performed on a single state. Only if all the questions used in a code are compatible with each other can the classical code be converted into a quantum code. Because of this constraint, attempts to date to make good LDPC-based quantum codes have failed.

Brun *et al.* show that the compatibility requirement can be circumvented if the sender and receiver share a particular type of quantum state (called an "entangled state") before transmission (see the figure). Entanglement is a purely quantum-mechanical phenomenon allowing, among other things, stronger correlations between a pair of distant quantum systems than would be possible were they purely classical. The prior connection between sender and receiver allows them to cancel any incompatibility in the encoding with an equal incompatibility in the decoding (a case where two wrongs do make a right), meaning that many more classical error-correcting codes, including some of the most efficient, can be converted to quantum codes. The original entangled state must be free of noise, but a successful transmission regenerates it, allowing further communication at no additional cost in entanglement.

This result is a great boon for a sender and receiver who wish to communicate on a regular basis, because they can generate entanglement once and then use it repeatedly for efficient quantum transmissions. It is less useful for a one-time connection or for storage of quantum information over time, but even there, a less efficient code could be used to generate the first collection of entanglement, followed by multiple iterations of the scheme of Brun *et al.* LDPC codes have also attracted interest as candidates to improve fault-tolerant quantum computation, but further work will be necessary to see if the ideas of Brun *et al.* can deliver the desired advances.

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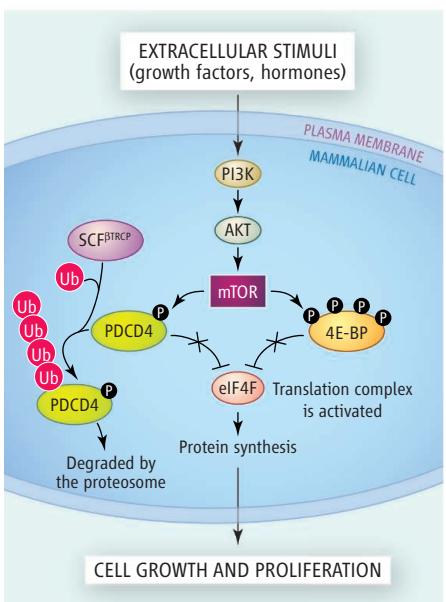
SIGNAL TRANSDUCTION

Protein Synthesis and Oncogenesis Meet Again

Nahum Sonenberg and Arnim Pause

A protein degradation process targets a factor that blocks protein synthesis and inhibits tumor growth. Enhanced degradation of this protein may provide a growth advantage to cancer cells.

The production of proteins is a prerequisite for cells to grow and proliferate (*1*). In response to mitogens, growth factors, and hormones, protein synthesis from messenger RNAs (mRNAs), frequently referred to as translation, is boosted. Many cellular signaling pathways that regulate translation factors have been elucidated. The most prominent pathway is one comprising phosphoinositide 3-kinase (PI3K) and two serine-threonine protein kinases, AKT and mammalian target of rapamycin (mTOR). The mTOR pathway transduces extracellular growth signals to the cell's translation machinery by the addition of phosphate molecules (*2*). Such phosphorylation directly controls the activity of the targets, including factors that initiate the translation process. On page 467 of this issue, Dorrello *et al.* (*3*) reveal a new signaling branch of the mTOR pathway that controls translation: the degradation of PDCD4 (programmed cell death protein 4). Not only is this factor phosphorylated by the mTOR pathway, but the modification marks it for destruction (see the figure). PDCD4 normally blocks translation and suppresses cell growth. Consequently, loss of PDC4 function is expected to result in a growth advantage to cells and ultimately lead to cancer.



Targeting protein synthesis. The eIF4F complex binds mRNA and promotes translation initiation in response to extracellular stimuli. The PI3K-AKT-mTOR signaling pathway targets two major translation inhibitors, PDCD4 and 4E-BP, for phosphorylation. This modification blocks their actions and allows protein synthesis to occur. This ultimately supports cell growth and proliferation. Phosphorylation of PDCD4 marks it for degradation. Ub, ubiquitin.

Control of translation occurs primarily at the initiation step, in which the 40*S* ribosomal subunit is recruited to mRNA and positioned at the initiation codon, the nucleotide sequence that specifies the first amino acid of the protein (*4*). The most general mechanism of translation initiation depends on the mRNA 5′ cap structure (m^7GpppN, where N is any nucleotide). The cap structure, present on all mRNAs synthesized in the cell's nucleus, is bound in the cytoplasm by a cap-binding protein complex called eIF4F (eukaryotic initiation factor 4F). eIF4F is composed of three subunits: eIF4E, the cap-binding subunit; eIF4A, an RNA helicase that unwinds the mRNA 5′ secondary structure; and eIF4G, a scaffolding protein that binds to other initiation factors.

Recognition of mRNA by eIF4F is a major target for translation regulation, and one of the best-studied mechanisms is the control of eIF4F assembly by a family of repressor proteins called 4E-BPs (4E-binding proteins). These proteins compete with eIF4G for binding to eIF4E and consequently inhibit cap-dependent translation (*5*). Importantly, the interaction of 4E-BPs with eIF4E is reduced as a consequence of phosphorylation on several serine and threonine residues of 4E-BP. The mTOR signaling pathway is the major contributor to 4E-BP phosphorylation (*6*). Thus, an important mechanism by which the mTOR

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pathway modulates cell growth and proliferation is through the control of translation initiation. mTOR phosphorylates directly several substrates, including 4E-BPs and S6 kinase. In turn, S6 kinase phosphorylates several substrates, including the ribosomal protein S6, SKAR, and eIF4B (*6*–*8*). Dorrello *et al.* identify PDCD4 as a new substrate for S6 kinase.

PDCD4 inhibits the RNA helicase activity of eIF4A, as well as its incorporation into the eIF4F complex (*9*). PDCD4 is overexpressed in cell cycle–arrested cells, and its expression is reduced in cancer cells. Reexpression of PDCD4 in cancer cells induces apoptosis and inhibits tumor growth. Dorrello *et al*. report that PDCD4 is rapidly degraded upon phosphorylation by S6 kinase, in response to activation of the mTOR pathway by growth factors. Degradation of PDCD4 is mediated by the E3 ubiquitin ligase complex $SCF^{\beta TRCP}$ (SKP1–CUL1–F-box), which tags its substrates with ubiquitin molecules for degradation by the cell's proteosome. In the absence of growth factors, PDCD4 remains phosphorylated, resulting in the inhibition of eIF4A, protein synthesis, and cell growth. Phosphorylated PDCD4 binds to $SCF^{\beta TRCP}$, becomes ubiquitinated, and is subsequently degraded by the proteosome. Thus, elimination of PDCD4 frees eIF4A to be incorporated into eIF4F for stimulation of cap-dependent translation initiation. It is intriguing that the mRNA-binding complex eIF4F is the target of two different translation inhibitors, 4E-BP and PDCD4, both of which are regulated by the mTOR pathway. The mTOR pathway has been strongly implicated in the etiology of many human cancers, thus linking cell growth, translation, and oncogenesis.

Dorrello *et al*. were searching for substrates for $SCF^{\beta TRCP}$, a multisubunit complex that contains an E2 ubiquitin-conjugating enzyme and substrate recognition subunits called F-box proteins (of which there are 68) (*10*). One of the F-box proteins is βTRCP. $SCF^{\beta TRCP}$ is constitutively active in the cell and selects substrates based on their phosphorylation, which enables binding to βTRCP. Dorrello *et al*. discovered new substrates for $SCF^{\beta TRCP}$ by using mass spectrometry to identify associated, ubiquitinated proteins. This method is very efficient because substrates of E3 ligases are of low abundance in the cell.

The study by Dorrello *et al*. represents the second example of control of translation initiation by the ubiquitin system. Recently, Yoshida *et al*. showed that the amount of Paip2, a translational repressor, is controlled by binding to the E3 ligase EDD (*11*). Paip2 binds to poly(A)-binding protein (PABP), a eukaryotic protein that binds to the 3′ poly(A) tail on mRNA to control translation. Interestingly, the binding of Paip2 to EDD is determined by the amounts of PABP in the cell, because PABP shares a common sequence with EDD. It will not be surprising if we find that translational control through ubiquitination is a widespread mechanism to regulate translation and, ultimately, cell growth.

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ASTRONOMY

Cosmic Rays Track the Rotation of the Milky Way

Energetic cosmic rays are coming from a particular region of the sky and rotating with our arm of the Milky Way. Such data may help us understand how our Galaxy interacts with the Sun's magnetic field.

Marc Duldig

Cosmic rays are extremely high-energy nuclei that travel close to the speed of light. They are ubiquitous in the Milky Way and make up a substantial fraction of the total energy of the Galaxy, equivalent to the energy in large-scale magnetic fields and thermal gases. Their composition largely reflects the natural abundance of the elements in the Galaxy, mostly protons (hydrogen nuclei), some alpha particles (helium), and a tiny fraction of the heavier elements. Being charged particles, they are deflected when crossing magnetic fields, but the amount of deflection is dependent on their momentum. The cosmic-ray flux at energies high enough to undergo minimal deflection is so small that sources have proved impossible to observe directly. On page 439 of this issue, however, Amenomori *et al.* (*1*) report the direct observation of an excess signal in cosmic rays coming from the Cygnus region of the sky using a detector array in Tibet. This excess could be either cosmic rays of very high energy or high-energy gamma rays that would likely be associated with cosmic-ray sources. Furthermore, they have also shown that the cosmic-ray gas at these very high energies is rotating with the local spiral arm of the Galaxy, confirming behavior previously only seen at lower energies with cosmic rays influenced by the Sun's extended magnetic field.

The difficulty in achieving such observations can be most readily understood when we look at the full cosmic-ray spectrum, as shown in the figure. The spectrum is approximately a power law, but there are features within it that mark probable changes in the sources. Below about 10^{15} eV, they are almost certainly produced in the shocks from supernovae, but at higher energies there is a steepening in spectrum and a change in the relative elemental abundances, indicating changing source mechanisms. There are further changes in composition at the "ankle," and the origin of particles at the highest energies observed is problematic.

At the lowest energies, the cosmic rays are plentiful but are heavily influenced by the solar magnetic field, which is carried beyond the planetary orbits [100 astronomical units (AU) or more, where 1 AU is the mean Earth-Sun distance, or about 1.5×10^8 km] by the gusty plasma wind that emerges from the Sun (the solar wind). This field is complex and dynamic, with shocks propagating from active regions on the Sun and an outer bound-

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