Tel2 Finally Tells One Story

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Science **320**, 60 (2008);
DOI: 10.1126/science.1155132

CELL SIGNALING

Tel2 Finally Tells One Story

The ability of a protein to interact with an entire family of phosphorylating enzymes explains its diverse functions across species.

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The recently published work by Takai *et al.* (*1*) on the protein TEL2 is reminiscent of the tale in which six blind men were each asked to describe an elephant by touching it. Each one touched a different part, and thus each provided a strikingly different description of what an elephant is like. One touched the elephant's broad and sturdy side and thought it felt like a wall. Another touched its tusk, which felt like a spear. A third touched its trunk, which felt like a snake. The fourth, fifth, and sixth men touched its knee, ear, and tail, which were mistaken for a tree, a fan, and a rope, respectively. The story illustrates the importance of getting the whole picture, which is what the new study provides about TEL2, whose many, seemingly unrelated functions have been puzzling.

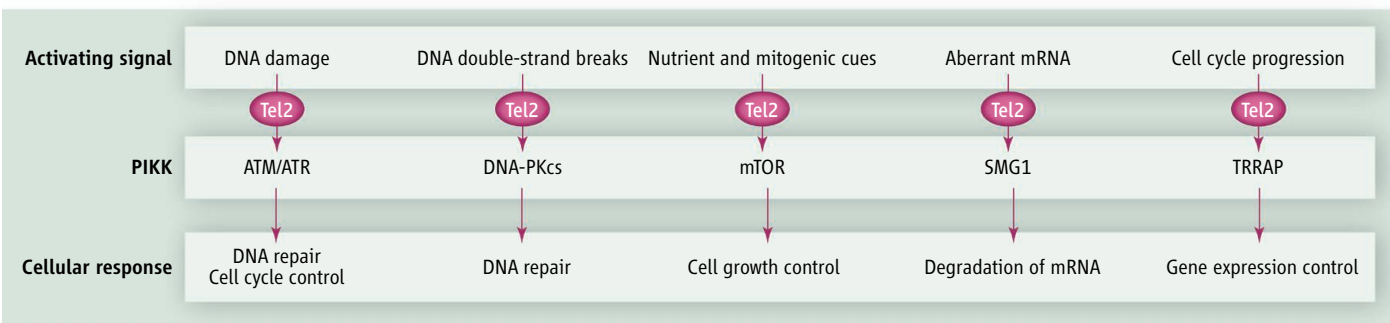
The Tel2 story begins in 1986, when Lustig and Petes discovered mutant strains of the budding yeast *Saccharomyces cerevisiae* that had abnormally short telomeres (*2*), the physical ends of eukaryotic chromosomes. They named the two identified strains *tel1* and *tel2*, whose mutated genes were cloned 10 years later (*3*, *4*). Much is now known about the yeast gene *TEL1*. It encodes an evolutionarily conserved enzyme that localizes to short telomeres, where it phosphorylates protein substrates and increases the activity of telomerase, the ribonucleoprotein complex that lengthens telomeres. Ataxia telangiectasia mutated (ATM), the human ortholog of Tel1, is well known for reacting to DNA double-stranded breaks by eliciting a DNA damage response.

By contrast, the functional role of Tel2 has been a more difficult puzzle to solve. Tel2 is a well-conserved protein that is essential for yeast viability. Determining the precise role of Tel2 has been complicated by its many apparently nonoverlapping functions reported in various organisms. In addition to maintaining telomere length in *S. cerevisiae*, it functions in the DNA replication checkpoint in the fission yeast *Schizosaccharomyces pombe* and in humans, coupling the onset of cell division with the successful replication of DNA (*5*–*7*). In the nematode *Caenorhabditis elegans*, however, hypomorphic alleles (forms of a gene in which the encoded protein has reduced function compared with the wild-type allele) of *clk-2/rad-5* (the *TEL2* ortholog in *C. elegans*) not only can cause stress during DNA replication and hypersensitivity to DNA double-strand breaks, but also can increase life span and reduce the rate of numerous physiological processes, including embryonic and postembryonic development, and reproduction (*8*–*10*).

The work by Takai *et al.* provides a unifying model for all the reported functions of mammalian Tel2 and its orthologs. Through a very careful and systematic analysis of the phenotype of *Tel2*-null mouse cells and biochemical protein interaction studies, the authors discovered that TEL2 directly interacts with all six of the mammalian phosphatidylinositol 3-kinase–related protein kinases (PIKKs). Absence of TEL2 substantially reduced the expression level of all PIKKs in mouse cells, impinging on their function (see the figure). Because a direct physical association between Tel2 and PIKKs was also recently observed in fission yeast (*11*), the function of Tel2 as a stabilizer of these kinases may also be conserved.

PIKKs are a family of enzymes with diverse functions. There are six PIKKs in mammals: ATM, ATM and Rad3 related (ATR), DNA-dependent protein kinase catalytic subunit (DNA-PKcs), mammalian target of rapamycin (mTOR), suppressor with morphological effect on genitalia 1 (SMG1), and transformation/transcription domain–associated protein (TRRAP). ATM is the human ortholog of *S. cerevisiae* Tel1, which explains the short telomeres seen in budding yeast *tel2* mutants in which Tel1 may be unstable. ATM and ATR are key regulators in the DNA damage response, accounting for the hypersensitivity to DNA damage and DNA replication checkpoint defects in humans, fission yeast, and *C. elegans tel2* mutants. mTOR has an essential role in cell growth by regulating the cellular response to changes in environmental cues, mitogenic signals, and nutrient availability, offering an explanation for the pleiotropic phenotypes seen in *clk-2/tel2* mutants in *C. elegans*.

However, much remains unknown about what exactly Tel2 is doing and how it is doing it. Note that the mechanisms by which Tel2 stabilizes PIKKs and the process through which PIKK degradation occurs in *Tel2*-deficient cells have yet to be elucidated. Inhibition of the proteasome did not affect PIKK degradation, and Takai and colleagues speculate that Tel2 may protect PIKKs from cleavage by a specific protease. Perhaps most intriguing is why Tel2 should impinge on so many apparently disconnected signaling pathways that respond to very different envi-



Diverse roles. The protein Tel2 interacts with phosphatidylinositol 3-kinase–related protein kinases (PIKKs) in mammalian cells, each of which functions in a different signaling pathway that responds to a specific cellular stress. How Tel2 function is coordinated among these pathways remains to be determined.

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Published by AAAS

ronmental cues. It seems unlikely that all PIKKs should be regulated by Tel2 in a coordinated fashion. A more attractive hypothesis is that the interaction of Tel2 with PIKKs is regulated individually, to provide a fast switch to turn signaling pathways on or off in response to changes in the environment. Of course, this opens up many questions about regulatory mechanisms, and the yeast and nematode model systems may be powerful tools to explore this area.

It also remains to be seen if Tel2 influences the enzymatic or cellular properties of PIKKs. Indeed, recent work by Anderson *et al.* (*12*) shows that the *tel2-1* mutant allele in *S. cerevisiae* not only causes a decrease in the amount of Tel1 protein (the yeast ortholog of mammalian ATM) expressed, but that Tel2 may also help Tel1 to associate with DNA double-strand breaks in this organism. Notwithstanding, by providing one model by which all the *tel2* phenotypes could potentially be satisfyingly explained, Takai and colleagues have given researchers a foundation for future hypotheses and experiments. They have allowed us to see the entire Tel2 elephant.

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13. M. C. is supported by a Human Frontier Science Program (HFSP) postdoctoral fellowship. Work in the laboratory is supported by grants from the Swiss Cancer League, the Swiss National Science Foundation, the HFSP Program, and the European Union 6th and 7th Framework Programmes.

10.1126/science.1155132

ASTRONOMY

Small-Scale Observations Tell a Cosmological Story

Graphite whiskers found in meteorites provide clues to the chemical environment in the early solar system.

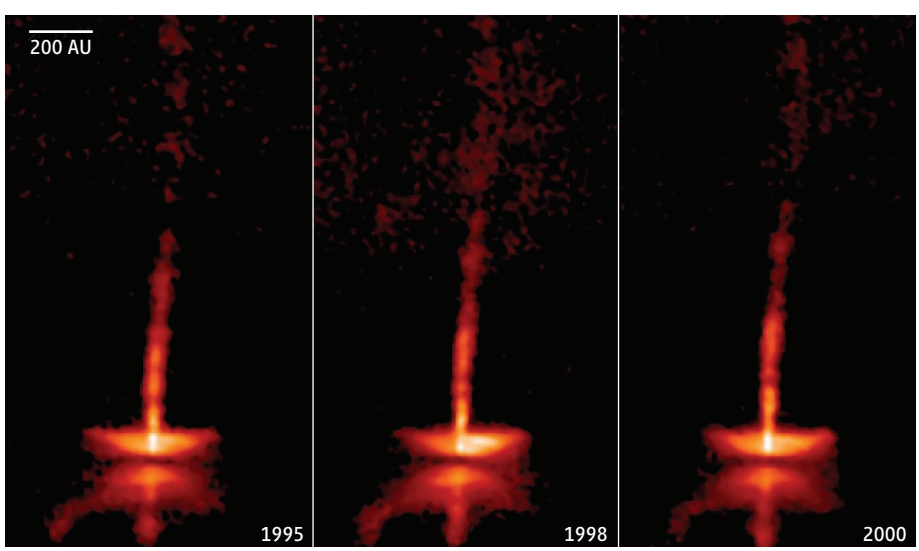
Philip A. Bland

Meteorites are the oldest rocks to which we have access, dating back 4567 million years (*1*), to an epoch before planets, when our solar system was nothing more than a disk of dust and gas. They contain a record of that earliest period of solar system history, including the variety of local stellar sources that contributed to our protoplanetary disk and the physical and chemical processes that occurred within it. On page 91 of this issue, Fries and Steele (*2*) report their discovery of graphite whiskers (GW) in meteorites. Their observation has importance for our understanding of the environment of the early solar system, and GWs may have broader astrophysical and cosmological implications as well.

The most primitive meteorites—with textures, mineralogy, and chemistry comparatively unmodified since their accretion—are known as carbonaceous chondrites. These rocks have a composition approaching that of the Sun (for elements other than the noble gases and H, C, N, and O) (*3*). They are also hugely heterogeneous, containing spherical igneous inclusions known as chondrules, which probably formed by localized heating events in the body of the disk (*4*), and occasional calcium-aluminium-rich inclusions (CAIs) that may have formed very close to the proto-Sun (*4*). All of this is bound together with a fine-grained "matrix" that is likely (at least in part) a remnant of the disk itself (*5*). The matrix contains presolar material: micrometer- and submicrometer-sized grains, formed in the atmospheres of other stars, which we can analyze in the lab (*6*).

Studies of carbonaceous chondrites are relevant to questions beyond the origins of our own solar system, complementing astronomical observations of protoplanetary disks and young stellar objects and (in the case of presolar grains) astrophysical models of stellar nucleosynthesis and the chemical and dynamic evolution of the Galaxy (*6*). Fries and Steele present a Raman imaging spectroscopy study of three carbonaceous chondrites in which they find a highly unusual carbon allotrope in the form of graphite whiskers, which have never before been observed in meteorites or cosmic dust.

Graphite whiskers are postulated to be a component of the interstellar (and intergalac-



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Growing whiskers. A protoplanetary disk showing bipolar outflows: A potential mechanism for launching graphite whiskers, condensing close to the young star, into interstellar space.

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