from the northern North Atlantic, where ^{14}C reservoir ages of surface waters varied strongly during the last glacial and deglacial periods (that is, before 10,000 calendar years B.P.).

The new results based on the stratigraphic method can be used successfully to calibrate ^{14}C ages (see the figure). Between 33,000 and 41,000 calendar years B.P., whereas previous records disagree by up to 5000 calendar years, the new data sets agree within the errors. This confirms the reliability of the stratigraphic method applied to these two distant and very different marine environments. The correct calibration curve thus probably runs between the Lake Suigetsu and Bahamian speleothem data sets.

These new results have important implications for archaeology. Consider the prehistoric paintings in the Chauvet Cave of southern France, which were created at about 31,000 ^{14}C years B.P. (*13*) (red horizontal arrow in the figure). According to the new stratigraphic data (*10*, *12*) and other results presented in Wellington, the calibrated age is almost 36,000 calendar years B.P. (black vertical arrow). The earlier Bahamian speleothem data yield ~38,000 calendar years B.P. (purple vertical arrow) and the Lake Suigetsu record gives ~33,000 calendar years B.P. (green vertical arrow), dates that are respectively too old and too young.

The new radiocarbon results also have wide implications for geochemistry and geophysics. For example, the observed differences between the ^{14}C and true ages reflect deviations of the atmospheric $^{14}C/^{12}C$ ratio, the long-term trend of which is modulated by the geomagnetic field. A well-known magnetic excursion, the Laschamp event, dated by Ar-Ar at ~41,000 calendar years B.P. (*14*), resulted in an abrupt increase of cosmogenic nuclide production (such as ^{14}C, ^{10}Be, ^{36}Cl, and ^{41}Ca). The new data from the Cariaco Basin (*10*) and the Iberian Margin (*12*), together with previous coral data (*15*), indicate that the atmospheric $^{14}C/^{12}C$ ratio reached a maximum of about 700 per mil above the modern one at ~39,000 to 41,000 calendar years B.P. Taking into account a millennium-scale phase shift linked to the carbon cycle, the calendar age for the Laschamp event is thus ~40,000 to 42,000 calendar years B.P. This is fully compatible with recent determinations, in the very same Iberian Margin core, of a ^{10}Be maximum (*16*) and a magnetic paleointensity minimum (*17*) at ~41,000 to 42,000 calendar years B.P. Further independent confirmation of this calibration point comes from ^{10}Be and ^{36}Cl concentration maxima in ice sections dated at ~41,000 calendar years B.P. in the Greenland Summit ice cores (*18*, *19*).

Significant progress is expected in the near future from the stratigraphic method for two main reasons. First, the recently drilled NorthGRIP ice core (*20*) will soon provide improved accuracy and precision for the calendar time scale up to 50,000 calendar years B.P., which is the backbone of the stratigraphic method. Second, additional data will allow researchers to verify and complement the emerging agreement observed between several data sets beyond 26,000 calendar years B.P. (see the figure). In the framework of the international IMAGES program, the research vessel *Marion Dufresne* has recently drilled several new sediment cores from the Iberian Margin and Cariaco Basin. This should increase the ^{14}C data base and permit measurement of other interesting parameters such as ^{10}Be concentrations and magnetic paleointensity. The hope is that a complete calibration curve, reaching back to 50,000 calendar years B.P., will be presented during the next International Radiocarbon Conference in Oxford, UK, in 2006.

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NEUROSCIENCE

Calcium and CREST for Healthy Dendrites

Gregory S. X. E. Jefferis, Takaki Komiyama, Liqun Luo

Neurons use their spectacular dendritic trees to receive and integrate information from thousands of input neurons. How are these elaborate branching structures built during development? Both intrinsic genetic programs and extrinsic signals are thought to shape the dendritic trees of particular classes of neurons (see the figure) (*1*). Intrinsic factors could be general or class-specific transcription factors that are switched on during neuronal development. These transcription factors may regulate additional molecules such as cell surface receptors that bind to growth and guidance cues. Extrinsic signals include these growth and guidance cues and later may take the form of neuronal activity during the formation of synapses between neurons (synaptogenesis) (*2*). In theory, extrinsic signals could act locally on cytoskeletal dynamics, directly changing the arborization pattern of dendrites. They could also act globally by regulating transcription and thereby driving the production of new proteins. Ghosh and colleagues have shown that dendritic growth of cortical neurons in culture is stimulated by Ca^{2+}-induced transcription (*3*). Now, on page 197 of this issue, they take their work a step further with their identification of CREST (Ca^{2+}-responsive transactivator) as an essential component of the activity-dependent transcriptional response that stimulates dendritic growth (*4*).

Many long-lasting effects of electrical activity on neuronal development and function depend on Ca^{2+}-regulated transcription (*5*). To identify new Ca^{2+}-responsive transcriptional activators, Aizawa *et al.* (*4*) used an interesting expression cloning strategy. Taking advantage of the fact that many transcription factors have separable DNA binding and activation domains, they fused cDNAs from a library made from rat developing brain with the DNA binding domain of the yeast Gal4

The authors are in the Department of Biological Sciences and Neurosciences Program, Stanford University, Stanford, CA 94305, USA. E-mail: lluo@stanford.edu

transcription factor. When transfected into cultured neurons, some fusion proteins (including CREST) caused activation of a Gal4-dependent reporter gene only when the neurons became depolarized. CREST does not possess a DNA binding domain. Rather, it appears to be a transcriptional coactivator that interacts with DNA binding proteins to increase the transcription of target genes.

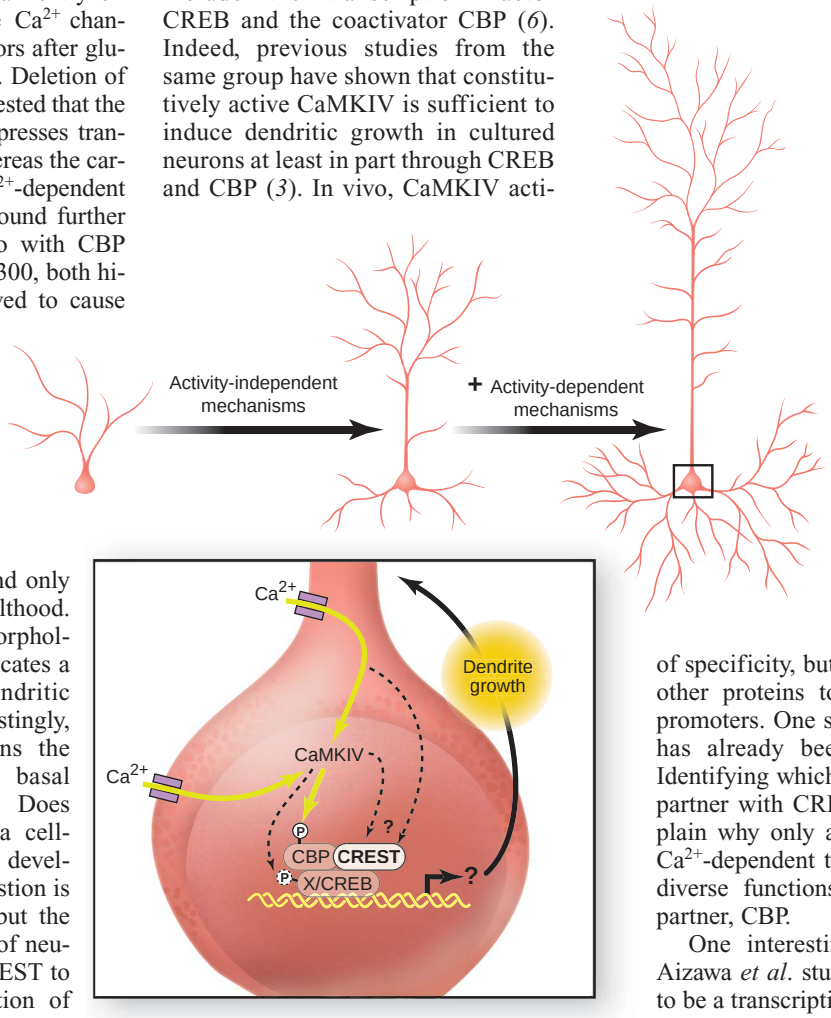
In primary cultured neurons, the CREST-Gal4 fusion protein stimulated transcription in response to Ca^{2+} entry either through voltage-sensitive Ca^{2+} channels or through NMDA receptors after glutamate was applied to neurons. Deletion of different protein domains suggested that the amino terminus of CREST represses transcription in the basal state, whereas the carboxyl terminus mediates Ca^{2+}-dependent activation. Aizawa *et al.* (*4*) found further that CREST interacts in vitro with CBP (CREB binding protein) and p300, both histone acetyltransferases believed to cause transcriptional activation by opening up chromatin.

The evidence that CREST is essential for dendritic development comes from mice that are deficient in CREST. These mice are viable at birth, but their brains are smaller than those of wild-type animals, and only 20% of the mice reach adulthood. Golgi staining to reveal the morphology of individual neurons indicates a substantial reduction in dendritic growth and branching. Interestingly, in cortical pyramidal neurons the deficit appears specific to basal rather than apical dendrites. Does CREST act directly and in a cell-autonomous manner to direct development of dendrites? This question is difficult to address in vivo, but the authors used in vitro cultures of neurons from animals lacking CREST to prove their case. Depolarization of neurons stimulates dendritic growth and branching of cultured cortical neurons from wild-type animals by about threefold. Remarkably, cultured neurons from CREST-deficient animals, while exhibiting comparable dendritic growth and branching under quiescent conditions, fail to show a boost in dendritic growth and branching in response to depolarization. Reintroduction of a CREST transgene into the mutant neurons rescued these defects. So, at least in culture, CREST is required within individual neurons for depolarization-induced dendritic development.

This study raises a number of interesting questions. First, how do Ca^{2+} signals actually activate CREST? Ca^{2+} can regulate the phosphorylation of transcription factors through protein kinases and phosphatases; Ca^{2+} can trigger translocation of transcription factors from the cytosol to the nucleus; it also can bind to and directly activate transcription factors (*5*). One of the best-characterized Ca^{2+} effectors is nuclear Ca^{2+}-calmodulin–dependent kinase IV (CaMKIV). Targets of CaMKIV include the transcription factor CREB and the coactivator CBP (*6*). Indeed, previous studies from the same group have shown that constitutively active CaMKIV is sufficient to induce dendritic growth in cultured neurons at least in part through CREB and CBP (*3*). In vivo, CaMKIV activation is likely to be complemented by sustained MAP kinase signaling (*5*). Is CREST directly regulated by Ca^{2+}? It does not possess a Ca^{2+} binding site, resides solely in the nucleus irrespective of Ca^{2+} levels, and there is no evidence yet that it is regulated by phosphorylation. The only clue comes from its binding to CBP. Might Ca^{2+} activation of CREST actually occur indirectly through CBP and perhaps CREB? This remains a viable hypothesis. Of course, different transcriptional complexes can assemble at different promoters, so the fact that CREB and CBP interact in one context does not mean that they must do so at CREST-regulated genes.

How does CREST regulate transcription of specific genes? Because it does not bind to DNA, it must associate with other transcription factors to achieve this. Aizawa, Ghosh and their colleagues point to the interaction of CREST with the CBP coactivator as a potential source of specificity, but CBP must also rely on other proteins to assemble at specific promoters. One such transcription factor has already been mentioned: CREB. Identifying which DNA binding proteins partner with CREST should help to explain why only a subset of genes show Ca^{2+}-dependent transcription despite the diverse functions of CREST's binding partner, CBP.

One interesting implication of the Aizawa *et al.* study is that there appears to be a transcriptional program dedicated to activity-dependent regulation of dendritic growth. What kind of target genes might CREST regulate to produce these effects? Potential targets for dendritic growth include a diverse array of secreted molecules, cell surface receptors, cytoskeletal regulators, and other signaling proteins (*1*), some of which are known to be Ca^{2+}-dependent (*7*). Recently, other transcription factors have been shown to be intrinsic regulators of different aspects of dendritic development, including dendritic-tree complexity (*8*, *9*) and dendritic-targeting specificity (*10*). How similar are intrinsic and activity-regulated transcription programs? Identifying targets



Ca^{2+} and dendrite development. Early stages of dendrite development depend on the interaction of the intrinsic program within the developing neuron with external guidance cues (activity-independent). At later stages, neuronal activity in the form of depolarization also contributes to dendritic development (activity-dependent). Transcriptional regulation by Ca^{2+} ions that enter the cell during electrical depolarization underlies the long-lasting influences of neuronal activity. In one key signaling pathway, Ca^{2+} activates CaMKIV, which phosphorylates and activates CREB and CBP. Aizawa *et al.* (*4*) identify CREST as a component of a Ca^{2+}-dependent transcriptional complex including CBP and an unknown DNA binding protein (X). This complex activates transcription of target genes that promote dendritic growth.

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of these transcription programs is an important direction for future research. Finally, in addition to developmental expression, CREST is also expressed in a subset of adult neurons implicated in plasticity (*4*). This observation is consistent with the notion that the same molecules and mechanisms that help to build dendritic trees during development might also be used to modify their structures after learning and experience.

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PLANETARY SCIENCE

Weak Faults—Rotten Cores

Robert E. Holdsworth

When Earth's crust deforms, earthquakes can be triggered by displacements along fault zones. Such fault zones can be sites of repeated deformation for hundreds of millions of years, suggesting persistent weakness relative to the adjacent crust. In addition, data on surface heat flow and stress orientations around crustal-scale fault zones such as the San Andreas fault in California indicate that they are much weaker than expected from laboratory models of friction. Yet despite 30 years of research, the causes of the inferred weakness—and even the existence—remain controversial (*1, 2*).

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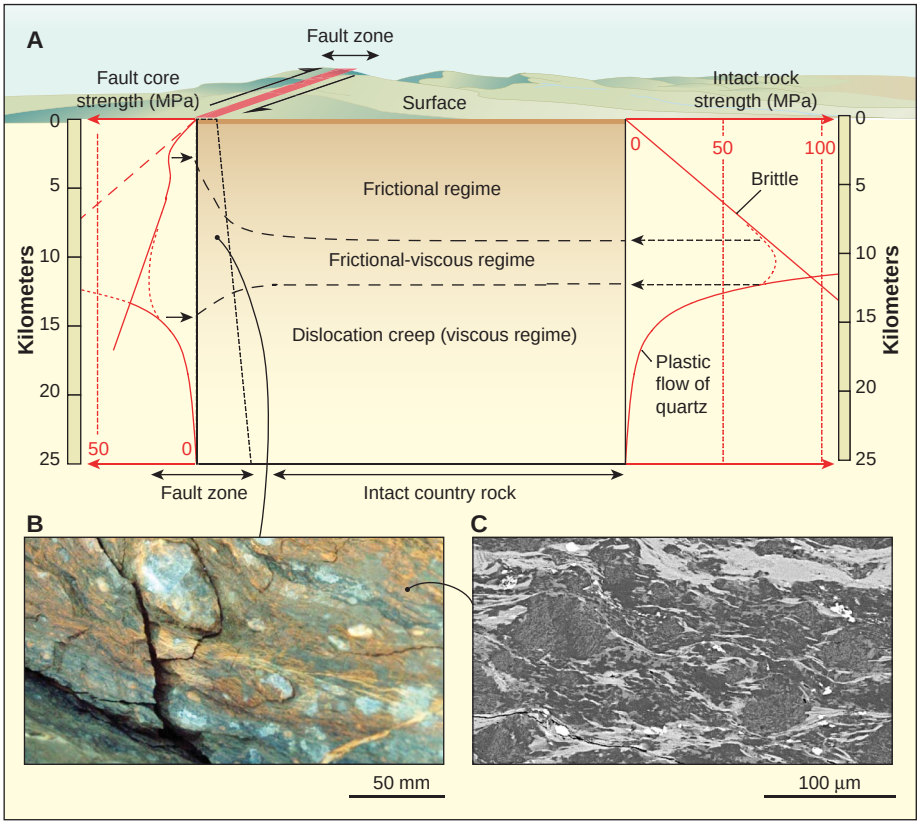
One problem is that much of the geophysical data cited as evidence for weakening lacks sufficient resolution to determine its underlying mechanical causes. Recently, additional insights have been gained from geological studies of ancient fault cores exposed at the surface and laboratory experiments on the deformation of materials that closely resemble fault rocks. These studies reveal that weakening originates at the scale of individual grains in mid-crustal fault networks whose natural interconnectivity then helps to transmit such effects to larger scales.

Two classes of continental faults are particularly likely to be weak over long time scales: low-angle normal faults (*3*) and reactivated faults (*4*). The ancient deep roots of these structures are often exhumed and exposed at the surface by major periods of tectonic activity. Assuming that the ancient examples are representative of what happens at depth today, direct study of weakening mechanisms operating within these faults may be possible, especially where they cut through the main load-bearing region between 5 and 15 km, close to the brittle-plastic transition (see the figure, A, right-side profile) (*5*). Ancient exposed mid-crustal fault cores preserve strikingly similar evidence for grain- and aggregate-scale weakening processes [see (*6*, *7*)].

In the core of the fault where strain is high, "cataclastic" textures indicative of grain-scale brittle crushing are overprinted by and smeared out into low-temperature foliations or mineral alignments suggesting ductile flow (see the figure, B). This results from pervasive fluid influx that alters the load-bearing mineral phases. The alteration produces fine-grained aggregates of weak, platy minerals (micas, clays) that align to form an interconnected network (see the figure, C) (*8*). Fluid influx also triggers widespread stress-induced dissolution-precipitation deformation mechanisms in the preexisting, finely crushed fault rocks. The permanent weakening effect caused by all these processes is vividly illustrated by the preferential localization of most subsequent displacements into the foliated fault cores (*7*).



The microphysics of faults. (**A**) Right side, experimentally derived strength-versus-depth profiles for intact rock (*5*) based on traditional brittle-plastic rheology. Left side, strength profile for a vertical fault, with a broadened mid-crustal "frictional-viscous" regime characteristic of a weak, fluid-infiltrated and altered fault zone (*9*). (**B**) Natural example of brittle cataclasite breccia overprinted by mica-rich foliation, representing a transition to frictional-viscous behavior. (**C**) Scanning electron microscope image of foliated fault rock in which the mica-rich layers formed by alteration of feldspars form an interconnected weak layer at the microscopic scale. Images in bottom panel are of fault rocks from core of Median Tectonic Line, Japan (taken by S. Jefferies and M. Albers).

The author is in the Department of Earth Sciences, University of Durham, DH1 3LE, UK. E-mail: r.e.holdsworth@durham.ac.uk