IN BRIEF

NEURODEGENERATIVE DISEASE

BACE1 deficiency rescues memory deficits and cholinergic dysfunction in a mouse model of Alzheimer's disease.

Ohno, M. *et al. Neuron* **41**, 27–33 (2004).

BACE1 has been identified as one of two key proteases that cleave the amyloid precursor protein to generate the Aβ peptide thought to be central to the pathogenesis of Alzheimer's disease (AD). The development of BACE1 inhibitors as potential therapeutics for AD is supported by this study, which provides the first demonstration that *BACE1* gene deletion can rescue memory deficits in an AD animal model by lowering brain Aβ levels.

STRUCTURAL GENOMICS

Rapid refinement of crystallographic protein construct definition employing enhanced hydrogen/deuterium exchange MS.

Pantazatos, D. *et al. Proc. Natl Acad. Sci. USA* **101**, 751–756 (2004).

Unstructured regions of proteins are an important factor in the frequent failure of efforts to produce protein crystals suitable for structure determination by X-ray crystallography. Removing these regions can help address this issue. Pantazatos *et al.* describe the application of a general approach to identify these unstructured regions, and show that it can aid the high-throughput production of derivatives of poorly crystallizing proteins that show greatly improved crystallization.

CARDIOVASCULAR DISEASE

A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease.

Stone, G. W. *et al. N. Engl. J. Med.* **350**, 221–231 (2004).

Implantation of coronary stents is commonly used to relieve an obstruction due to atherosclerosis, but restenosis — re-narrowing at the site at which treatment was performed — still occurs in a significant number of patients, often necessitating repeated revascularization procedures. As a key cause of such restenosis is the proliferation and migration of smooth-muscle cells, this large-scale trial assessed a stent that slowly released the cytotoxic drug paclitaxel, and found that it was safe and that it markedly reduced the rates of restenosis compared with bare-metal stents.

REGENERATIVE MEDICINE

Dedifferentiation of lineage-committed cells by a small molecule.

Chen, S. *et al. J. Am. Chem. Soc.* **126**, 410–411 (2004).

The potential of progenitor cells in cell-replacement therapy — for example, in neurodegenerative diseases — has attracted considerable attention, but a key problem is obtaining appropriate cells. The ability to dedifferentiate lineage-committed cells might overcome this problem, and Chen *et al.* have identified a small molecule that causes mouse muscle cells to dedifferentiate into progenitor cells, which can then redifferentiate into bone or fat cells.

RESPIRATORY DISEASES

Hitting the MARCKS

Since discovering that myristoylated, alanine-rich C-kinase substrate (MARCKS) protein is required for secretion of mucin (the glycoprotein component of mucus) from cultured human epithelial cells, Kenneth Adler and his team have been searching for a means of inhibiting this process *in vivo*. Success would pave the way for the development of therapies to control the mucus hypersecretion that is a hallmark of pulmonary diseases such as asthma, chronic bronchitis and cystic fibrosis. A recent advanced online publication in *Nature Medicine* describes the first step on this path.

In a previous *in vitro* study, Adler and colleagues showed that an N-terminal 24-amino-acid fragment of MARCKS, known as MANS, attenuated mucin secretion in a concentration-dependent manner, presumably by competitively inhibiting the binding of MARCKS to the membranes of mucin-secreting granules within epithelial cells. Now the team has shown that intratracheal instillation of MANS blocks mucus hypersecretion in a mouse model of asthma.

Mucin secretion at rates fivefold greater than baseline was elicited in ovalbumin-sensitized mice by administration of aerosolized methacholine. Pretreatment with MANS inhibited this hypersecretory response in a concentration-dependent manner, whereas a missense N-terminal sequence of MARCKS had no effect. Basal levels of mucin secretion in non-methacholine-exposed mice were also lowered by MANS treatment.

Histological sections of bronchi from MANS-pretreated, methacholine-exposed mice revealed that mucin was retained in epithelial cells, rather than being released into the lumen as was the case in methacholine-challenged controls. On the basis of ultrastructural evidence showing an association of MARCKS with mucin granule membranes and the inhibition of this interaction by MANS peptide, the authors propose that MARCKS guides mucin granules during the secretory process by physically linking the granule membranes to the cytoskeleton. These findings validate a new target for the treatment of mucus hypersecretion, for which there is presently no effective therapy.

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References and links

ORIGINAL RESEARCH PAPER Singer, M. *et al.* A MARCKS-related peptide blocks mucus hypersecretion in a mouse model of asthma. *Nature Med.* 11 January 2004 (doi:10.1038/nm983)

FURTHER READING Li, Y. *et al.* MARCKS protein is a key molecule regulating mucin secretion by human airway epithelial cells *in vitro*. *J. Biol. Chem.* **276**, 40982–40990 (2001) | Corry, D. B. Emerging immune targets for the therapy of allergic asthma. *Nature Rev. Drug Discov.* **1**, 55–64 (2002)