CELL BIOLOGY

2010: Signaling Breakthroughs of the Year

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Members of the Editorial Board nominated as signaling breakthroughs insights gained from the "mega"—large-scale systems analyses—and the "micro"—protein structures—along with new findings in metabolism and genetics. In addition, research studies that may lead to new therapeutic avenues for cancer, diabetes, and Alzheimer's disease were selected as breakthroughs, along with the identification of unexpected heterogeneity of innate immune cells.

The editors of *Science Signaling* are pleased to launch a new year of cell signaling research with our annual feature, *Signaling Breakthroughs of the Year*. To compile our list, we asked members of the *Science Signaling* Editorial Board to provide nominations for articles that represented the most exciting advances in signal transduction research of 2010. Although any major advance in cell signaling is fair game for inclusion, we suggested that nominators pay particular attention to unexpected developments and advances likely to open up new research directions. We winnowed down the list of nominated articles—every one of which represented a notable advance—to the final list presented here. These finalists include studies that employed large-scale analyses; new findings in metabolism and genetics; research pertinent to cancer, diabetes, and Alzheimer's disease; insights based on protein structure; and identification of the vast heterogeneity of mucosal-associated innate immune cells. We thank all of the scientists who provided nominations this year: Ivan Dikic (Goethe University Medical School, Germany), Henrik Dohlman (University of North Carolina Chapel Hill, USA), David Fruman (University of California, USA), Tony Hunter (Salk Institute, USA), Randall Moon (University of Washington, USA), Michele Pagano (New York University School of Medicine, USA), Norbert Perrimon (Harvard Medical School, USA), Solomon Snyder (Johns Hopkins University, USA), Eric Vivier (Centre d'Immunologie de Marseille-Luminy, France), and John Walker (University of Missouri, USA).

Cell signaling has traditionally been described in terms of signaling "pathways," in which an extracellular or intracellular stimulus sets into play a series of molecular events that lead to a predictable response, or set of responses. Researchers have long known, of course, that this represents an oversimplified view of the intricately choreographed molecular dance that takes place inside each of our cells. The importance of looking beyond linear signaling pathways to networks of molecular interactions emerged as one theme in last year's *Signaling Breakthroughs of the Year*. This year's nominations continued that trend, with research involving large-scale screens that enable such network-level analyses garnering nominations from six scientists. Some of these nominations emphasized the new insights arising from such studies and others the overall promise of the approach, but all involved research that relied on the simultaneous analyses of numerous cellular components. In making his nomination for "Large Scale Screens," Moon argued for their importance because of their ability "to push studies of signaling pathways away from looking at a single component and its regulation, into the realm of analysis of large populations of proteins.… This is a clear departure from decades-old approaches of studying signaling, and will have as a consequence the development of technologies and bioinformatics to characterize changes in hundreds of signaling components simultaneously, and to elucidate how they change over time. This is a prerequisite for establishing predictive mathematical models of signaling. This is turning signal transduction studies into Systems Biology."

As an example of the promise of such large-scale analyses in advancing cell signaling, Moon nominated a study by Li *et al.* (*1*) of in vivo interactions between proteins and hydrophobic small metabolites, which showed that some 20% of yeast kinases were associated with such metabolites, suggesting that small metabolites—which constitute the majority of cellular components—might play a broader role in regulating protein function than has generally been appreciated. Fru-

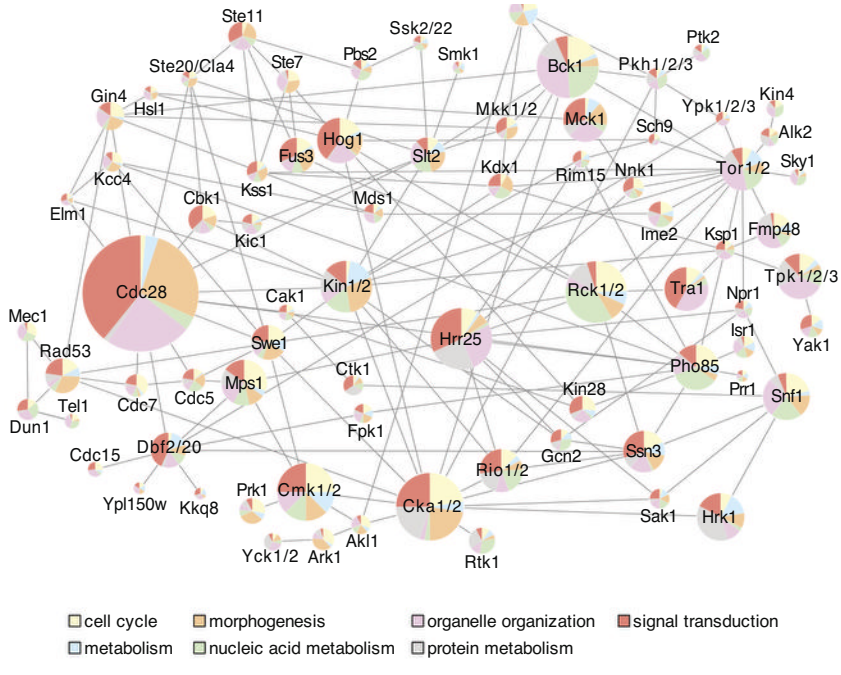

Fig. 1. A kinase-kinase interaction network connects the proteome of budding yeast.

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man, commenting that several papers in the last year had contributed substantially to our understanding of microRNA function in the immune system, noted that Kuchen *et al*. (*2*) "used ultra high-throughput sequencing to catalog microRNA expression across different immune cell subsets during development and after antigen-dependent differentiation." Hunter and Walker both nominated an article by Breitkreutz *et al*. (*3*) that used mass spectrometric analysis to identify a network of interacting kinases and phosphatases in budding yeast, shedding light on how they work together to coordinate cellular activity and uncovering connections that suggest unanticipated functions for these signaling proteins (Fig. 1). For instance, the cell cycle phosphatase Cdc14 emerged as a major network hub, with connections to mitogen-activated protein kinase (MAPK) signaling, cell metabolism, and the DNA damage response, which acts a crucial defense against tumor development and, as such, itself appeared as the focus of several notable papers.

Both Hunter and Pagano nominated papers that used large-scale screens to identify new players in the DNA damage response. In making his nomination, Pagano explained, "The activation of cellular checkpoints in response to DNA damage presents an important early barrier to the development of tumors. Inactivation of DNA damage proteins not only removes this block to proliferation, but subsequent mutations resulting from failures in the DNA damage response can further promote tumorigenesis, making the inactivation of the DNA damage response a hallmark of human cancer. In 2010, several genome-wide RNAi screens and proteomic screens … identified novel genes involved in the DNA damage response and in DNA repair" (*4*–*8*). The Fanconi anemia (FA) pathway is specifically associated with the repair of interstrand crosslinks, lesions that block DNA replication. Thus, individuals with this genetic disorder show various developmental abnormalities, enhanced susceptibility to cancer, and hypersensitivity to interstrand crosslinking agents, including some antineoplastic drugs. The study by Smogorzewska *et al*. (*4*), which used an shRNA screen to identify FAN1 (for FANCD2-associated nuclease 1) as a repair nuclease recruited to sites of DNA damage as part of the FA pathway, also caught Hunter's eye, along with a separate study, by Kratz *et al*., that implicated FAN1 in the FA response, showing that cells depleted of this nuclease showed enhanced sensitivity to interstrand crosslinking agents (Fig. 2) (*9*). MacKay *et al*. (*10*) published a third study implicating FAN1 in the FA pathway. FAN1 recruitment depends on its ubiquitin domain, and on the ubiquitylation of FANCD2 (a component of the FANCI-FANCD2 complex that coordinates DNA repair).

Dikic nominated a paper by Behrends *et al*. that provided a network view of autophagy, another cellular process in which ubiquitylation plays a crucial role, in human cells under basal autophagic conditions (*11*), saying "[t]his is an initial snapshot containing a network of 751 interactions among 409 interacting proteins. It will serve as a starting point for future challenges in monitoring dynamic changes in autophagy networks under different cell conditions". Dikic also noted the development of ubiquitin chain linkage-specific antibodies, and their invaluable role in dissecting the dynamics of ubiquitin signaling pathways (*12*). In a final study pertinent to this posttranslational modification, Hunter nominated a paper by Doyle *et al*. (*13*) identifying a function for melanoma antigen (MAGE) proteins (many of which are expressed aberrantly in various cancers, where they have served as functionally enigmatic targets for cancer immunotherapy) as binding to and enhancing the activity of a subset of RING domain ubiquitin ligases.

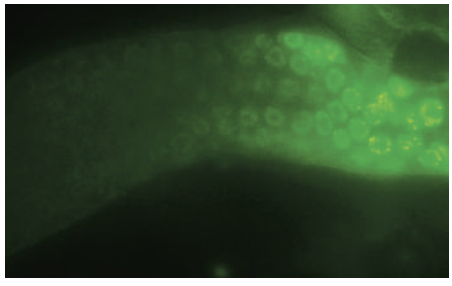

Fig. 2. Cisplatin promotes FAN1 recruitment to sites of DNA damage in *C. elegans* germline cells.

Whereas the MAGE proteins have provided a target for cancer therapy simply by virtue of their aberrant expression in malignant cells, one of the hopes and promises of cell signaling research is that a better understanding of cell function—and of how it can go awry—could lead to new and improved ways to combat disease. Cell metabolism—the series of enzymatic reactions whereby cells break down nutrients to obtain energy and use energy to synthesize macromolecules from simpler components—has been so thoroughly studied that it might seem surprising that new secrets in this fundamental area of cell biology remain to be uncovered. The next three nominations, which do just that, concern breakthroughs in our understanding of metabolic abnormalities in cancer cells. The observation that cancer cells, unlike nonmalignant cells, show aerobic glycolysis associated with increased production of lactate (the Warburg effect) dates back to the first half of the last century. This metabolic shift is associated with the presence of the M2 isoform of the glycolytic enzyme pyruvate kinase. Although cancer cells show increased glucose consumption, the presence of pyruvate kinase M2 is associated with decreased enzymatic activity compared to that of the M1 isoform, which is typically found in normal differentiated tissues. Hunter and Perrimon both nominated a paper by Vander Heiden *et al*. (*14*) that explored this paradox and unearthed an alternative glycolytic pathway that may enable cancer cells to escape feedback inhibition of glycolysis by limiting the production of adenosine triphosphate. A study by Fang *et al*. (*15*) provided additional insight into the Warburg effect, linking increased activation of the protein kinase Akt following loss of the tumor suppressor PTEN to aerobic glycolysis through an increase in the expression and activity of the endoplasmic reticulum enzyme ENTPD5 (ectonucleoside triphosphate diphosphohydrolase 5).

Malignant gliomas commonly harbor mutations in the cytosolic enzyme isocitrate dehydrogenase 1 (IDH1), which render it unable to catalyze the conversion of isocitrate to α-ketoglutarate. Notably, these mutations are present in only a single allele of the tumor cells. In his next nomination, Hunter proposed a pair of papers that shed light on the underlying mechanism (*16, 17*), implicating an unexpected gain of function ability to produce the oncogenic metabolite 2-hydroxyglutarate—rather than the loss of normal function—in the contribution of mutations in IDH1 (and in its mitochondrial homolog IDH2) to cancer pathogenesis.

Cancer cells show numerous abnormalities unrelated to aberrant metabolism, of course, some of which are more closely allied to classical signal transduction pathways. Many cancers show increased signaling through the Ras to Raf to MEK (mitogen- or extracellular signal–regulated protein kinase kinase) to ERK (extracellular signal–regulated protein kinase) MAPK (mitogen-activated protein kinase) signaling pathway, which functions downstream

of mitogenic stimuli. Activating mutations of Ras are common in various cancers, and activating mutations of the BRAF isoform of Raf are particularly notable in melanoma. Some BRAF mutants found in human melanomas, however, are catalytically inactive. Perrimon nominated a paper by Heidorn *et al*. (*18*) that shed light on this apparent paradox by showing that catalytically inactive BRAF loses its capacity for autoinhibition and, when expressed with constitutively active Ras, cooperates with Ras to hyperactivate the CRAF isoform of Raf and thereby enhance signaling through MEK and ERK. As Perrimon noted, these findings not only provide insight into basic mechanisms underlying tumorigenesis, they also have substantial implications for the treatment of BRAF melanomas, in that BRAF inhibitors also enhanced signaling through CRAF in tumors containing oncogenic Ras.

Genetics is as well trodden an area of biology as metabolism, but, like metabolism, retains the capacity to provide unexpected discoveries. A surprisingly large fraction of the human transcriptome does not encode proteins. The existence of regulatory functions for small RNAs—including microRNAs—is well established, and new functions for these noncoding RNAs continue to emerge. Pseudogenes, however, which resemble coding genes but cannot encode proteins because they have acquired various mutations (such as premature stop codons or frameshifts), have been viewed as largely lacking in function. Fruman nominated a paper by Poliseno *et al*. (*19*) showing that expressed pseudogenes could regulate the expression of cancer-related partner genes by competing for regulatory microRNAs, conferring oncogenic or tumor suppressor functions on the regulatory pseudogenes. As Fruman explained, "Overexpression of the pseudogene enhances expression of the partner by providing a decoy for microRNAs; conversely, reduced expression of the pseudogene leads to reduced expression of the partner. As proof of concept, the authors demonstrated tumor suppressor function of *PTENP1*, a pseudogene partner of the tumor suppressor *PTEN*. Similarly, the pseudogene *KRAS1P* enhances the expression of the oncogene *KRAS*. This novel finding provides a new mechanism for tuning signaling transduction outputs, with important implications for tumor biology and probably for other physiological systems."

Cancer is not the only disease where a better understanding of cell signaling could potentially lead to improved therapies, and Hunter and Snyder nominated breakthroughs that may lead to better treatments for two other human scourges—diabetes and Alzheimer's disease. Like cancer, type 2 diabetes is associated with metabolic abnormalities. The link between obesity, metabolic syndrome, and type 2 diabetes, which is associated with insulin resistance, is well known. Drugs that activate the nuclear receptor PPARγ (peroxisome proliferator–activated receptor γ) increase insulin sensitivity, and have, therefore, been used to treat diabetes. However, PPARγ agonists can have adverse side effects, and, curiously, their ability to enhance insulin sensitivity does not correlate with their ability to activate PPARγ. Hunter nominated a paper by Choi *et al*. (*20*) showing that these drugs appeared

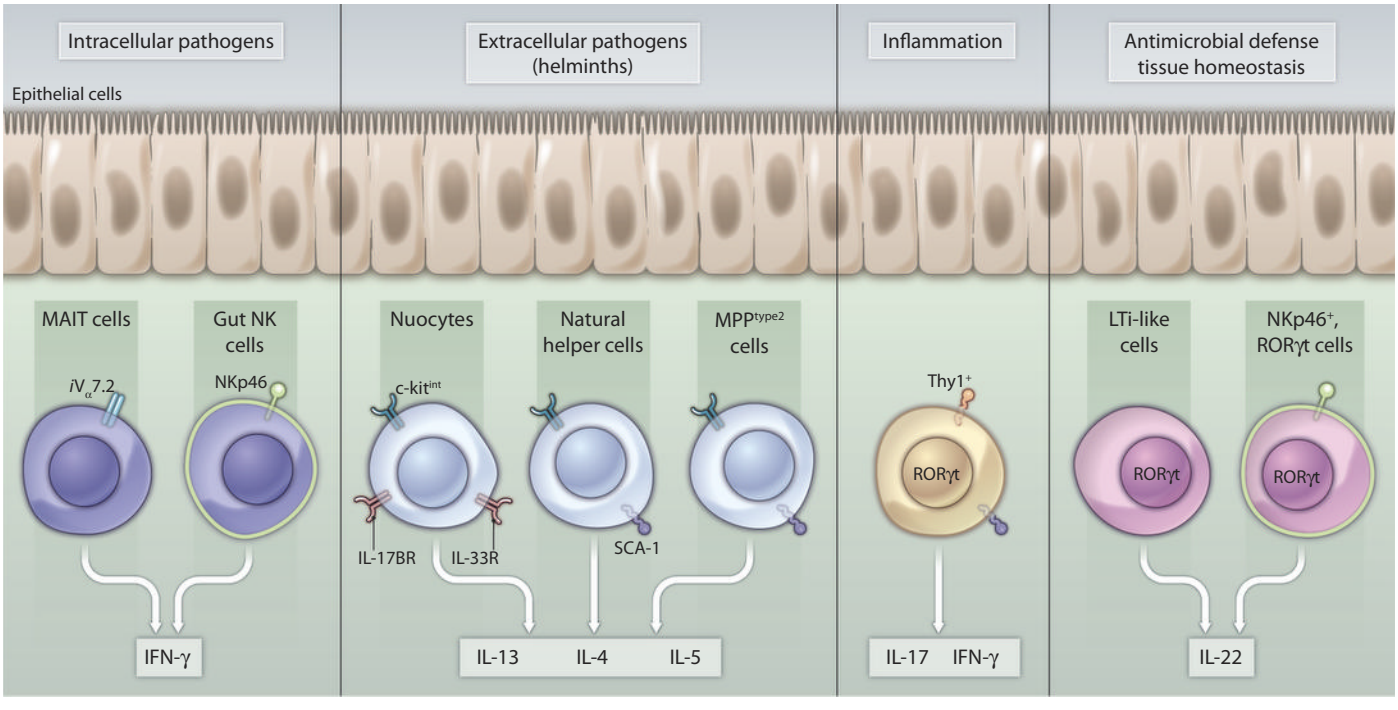

Fig. 3. Gut innate lymphoid cells. Innate lymphoid cells of the mucosal-associated lymphoid tissues of the gut can be identified by various markers and grouped according to their functions and the cytokines they produce. MAIT (mucosal-associated invariant T lymphocytes) cells and gut NK cells produce γ-interferon (IFN-γ) and play a role in the defense against intracellular pathogens. Nuocytes, Natural Helper Cells, and MPP$^{type\ 2}$ (multipotent progenitor type 2) cells produce interleukins (IL)-4, -5, and -13, and mediate defense against extracellular pathogens, such as helminths. A population of innate lymphoid cells that express Thy-1, stem cell antigen 1 (SCA-1), and the retinoic-acid-related orphan receptor (ROR)-γt and secrete IL-17 have been implicated in inflammatory responses. Lymphoid-tissue inducer (LTi)-like cells and NKp46$^+$, RORγt$^+$ cells secrete IL-22 and appear to both have antimicrobial functions and participate in mucosal tissue homeostasis. This latter population resembles gut NK cells in bearing cell surface NKp46 receptors. iV_α 7.2, invariant T cell antigen receptor α-chain; c-kit^{int}, intermediate abundance of the c-kit receptor tyrosine kinase.

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to act by a mechanism distinct from classical PPARγ agonism but which instead depended on their ability to inhibit the activating phosphorylation of PPARγ by Cdk5 (cyclin-dependent kinase 5), a discovery that could lead to the development of better antidiabetic drugs.

Efforts to develop drugs that target the proteolytic enzyme γ-secretase, which is responsible for the accumulation of the neurotoxic peptide β-amyloid associated with Alzheimer's disease, have been confounded by the fact that γ-secretase has numerous substrates. In nominating research by He *at al*. (*21*) that may provide a way around this dilemma, Snyder explained, "Drug companies have sought inhibitors of this enzyme, but it also participates in the Notch developmental pathway so that inhibitors identified thus far are toxic. Greengard's team discovered a novel protein called γ-secretase activating protein (GSAP) which dramatically enhances activity of the enzyme without involving Notch. Drugs inhibiting GSAP decrease amyloid β-peptide without affecting Notch signaling."

In conjunction with his M.D./Ph.D. student Moe Gadalla, Snyder nominated a study by Vierbuchen *et al*. (*22*) with implications for various neurodegenerative disorders and, more generally, for the field of regenerative medicine. Cell lineage commitment during development has been viewed as an irreversible process. Among the breakthroughs we reported for 2007 was the discovery that small defined sets of transcription factors could be used to reprogram somatic cells back to pluripotent stem cells. As Snyder noted, the current paper "went one step further" in showing that a mixture of genes (*Ascl1*, *Brn1*, and *Myt1l*) encoding three transcription factors was sufficient to directly and efficiently convert cells of a nonneural lineage (mouse embryonic or postnatal tail tip fibroblasts) into functional neurons. Bypassing the stem cell stage, this approach holds the promise of generating patient-specific neurons to replace those lost to injury or disease.

Although improved therapies to combat disease are a potential exciting outcome of breakthrough signaling research, it's better to avoid getting sick in the first place. This, of course, is the job of the immune system, perhaps the only system in the body to rival the nervous system in complexity. Vivier nominated a series of articles revealing that the immune system is even more complex than previously appreciated (*23*–*32*). These articles showed that—rather than existing as a homogeneous population—there is a tremendous heterogeneity of the innate lymphoid cells of the mucosal-associated lymphoid tissues of the gut and determined that these different cell types could be grouped according to their functions and the cytokines that they produce (Fig. 3).

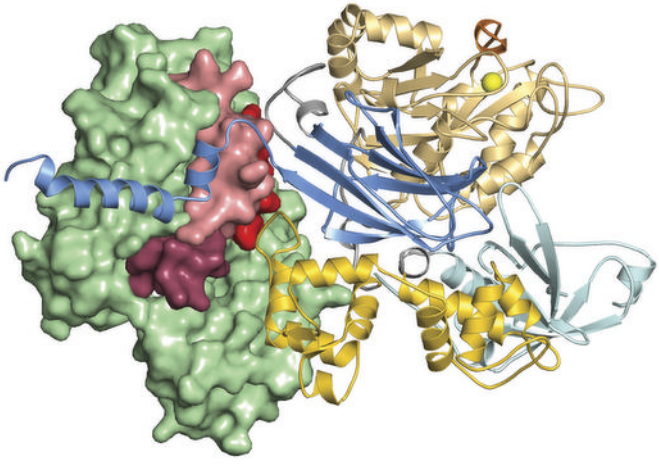

Fig. 4. Structure of $G\alpha_q$ in a complex with phospholipase C-β3.

The last series of nominations shifted the focus to the molecular level. Dohlman nominated a paper by Waldo *et al*. (*33*) that explored the mechanisms through which Gα subunits of the G_q family of heterotrimeric guanine nucleotide–binding proteins ($G\alpha_q$) activate their effector phospholipase C–β (PLC-β) and are, in turn, inactivated by it (Fig. 4). "About half of all neurotransmitter signaling (and in particular neurotransmitter regulation of blood pressure) is mediated by the $G\alpha_q$-class of G proteins. Like other G proteins, $G\alpha_q$ undergoes repeated cycles of activation and inactivation, and these steps are accelerated by receptors and RGS proteins, respectively. $G\alpha_q$ is also inactivated upon binding to its effector enzyme, phospholipase C-β. Thus couplings that promote signaling also serve to abrogate signaling, a phenomenon known as 'kinetic scaffolding.'" A crystal structure of $G\alpha_q$ in complex with PLC-β3 has revealed the molecular basis for kinetic scaffolding. Most unexpectedly, the structure also revealed subtle but functionally important similarities to the complex of G proteins with RGS proteins. Thus, despite a complete lack of sequence similarity, PLC-β3 and RGS proteins appear to act in very much the same way at the atomic level. The findings are noteworthy for their fundamental importance to neurotransmitter signaling, but also as a striking example of convergent evolution."

Although ubiquitylation featured prominently in this year's nominations, phosphorylation remains perhaps the most familiar—dare I say, beloved—posttranslational modification. The last three nominations—all by Hunter—concerned some surprising discoveries about kinase regulation, specificity, and function. The first of these was for a paper by Zheng and Jia reporting the structure of the *Escherichia coli* enzyme isocitrate dehydrogenase kinase/phosphatase (AceK) (*34*). Considered one of the most primitive of the protein kinases, AceK has the remarkable ability to function as either a kinase or as a phosphatase to respectively inhibit or activate isocitrate dehydrogenase. Inhibition of isocitrate dehydrogenase diverts isocitrate to glyoxylate, thereby bypassing part of the Krebs cycle. AceK is subject to allosteric regulation by a number of small molecules, and structural and mutational analyses enabled the authors to propose a mechanism for regulation of the switch between its kinase and phosphatase activity. The nonreceptor tyrosine kinase Syk (spleen tyrosine kinase) plays a prominent role in B cell receptor (BCR) signaling, phosphorylating tyrosine residues in the immunoreceptor tyrosine-based activation motif (ITAM) of Ig-α, and in various other proteins mediating BCR signaling pathways. A paper by Heizmann *et al*. (*35*) revealed that, like AceK, Syk was multifunctional—acting not as a kinase and a phosphatase, but as a dual-specificity kinase, capable of phosphorylating serine as well as tyrosine residues. The kinase mTOR (mammalian target of rapamycin) is perhaps the single enzyme that has been featured most prominently in our *Signaling Breakthroughs* features, and this year's article closes with a nomination for an article by Oh *et al*. (*36*) on mTOR function. mTOR, which coordinates information about growth factor abundance, energy status, and nutrient availability to regulate cell growth and proliferation, signals through distinct complexes, mTORC1, and mTORC2. Acting through mTORC1, mTOR phosphorylates translation initiation factors and ribosomal proteins to promote the initiation of translation; Oh *et al*. now show that mTORC2 is associated with ribosomes and phosphorylates the nascent Akt peptide dur-

ing translation, thereby insuring proper folding and enabling mTOR to couple protein translation to quality control.

This year's nominations show that signal transduction research remains an exciting and biomedically relevant area and that new insights continue to come from many biological disciplines and different research approaches, from the reductionist to the systems level.

Related Resources

Editorial Guides

- E. M. Adler, 2009: Signaling breakthroughs of the year. *Sci. Signal.* **3**, eg1 (2010).
- E. M. Adler, 2008: Signaling breakthroughs of the year. *Sci. Signal.* **2**, eg1 (2009).
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- W. Wong, Focus Issue: Metabolic signals. *Sci. Signal*. **3**, eg12 (2010).
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- N. R. Gough, Focus Issue: Demystifying mTOR signaling. *Sci. Signal*. **2**, eg5 (2009).

Editors' Choice

- L. B. Ray, Budding yeast kinome revealed. *Sci. Signal*. **3**, ec159 (2010).
- L. B. Ray, Glucose metabolism revisited. *Sci. Signal*. **3**, ec289 (2010).
- L. B. Ray, Connecting signaling and metabolism in cancer. *Sci. Signal*. **3**, ec380 (2010).
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Perspectives

- M. C. Hall, Proteomics modifies our understanding of cell cycle complexity. *Sci. Signal.* **3**, pe4 (2010).
- C. V. Dang, PKM2 tyrosine phosphorylation and glutamine metabolism signal a different view of the Warburg effect. *Sci. Signal*. **2**, pe75 (2009).
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- M. P. Mattson, ER calcium and Alzheimer's disease: In a state of flux. *Sci. Signal.* **3**, pe10 (2010).
- D. R. Alessi, L. R. Pearce, J. M. García-Martínez, New insights into mTOR signaling: mTORC2 and beyond. *Sci. Signal.* **2**, pe27 (2009).

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