A quantum computer can process each of these classical values in quantum parallelism, so that exponentially many computations are performed at once. In principle, this phenomenon allows more work to be done in a short quantum computation involving a few thousand qubits than would be possible for a classical computer the size of the universe.

To solve the database search problem, Grover starts by setting a quantum register to a superposition of all possible names in the phone directory. A single access to the database (which may involve a computation if it is virtual) creates a superposition of all possible pairs of matching names and phone numbers. The resulting quantum state contains the desired pair, but with vanishingly small amplitude—the measure of how much it contributes to the global state—compared to the multitude of unwanted pairs. If the register were observed at that point, the odds of obtaining the relevant answer would be as small as if an arbitrary name had been tried at random by a classical computer.

Grover's discovery is a clever sequence of simple operations on the register's state. This process can be thought of as a sort of "quantum shake," which, contrary to a classical shake, brings order rather than disorder. Just as crests reinforce each other when ripples meet in water, Grover's shake uses quantum interference effects to increase the amplitude of the pair that contains the target phone number at the expense of all other pairs. This increase is so subtle that the probability of obtaining the desired result by observing the quantum register after a single shake is almost as small as before. However, the shake can be repeated over and over again, gradually boosting the amplitude of the correct answer to a detectable level. Provided the solution is unique, it is found with near certainty if the quantum register is observed after $(\frac{\pi}{4})N^{1/2}$ shakes, where N is the size of the database.

To use an analogy from Kristen Fuchs (*3*), Grover's quantum searching technique is like cooking a soufflé. You put the state obtained by quantum parallelism in a "quantum oven" and let the desired answer rise slowly. Success is almost guaranteed if you open the oven at just the right time. But the soufflé is very likely to fall—the amplitude of the correct answer drops to zero—if you open the oven too early. Furthermore, the soufflé could burn if you overcook it: strangely, the amplitude of the desired state starts shrinking after reaching its maximum (*4*). After twice the optimal number of shakes, you are no more likely to succeed than before the first shake.

Grover's algorithm is still theoretical, as is the earlier quantum algorithm discovered in 1994 by Shor to factor large numbers, which would bring most of contemporary cryptography to its knees (*5*), because there are no quantum computers in operation today, and there is no conclusive evidence that there ever will be. This theoretical dream may turn into a technological nightmare (*6*). Nevertheless, several teams have started experimenting with basic quantum computation. In particular, the Institute for Quantum Information and Computing, led by Kimble at the California Institute of Technology, has received a $5 million grant from the Defense Advanced Research Project Agency to investigate the feasibility of quantum computing (*7*). Similarly, the Los Alamos Quantum Computation Project, led by Hughes, has received a significant grant from the National Security Agency. Other major efforts are led by Monroe and Wineland at the National Institute of Standards and Technology in Boulder, Colorado, and by Blatt and Zeilinger in Innsbruck, Austria. Related experiments are led by Haroche, Raimond and Brune at the École Normale Supérieure in Paris.

Showing too much unbridled optimism would be highly premature, but even the staunchest critics agree that exciting fundamental physics is likely to come out of these experiments. Most physicists expect that currently planned experiments, involving a few quantum bits and gates, will allow the production and study of counterintuitive quantum states that have been theoretically predicted but never observed. Moreover, these experiments may provide valuable technical expertise regarding the feasibility of larger scale quantum computation. Although it may turn out that a practical implementation of such brilliant ideas as Grover's quantum search algorithm will never be realized, intriguing new ideas have already emerged from the study of quantum information theory, such as quantum cryptography (*8*), quantum teleportation (*9*), and quantum error correction (*10*). Whatever the future has in store for quantum computation, fundamental physics will benefit from it.

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SIGNAL TRANSDUCTION

Akt Signaling: Linking Membrane Events to Life and Death Decisions

Brian A. Hemmings

Modules made of protein kinases control cellular processes. This discovery—perhaps the most important in signal transduction research during the past 5 years—is typified by growth factor stimulation of the Ras-Raf–MAP kinase module (*1*). One of the many initial events that occur after growth factors bind to their cognate growth factor receptor tyrosine kinases (RTKs) is the recruitment and activation of the phosphoinositide 3-kinases (PI 3-kinases). Inositol lipids phosphorylated at the D3 position by PI 3-kinases act as second messengers somewhat analogous to cyclic adenosine 3′,5′-monophosphate (cAMP) and calcium. The serine/threonine protein kinase Akt (also called protein kinase B or PKB), identified first as an oncogene, is one of the major targets of PI 3-kinase–generated signals (*2–5*). Results on pages 661 and 665 of this issue of *Science* and elsewhere (*6–10*) now provide new information on the mechanism of signal propagation from RTKs to Akt and reveal that Akt may participate in growth factor maintenance of cell survival.

Crucial to the discovery of Akt (*11–13*) and its function was the recognition that Akt is a proto-oncogene (*12*) and the characterization of its pleckstrin homology (PH) domain (*14*). The recognition that PH domains can bind lipids suggested a mechanism linking the activation of PI 3-kinase and Akt activity (*6, 9, 10, 15*). PI 3-kinase activity is potently inhibited by wortmannin

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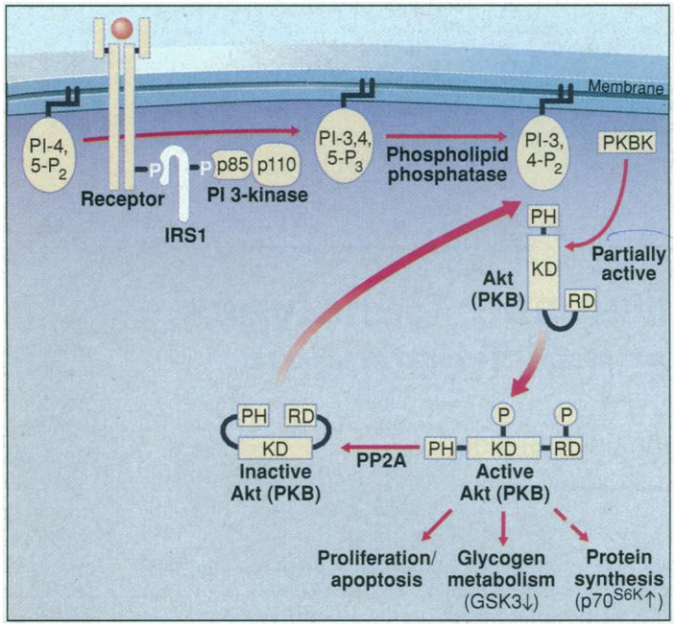
and by the structurally unrelated inhibitor LY294002. Both of these inhibitors can block the rapid activation of Akt (up to 50-fold) by platelet-derived growth factor, epidermal growth factor, basic fibroblast growth factor, insulin, and insulin-like growth factor–1 (IGF-1) (*2–5*, *16*). Activation of Akt by protein phosphatase inhibitors (*16*) is, however, relatively insensitive to wortmannin and LY294002, indicating that it is the lipid kinase activity of PI 3-kinase that mediates Akt activation by growth factors. These and other data place Akt firmly downstream of PI 3-kinase.

How does the generation of the PI 3-kinase–derived second messengers, phosphatidylinositol-3,4-bisphosphate (PtdIns-3,4-P_2) and PtdIns-3,4,5-P_3, promote activation of Akt? The current data indicate three steps: (i) translocation of the kinase to the membrane, (ii) attachment to the membrane by means of PH domain binding to phospholipid, and (iii) phosphorylation (see figure). The importance of translocation is emphasized by recent experiments (*17*, *18*) indicating that targeting of Akt to the membrane by the addition of a myristoylation motif to the NH_2-terminus can promote activation of the kinase by a mechanism that is resistant to wortmannin or LY294002 inhibition. Constructs lacking a PH domain but with the membrane-attachment myristoylation motif are activated to a similar extent as the native protein. This result not only indicates that the PH domain functions primarily to anchor the protein at the membrane, but it also suggests that the oncogenic potential of v-*akt* arises from creation of a myristoylation site at the NH_2-terminus and the consequent constitutive kinase activity. The high-affinity association of Akt with PtdIns-3,4-P_2 and PtdIns-3,4,5-P_3 not only provides a means for attaching the kinase to the membrane but also, as shown by Franke *et al.* (*6*) and elsewhere (*9*, *10*), in the case of PtdIns-3,4-P_2, promotes a conformational change leading to an increase of kinase activity.

However, the in vitro activation of Akt by PtdIns-3,4-P_2 (two- to sixfold) is modest compared with that induced by growth factor stimulation. The two phospholipids PtdIns-3,4-P_2 and PtdIns-3,4,5-P_3, which bind at micromolar concentrations to the PH domain, are normally not detectable in unstimulated cells (*19*) but accumulate transiently upon cell stimulation by growth factors. It is likely that this transient accumulation promotes the association of Akt with the membrane. What is the source of this PtdIns-3,4-P_2? The fact that wortmannin inhibits activation suggests that PtdIns-3,4-P_2 is derived from PtdIns-3,4,5-P_3 (the product of PI 3-kinase) by a phospholipid phosphatase (see figure). Both the recently described growth factor–stimulated inositol polyphosphate 5′-phosphatases (*20*) and the type II PI 3-kinases (*21*) could be important components in the overall regulation of PtdIns-3,4-P_2 amounts in the membrane.



Growth factor–promoted activation of Akt requires PI 3-kinase. Growth factor binding promotes recruitment and activation of PI 3-kinase after autophosphorylation of the receptor on tyrosine residues. PI 3-kinase at the membrane converts PtdIns-4,5-P_2 (PI-4,5-P2) to PtdIns-3,4,5-P_3 (PI-3,4,5-P3), and PtdIns-3,4-P_2 (PI-3,4-P2) is generated by inositol 5′-polyphosphatase. Akt is recruited to the membrane, undergoes a conformational change, and becomes phosphorylated (activated). Subsequently, Akt is released from the membrane to phosphorylate specific targets. Activation by IGF-1 also required insulin receptor substrate 1 (IRS1) (shown in white). KD, kinase domain; RD, regulatory domain.

PI 3-kinase activity ultimately leads to an increase in Akt kinase by promoting its phosphorylation, in addition to the direct allosteric effect of the lipid products of PI 3-kinase (*9*, *16*). Insulin and IGF-1 promote a 20- to 50-fold activation of kinase activity and phosphorylation of Akt at two sites: Thr^{308} in the T-loop and Ser^{473} on the COOH-terminal regulatory domain. Both phosphorylation events can be inhibited by wortmannin in vivo. Analysis of a mutant, kinase-dead Akt, revealed that Thr^{308} and Ser^{473} are phosphorylated by an upstream kinase (PKBK). The amino acid sequences around these two residues suggest that two distinct PKBKs are involved. Furthermore, the results of membrane targeting experiments indicate that the PKBKs are constitutively localized at the membrane. The scene is now set for the isolation of this upstream kinase, likely an effort of several laboratories.

It was proposed recently that inositol trisphosphate (IP_3), presumably generated from PtdIns-4,5-P_2 by phospholipase C–γ, could release PH domain–containing proteins from membranes (*15*); release of Akt from the membrane by IP_3 could also be a key regulatory step. After its release, Akt would become available to phosphorylate downstream targets until inactivated by dephosphorylation by protein phosphatase 2A (PP2A). The search for authentic in vivo substrates of Akt is of intense interest, given the number of physiological processes regulated by PI 3-kinase. The first identified physiological substrate of Akt was glycogen synthase kinase 3 (GSK3). Phosphorylation of GSK3 leads to inactivation of this kinase and stimulation of glycogen synthesis (*5*). The regulation of GSK3 by Akt is also likely to affect other aspects of cellular function because of its role in the regulation of protein synthesis, modulation of transcription factors (AP-1 and cAMP response element–binding protein) and the tumor suppressor adenomatous polyposis coli (APC), cell fate determination (in *Drosophila*), and dorsoventral patterning (in *Xenopus*) (*5*, *22*). Other data suggest that Akt is upstream of the p70 ribosomal protein s6 kinase but the connection is likely to be indirect (*3*).

The new data by Dudek *et al.* (*7*) demonstrate that Akt is important for the survival of cerebellar neurons. Thus the "orphan" kinase has now moved to center stage as a crucial regulator of life and death decisions emanating from the cell membrane. Previous data (*23*) indicated that survival of several cell lines is PI 3-kinase–dependent, and the new results show that IGF-1 protects cerebellar neurons from apoptosis (cell death) by activating Akt. This conclusion is based on the authors demonstration that expression of exogenous Akt enhances cell survival by dramatically reducing apoptosis and that transfection of dominant negative mutant kinase constructs (kinase-dead or PH domain) inhibited survival of neurons promoted by IGF-1.

Nerve growth factor (NGF) also promotes

Akt activation in pheochromocytoma PC12 cells, suggesting that kinase activation is also involved in the survival promoted by NGF (*24*). The implication from the new work is that the Akt signaling pathway is able to prevent apoptosis of neurons after NGF treatment. Does activated Akt protect cells from programmed cell death promoted by other stimuli and physiological conditions? Interestingly some reports (*25*) indicate growth factor–induced neurite outgrowth in PC12 cells is inhibited by wortmannin, suggesting yet another role for Akt.

Are other PH domain–containing protein kinases (about 12 at the last count) also recruited to the membrane and activated by PI 3-kinase? Only time will tell if they are all as interesting as Akt.

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NEUROSCIENCE

Alzheimer's Disease: Genotypes, Phenotype, and Treatments

Dennis J. Selkoe

New research findings on Alzheimer's disease (AD) emerge at a furious pace, at first appearing to obscure rather than illuminate a unified mechanism of disease that could simplify the search for therapies. But several recent reports, coupled with earlier observations from many laboratories, now suggest a clarifying pattern—that all four known genetic alterations underlying familial AD increase the production or deposition (or both) of the amyloid β protein (Aβ) in the brain. Moreover, studies of humans with AD or trisomy 21 (Down syndrome), and of transgenic mouse models, all indicate that Aβ accumulation in the cerebral cortex is an early and invariant event in the development of AD pathology, preceding other brain lesions and clinical symptoms by many years or decades.

The central quest of research on AD is to identify the steps in its pathogenesis that, if inhibited, would slow or prevent the disease. All AD patients develop neuritic plaques in brain areas subserving memory and cognition. These plaques consist of extracellular masses of Aβ filaments intimately associated with dystrophic dendrites and axons, activated microglia, and reactive astrocytes. Virtually all patients also have many neurofibrillary tangles, intraneuronal bundles of paired helical filaments composed of highly phosphorylated forms of the microtubule-associated protein, tau. Aβ also accumulates in many nonfilamentous extracellular deposits that lack altered neurites and glia (diffuse plaques). These are composed of the slightly longer and more amyloidogenic 42-residue form of Aβ ($Aβ_{42}$), whereas neuritic plaques contain both $Aβ_{42}$ and the far more abundantly produced $Aβ_{40}$ peptide. Aβ is formed by specific endoproteolytic cleavages of the β-amyloid precursor protein (βAPP), which is encoded by a gene on chromosome 21, and is constitutively secreted by both brain and nonbrain cells into extracellular fluids throughout life.

βAPP missense mutations located at or near the sites of endoproteolysis are a rare cause of familial AD (see table). All of these βAPP mutations have been studied in transfected or primary cells, and all increase Aβ secretion, particularly $Aβ_{42}$ (*1*, *2*). Furthermore, plasma Aβ levels are significantly increased in some mutation carriers, even presymptomatically (*2*). As a result, it is now widely accepted that βAPP mutations cause AD by enhancing the cleavages that generate Aβ, thereby promoting amyloidogenesis. There is no evidence that normal βAPP function is impaired by the mutations, probably because only a small fraction of all βAPP molecules in the cell actually undergoes the Aβ-generating cleavages, even in individuals with the mutations.

The second gene to be implicated in familial AD is apolipoprotein E (apoE). Inheritance of one or two apoE4 alleles increases the likelihood and decreases the age of onset of AD (*3*). The only consistently confirmed phenotypic clue to its mechanism is that AD patients carrying apoE4 alleles show a significant, dose-dependent increase in the density of Aβ deposits (in particular, those contain-

Chromosome	Gene defect	Age of onset	Aβ phenotype
21	βAPP mutations	50s	↑ Production of total Aβ peptides or of $Aβ_{42}$ peptides
19	apoE4 polymorphism	60s and older	↑ Density of Aβ plaques and vascular deposits
14	Presenilin 1 mutations	40s and 50s	↑ Production of $Aβ_{42}$ peptides
1	Presenilin 2 mutations	50s	↑ Production of $Aβ_{42}$ peptides

Genetic factors predisposing to Alzheimer's Disease: Relationships to the β-amyloid phenotype. Additional chromosomal loci exist but are not yet specifically identified.

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