cally, suppression of MEF2A by RNA interference prevented the formation of dendritic claws, the branched structures positioned at the tips of the short stunted granule cell dendrites. Because granule cells receive the majority of glutamatergic inputs on these dendritic claws, MEF2A-deficient cells receive fewer synaptic inputs than do MEF2A-expressing cells.

These seemingly opposite actions of MEF2 isoforms in hippocampal neurons and cerebellar granule cells are likely caused by differential regulation of MEF2 by two posttranslational modifications: phosphorylation and sumoylation (see the figure). First, both studies suggest a model whereby phosphorylation of a serine residue in MEF2 prevents activation of MEF2 target genes. Calcium influx through NMDA (N-methyl-D-aspartate) receptors as well as through voltage-gated calcium channels activates the phosphatase calcineurin, which in turn dephosphorylates MEF2. This then triggers MEF2-dependent transcription. The MEF2A target genes ultimately mediate synapse disassembly. Shalizi and colleagues suggest that in cerebellar granule neurons, MEF2A may primarily act as a transcriptional repressor. This functional switch from activator to repressor is controlled by a second posttranslational modification: sumoylation. In the phosphorylated form, MEF2A is further modified with a sumo subunit, an 11-kD polypeptide covalently attached to a lysine residue. Shalizi et al. suggest that phosphorylated and sumoylated MEF2A represses transcription of target genes and thereby promotes synaptic differentiation in cerebellar granule neurons. Conversely, either loss of MEF2A expression or MEF2A activity by its desumoylation (and subsequent acetylation) permits transcription of target genes and inhibits postsynaptic differentiation (see the figure). Shalizi et al.’s data suggest that MEF2A is not required for the activation of these synapse-disassembly genes in granule cells, only for their repression. This sumoylation switch might underlie the differential effect of MEF2 on synapse number in cerebellar and hippocampal neurons.

Both studies explored candidate genes that are directly regulated by MEF2. In cultured hippocampal neurons, transcriptionally active (dephosphorylated) MEF2 stimulates expression of SynGAP and Arc, two previously characterized neuronal signaling molecules. In cerebellar granule cells, sumoylated and phosphorylated MEF2A represses transcription of Nur77, which is itself a transcriptional regulator. It is noteworthy that all of these MEF2 targets act as inhibitors of synaptic differentiation, thereby providing a mechanism for the regulation of synapse number through the MEF2-dependent transcriptional program.

These two interesting studies add to earlier studies that explored mechanisms of calcium-dependent transcriptional regulation in developing neurons (2, 8). The exciting new twist in this story is the identification of a calcium-dependent (and hence activity-dependent) transcriptional program that inhibits rather than promotes the formation of synapses. Future work should clarify how synapse-promoting and synapse-inhibiting gene expression programs are coordinated. One attractive hypothesis is that MEF2-dependent gene products pose a homeostatic constraint on activity-dependent synapse formation. Perhaps the MEF2-dependent synapse disassembly pathway balances signals that promote dendritic growth and synapse formation. Alternatively, different calcium-dependent transcriptional programs may be selectively activated depending on the pattern of neuronal activation and intracellular calcium concentrations. A similar mechanism has been previously observed for calcium signaling in different forms of synaptic plasticity (9). Finally, MEF2 target gene products may act differentially on existing synapses by preferentially destabilizing inactive synapses. Such a mechanism would be well suited for sculpting the connectivity pattern of the brain in response to sensory experience and might contribute to the extensive synapse elimination observed during postnatal life.

References

ATMOSPHERIC SCIENCE

The Greenland Ice Sheet and Global Sea-Level Rise

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The flow of several large glaciers draining the Greenland Ice Sheet is accelerating. This change, combined with increased melting, suggests that existing estimates of future sea-level rise are too low.

The Greenland Ice Sheet gains mass through snowfall and loses it by surface melting and runoff to the sea, together with the production of icebergs and melting at the base of its floating ice tongues. The difference between these gains and losses is the mass balance; a negative balance contributes to global sea-level rise and vice versa. About half of the discharge from the ice sheet is through 12 fast-flowing outlet glaciers, most no more than 10 to 20 km across at their seaward margin, and each fed from a large interior basin of about 50,000 to 100,000 km2. As a result, the mass balance of the ice sheet depends quite sensitively on the behavior of these outlet glaciers.

Two changes to these glaciers have been observed recently. First, the floating tongues or ice shelves of several outlet glaciers, each several hundred meters thick and extending up to tens of kilometers beyond the grounded glaciers, have broken up in the past few years (5). Second, measurements of ice velocity made with satellite radar interferometric methods have demonstrated that flow rates of these glaciers have approximately doubled over the past 5 years or so (2, 5). The effect has been to discharge more

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www.sciencemag.org   SCIENCE  VOL 311  17 FEBRUARY 2006  963

10.1126/science.1124541
ice and, thus, to increase the mass deficit of the ice sheet from a little more than 50 km² year⁻¹ to in excess of 150 km² year⁻¹ (2). Increased velocity, combined with rapid dynamic thinning of up to 15 m year⁻¹ that cannot be accounted for by increased melting, may be linked to the loss of the mechanical buttressing effect of the ice tongues (2, 5, 6).

The outlet glaciers in question, including Jakobshavn Isbrae (see the first figure) in the west and Kangerdlugssuag Glacier (see the second figure) on the east coast of Greenland, are all south of 70°N, suggesting that there may be some linkage with changing climate. Satellite data from passive microwave instruments show that there has been a very marked increase in the area affected by summer melting and the length of the melt season on Greenland. Indeed, 2002 and 2005 are records for melt extent over the 27 years of observations (3). With these observations and a meteorological model to retrieve annual accumulation, runoff, and surface mass balance for

of which is derived from flow acceleration. This new information on velocity change more than doubles previous estimates of losses from the ice sheet to the global ocean (6, 7). Future monitoring of the velocity structure of the ice sheet, especially above 70°N where acceleration to date has been limited, is required. It is also necessary to understand better the nature and distribution of precipitation over Greenland. Increased accumulation in the ice-sheet interior, and even in some coastal areas, could offset losses attributable to surface melting at lower elevations (12). Existing and forthcoming satellites will continue to measure ice-surface elevation and any shifts in the rates of surface melting and accumulation. In a warming world, it is likely that the contribution to sea-level rise from Greenland is set to grow further, assuming that the observed acceleration in outlet-glacier velocities is sustained, with possible increases in precipitation providing the only prospect of short-term amelioration.

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