of an optoelectronic device requires an understanding of the main mechanism of the photovoltage generation in that device. Identification of the photothermoelectric effect as such a mechanism for graphene (*1*, *5*), together with the demonstration of external control (*1*), thus provides an opportunity to develop graphene-based optoelectronic devices.

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10.1126/science.1214560

CELL BIOLOGY

Growth Signaling from Inside

Sensing of amino acids inside lysosomes by a proton pump initiates a chain of events that stimulates cell growth.

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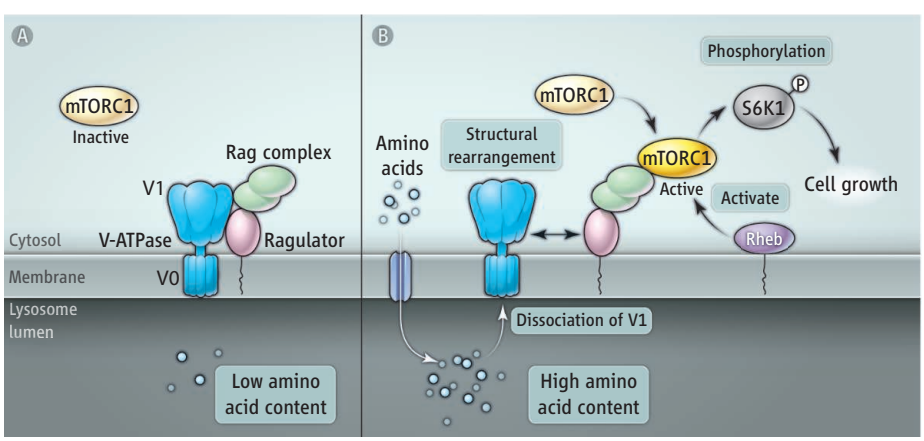
All cells have the ability to sense whether nutrients are scarce or abundant so that appropriate anabolic or catabolic programs can be initiated. A key sensor of nutrient status in eukaryotes is target of rapamycin (TOR) (*1*), an enzyme that phosphorylates a subset of proteins that function in cell growth and metabolism (*2*). In mammalian cells, TOR associates with accessory proteins to form mammalian TOR complex 1 (mTORC1) (*3*). Amino acids are potent activators of mTORC1 (*4*, *5*), but it has not been clear how mTORC1 senses amino acids within the cell. On page 678 of this issue, Zoncu *et al.* (*6*) describe how sensing amino acids occurs inside the lumen of lysosomes, the main degradative organelles in the cell.

Lysosomes are characterized by their acidity and content of degradative enzymes (*7*). Earlier work indicated that physical contact between mTORC1 and its activator, Rheb (*8*), at the lysosome determines whether amino acids can activate mTORC1 (*9*). Zoncu *et al*. therefore reasoned that lysosomes must play an important role in the amino acid–mediated activation of mTORC1. By using cultured cells from fruit flies and reducing the expression of genes with known roles in lysosomal biogenesis or functions, the authors found that vacuolar H^+–adenosine triphosphatase (v-ATPase), which pumps protons into lysosomes, is essential for TOR activation in response to amino acids. These observations were confirmed in cultured human cells by either chemical inhibition of the v-ATPase or reduced expression of the pump.

Earlier work revealed that amino acid–mediated activation of mTORC1 depends on the correct nucleotide loading of a heterodimeric guanosine triphosphatase (GTPase) complex of the Rag family (RagA/B and RagC/D) (*10*, *11*), which localizes to the lysosome by interaction with a Rag regulator (Ragulator) complex (*9*). Upon correct nucleotide loading and activation, the Rag complex can pull the cytosolic mTORC1 component Raptor from the cytosol to the lysosome membrane (see the figure). Rheb is localized exclusively to intracellular membranes and is therefore physically separated from cytosolic mTORC1 in the absence of amino acids. Zoncu *et al.* show that mTORC1 fails to accumulate at lysosomes after amino acid stimulation in the absence of an active v-ATPase, which suggests that the pump is part of the amino acid–driven sensory mechanism that targets mTORC1 to the lysosome in proximity to Rheb.

The v-ATPase is a multisubunit proton pump composed of one unit responsible for ATP hydrolysis (V1 sector) and one membrane domain that rotates upon ATP hydrolysis (V0) allowing protons to enter the lysosomal lumen and thereby acidify it. Semiquantitative mass spectrometry analyses and precipitation assays using recombinant proteins led to the hypothesis that Ragulator functions as a bridge linking the v-ATPase and the Rag GTPases together at the lysosome. Zoncu *et al.* further noted that amino acid stimulation and starvation reduces and strengthens, respectively, the interaction between Ragulator and the V1 but not the V0 sector. This suggests that amino acids control the interaction between Ragulator and the v-ATPase.



Amino acid sensing. (**A**) At low amino acid concentrations within the lysosome, Ragulator interacts with the v-ATPase and nucleotide loading of the Rag complex is incompatible with mTORC1 recruitment. (**B**) When amino acids are abundant, v-ATPase undergoes a structural rearrangement that alters the interaction surface between the v-ATPase and Ragulator. This changes the nucleotide loading of the Rag complex and results in recruitment of mTORC1. Rheb (in the lysosome membrane) activates mTORC1, which then phosphorylates growth-promoting targets such as S6 kinase 1.

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To further tease apart the function of the v-ATPase in amino acid signaling to mTORC1, Zoncu *et al.* used a cell-free system to reconstruct the amino acid–mediated binding of mTORC1 to Rag GTPases at lysosomes. Pure lysosomal fractions that were stimulated with amino acids could recruit purified Raptor, indicating that cytosol is dispensible for recruitment of Raptor to the lysosomal Rags. This suggests that amino acids do not act on the cytoplasmic face but function from the lysosomal lumen to alter v-ATPase structure. This reduces the pump's association with Ragulator, leading to activation of Rag GTPases and recruitment of Raptor (mTORC1). Moreover, permeabilization of the lysosomal fraction, which kept the v-ATPase interactions intact but allowed leakage of amino acids out of the organelle, abolished the amino acid–driven recruitment of Raptor. This supports the idea that lysosomes contain all the components necessary to sense amino acids and activate mTORC1.

The study of Zoncu *et al.* suggests that amino acids signal their presence from within the lysosome and translate this presence through a domino effect that activates the Rag GTPase complex to mediate proximity between mTORC1 and Rheb at this compartment. It is still not clear how amino acids in the lysosome lumen can cause structural alterations of v-ATPase and how this translates into nucleotide loading and activation of the Rag complex. In this respect, it is noteworthy that although v-ATPase is required for mTORC1 activation, its strong interaction with Ragulator during amino acid suppression suggests an inhibitory role toward the Rag complex as well (*6*). One scenario is that the altered affinity between Ragulator and the v-ATPase upon amino acid sensing may alter the conformation of Rags in a way that allows nucleotide loading. Future experiments might reveal whether the v-ATPase indeed functions directly in nucleotide loading or if this requires yet unidentified factors.

The central role of mTORC1 as a coordinator of nutrient responses is accompanied by a great interest in targeting mTORC1 pharmacologically. mTORC1 inhibitors are already in clinical use to treat certain cancers (*12*), and the fact that TOR inhibition can prevent neurodegeneration and increase the life span of model organisms has raised the possibility of using mTORC1 inhibitors as anti-aging drugs in humans (*13*–*15*). Advance in our understanding of how mTORC1 is activated is good news because it offers new strategies for therapeutic interventions of cancer, neurodegeneration, and aging.

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10.1126/science.1214355

ATMOSPHERIC SCIENCE

Ocean Effects of Blocking

Short-term weather events may drive ocean variability on time scales of several decades.

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Variations in the circulations of the Atlantic Ocean and the atmosphere above it influence societies far beyond the ocean basin itself. Scientists have long tried to understand and predict the dramatic year-to-year variability of the North Atlantic Oscillation (NAO) (*1*), but modeling the associated ocean-atmosphere interaction remains a challenge (*2*). Attention has turned to longer-term warming and cooling episodes of the North Atlantic Ocean. These variations—often referred to as Atlantic multidecadal variability (AMV)—are widely assumed to arise from variability in the ocean's overturning circulation (*3*), in which warm water flows northward near the ocean surface and returns southward at depth. In contrast, Häkkinen *et al*. argue on page 655 of this issue (*4*) that the AMV owes its existence to atmospheric events with time scales as short as a week.

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Central to the new work is the concept of blocking, in which the usual prevailing westerly winds (see the figure, panel A) are obstructed by a large-scale, stationary system, usually an anticyclone (panel B); rain-bearing cyclones are thereby diverted from their usual path, and regional impacts in temperature and precipitation can be severe, as in the Russian heat wave of 2010 (*5*). Blocking is a reversal of the usual pattern of cyclonic rotation of air masses north of the Atlantic jet and anticyclonic rotation to the south. Häkkinen *et al*. now propose that this reversal leads to a temporary change in the wind forcing that maintains the ocean's subpolar and subtropical gyre circulations. As a result of the changed wind forcing, the subpolar gyre contracts, opening up a pathway for warm saline water from the subtropics to move to higher latitudes. This has a direct effect on the temperature of the subpolar gyre and may also lead to changes in the overturning circulation.

Previous studies have focused on fixed spatial patterns of atmospheric variability, in particular, the seesaw in pressure between Iceland and the Azores known as the NAO. In contrast, Häkkinen *et al*. suggest that the gyre circulations can be forced by blocks occurring anywhere over the Atlantic, provided that the anticyclonic winds fall within the boundary of the subpolar gyre. Blocks over different parts of the Atlantic may then have the same effect on AMV, despite having very different relations to the atmospheric jets and patterns such as the NAO (*6*).

By focusing on relatively fast, intraseasonal atmospheric events, this theory mirrors a recent focus on these time scales in understanding low-frequency atmospheric variability such as the NAO itself. In this view, the interannual variations of the NAO are governed by the dynamics of short-term weather events such as blocking (*7*), although this issue is still disputed (*8*).

Häkkinen *et al*. suggest that the frequency of Atlantic blocking varies from decade to decade with the AMV. They focus on the role of blocking in driving AMV, but perhaps the biggest open questions are why blocking