NEUROBIOLOGY

Smells like mitochondria

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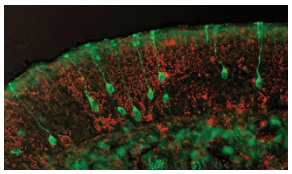

In olfactory sensory neurons (OSNs), activation of odorant receptors results in increased intracellular Ca^{2+} (Ca^{2+}) concentration, whereas termination of the response depends on the clearance of the excess Ca^{2+}. The tight regulation of cytosolic (Ca^{2+}_c) concentration is known to be critical for both the gain and subsequent adaptation to the odor sensation. Now, Fluegge *et al.* report that mitochondrial Ca^{2+} (Ca^{2+}_m) has a buffering role in the regulation of the olfactory response. Using bioluminescence to monitor a mitochondrial matrix–targeted, Ca^{2+}-sensitive photoprotein in genetically engineered mice, the authors observed an accumulation of Ca^{2+} in the mitochondria of the main olfactory epithelium upon odor exposure. Targeting of the mitochondrial inner membrane potential by a protonophore or a respiratory chain blocker caused alterations in Ca^{2+}_c fluctuations during the odor response, underlining the connection between the two pools of Ca^{2+}. Electrophysiology experiments in OSNs under conditions of impaired Ca^{2+}_m uptake showed that Ca^{2+}_m mobilization is important for mediating the sensitivity to a broad range of odor intensities but not for odor adaptation. In agreement with their indispensable role in odor sensation, mitochondria were dynamically recruited to OSN dendritic knobs upon odor stimulation. Altogether, this study revealed a previously uncharacterized role of Ca^{2+}_m in the broad response range and the sensitivity to odor sensation. *AC*

METABOLIC ENGINEERING

Assembling activity

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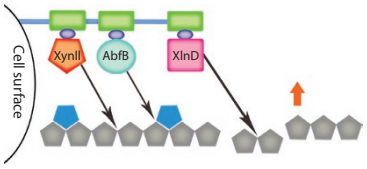

Multienzyme complexes organize enzymatic functions into defined architectures to speed transfer of intermediates and facilitate specialized reactions. The cellulosome assembles cellulose-degrading enzymes on the cell surface using a scaffoldin protein containing cohesin domains to anchor enzymes. Sun *et al.* now explore the portability of this system as well as the differential ability of two scaffoldins to assemble a 'minihemicellulosome' capable of degrading arabinoxylan and birchwood xylan into xylose. The authors generated strains expressing one or more of the hemicellulose-degrading enzymes XynII (an *endo*-1,4-β-xylanase), XlnD (a β-xylosidase) and AbfB (an α-L-arabinofuranosidase) as well as the scaffoldin CipA1, which contains a single cohesin domain, or CipA3, which contains three cohesin domains. Xylan degradation increased with increasing numbers of enzymes when they were displayed on the multi-cohesin CipA3, but the display of individual enzymes mediated by CipA1 did not yield the same increases in activity. AbfB function was particularly dependent on assembly, with the CipA1 display of all three enzymes only as effective as either the bifunctional XynII-XlnD CipA3 construct or the combined display of XynII and XlnD by CipA1. Integration of the XynII-XlnD CipA3 construct into a xylose-utilizing *Saccharomyces cerevisiae* strain allowed conversion of birchwood xylan into ethanol, yielding 0.31 g ethanol per g xylan consumed. These results set the stage for further explorations of the role of molecular organization in enzyme function. *CG*

STEM CELLS

Imatinib gets beta

Cell Stem Cell **10**, 412–424 (2012)

β-catenin, a central effector in the Wnt signaling pathway, is important for self-renewal in fetal but not adult hematopoietic stem cells. However, it is not known whether β-catenin is important for renewal of leukemia stem cells (LSCs) in BCR-ABL–induced leukemia. Imatinib, a first-line therapy for patients with BCR-ABL–induced leukemia, yields high rates of remission, but relapse often occurs, possibly because LSCs are resistant to imatinib. Heidel *et al.* now investigate whether β-catenin is required for LSC maintenance. In two mouse models, conditional genetic inactivation of the gene encoding β-catenin after engraftment of BCR-ABL–transformed LSCs did not affect the survival of the mice but reduced the number of LSCs. To determine whether β-catenin can affect disease progression in response to imatinib, the authors used genetic and chemical approaches to alter the amount of β-catenin. Indomethacin, an inhibitor of cyclooxygenase, decreased the amount of β-catenin alone and in combination with imatinib, whereas BIO, a GSK3β inhibitor, stabilized β-catenin in BCR-ABL–positive human cells or cells derived from the bone marrow of mouse models. Cells treated with indomethacin but not BIO had reduced colony formation compared to controls. Treatment of mice with imatinib and indomethacin resulted in fewer LSCs, delayed onset of disease and increased survival compared to animals treated with imatinib alone. Taken together, these data indicate that inhibiting β-catenin in combination with imatinib may provide an opportunity to eradicate LSCs. *AD*

RNA TRANSPORT

An hnRNP ruler

Science **335**, 1643–1646 (2012)

RNAs are synthesized by common transcriptional pathways but are trafficked to their cellular destinations by various RNA transport machineries. For instance, both spliceosomal U small nuclear RNAs (snRNAs) and mRNAs are transcribed by RNA polymerase II and undergo 5′-terminal capping, which is recognized by cap-binding complex (CBC). Their journeys then diverge, with snRNA trafficking in the nucleus being initiated by the phosphorylated adapter RNA export protein (PHAX) and mRNA export out of the nucleus being coordinated by RNA-binding adaptors such as Aly/REF. Previous studies have suggested that the transcript's length—with snRNAs typically being shorter than mRNAs—rather than its sequence controls the choice of RNA transport pathway. McCloskey *et al.* now identify a heterogeneous nuclear ribonucleoprotein (hnRNP) that serves as a 'molecular ruler' for RNA transport pathway selection. Using a biochemical approach, the authors purified a heterotetrameric complex of hnRNP C1/C2 (hnRNP C), which simultaneously binds larger RNAs (>200–300 nucleotides) and a subunit of their associated CBCs, an interaction that blocks PHAX binding. This assembly was validated in cells by showing that hnRNP C knockdown led to enhanced PHAX binding to RNA–CBC complexes and increased nuclear retention of mRNA constructs without affecting pre-mRNA splicing. Taken together, these observations suggest a model in which hnRNP C selectively binds longer RNAs and shunts them toward mRNA export pathways. *TLS*