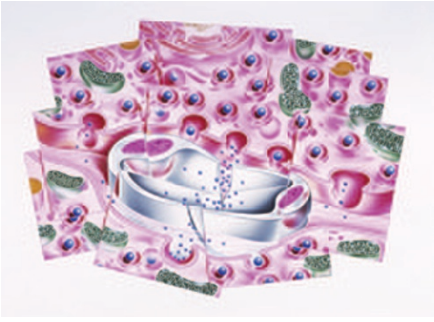
A new β cell model

The derivation of a human pancreatic beta cell line has been a heroic but elusive quest. Such a line would be a valuable tool to study normal beta cell function, model cell replacement therapy for diabetes and use in drug screening. Now, Philippe Ravassard and his colleagues (*J. Clin. Invest.* **121**, 3589–3597) finally describe the derivation of functional beta cells.

The authors used a sequential method, transducing human fetal pancreases with an immortalizing factor to prevent senescence and then grafting them into severe combined immunodeficiency (SCID) mice, which allowed proliferation and differentiation into beta cells. A second round of transduction with a different immortalizing factor and passaging through SCID mice enabled the authors to amplify the beta cells and subsequently culture them.

Ravassard *et al.* analyzed one of their cell lines and found it expressed characteristic beta cell markers and did not show significant expression of markers associated with other types of pancreatic cells. Moreover, the beta cells could secrete insulin in response to glucose stimulation and ameliorated chemically induced diabetes in a mouse model, demonstrating functionality. Thus, the derivation of this new beta cell line represents an important technical step forward. —*MS*



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■ GENETIC DISEASE

GRASPing mutant CFTR

The ΔF508 mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) is the most common disease-causing mutation found in people with cystic fibrosis, as, despite being functional, the ΔF508 CFTR protein cannot reach the cell surface. A new study shows that the activation of an unconventional secretion pathway mediated by Golgi reassembly stacking proteins (GRASPs) allows the transport of both this mutant and wild-type CFTR to the plasma membrane (*Cell* **146**, 746–760).

The misfolded ΔF508 CFTR usually remains a core-glycosylated immature form in the endoplasmic reticulum (ER) and cannot be secreted through the Golgi-mediated exocytic pathway. Heon Yung Gee and colleagues showed that this protein reached the membrane after blocking ER-to-Golgi trafficking *in vitro*. This transport route was mediated by inositol-requiring protein 1 (IRE-1), which activates the unfolded protein response (UPR). Using knockout and overexpression strategies in cultured cells, the authors found that GRASPs were required for this unconventional transport route. Interestingly, GRASP upregulation rescued the mutant CFTR without inducing the ER stress–mediated UPR, but IRE-1 was still needed for the phosphorylation and activity of GRASP. In mice harboring the ΔF508 CFTR mutation, transgenic expression of GRASP rescued the apical expression of the misfolded CFTR and increased survival.

Although rescue of ΔF508 CFTR through GRASP upregulation may be a potential drug strategy to treat cystic fibrosis, it remains to be shown whether other means of GRASP activation can recapitulate this effect in other *in vivo* models of cystic fibrosis. —*CP*

■ INFECTION

Hijacking an antibody

Genetic mutations often drive viral escape from antibody-mediated neutralization. A new study describes an alternative form of resistance where human cytomegalovirus (CMV) incorporates the antibody and uses it to subsequently infect new cells.

The human monoclonal IgG MSL-192 recognizes the viral glycoprotein H (gH) and blocks infection of fibroblasts with CMV *in vitro*. Clinical trials with MSL-109 were halted due to insufficient efficacy in treating patients with AIDS and CMV-induced retinitis.

Kate Manley *et al.* (*Cell Host Microbe* **10**, 197–209) found that, following multiple rounds of infection *in vitro*, an MSL-109–resistant CMV strain emerged. This resistance was reversible and was not associated with genetic changes. Instead, the antibody was taken up by CMV-infected cells. Once inside the cell, it interacts with gH and is incorporated into assembling virions during their maturation. The Fc domain of the incorporated MSL-109 is then used by CMV to infect nonimmune cells. Although the precise details of viral entry remain unclear, these findings provide insight into a previously undescribed mechanism of viral escape. —KDS

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New from NPG

Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy
Sigal, A. *et al. Nature* **477**, 95–98 (2011).
The authors propose a model to explain how an HIV reservoir can be maintained even in the face of antiretroviral therapy, via cell-to-cell spread of the virus, which could result in multiple viral infections per cell. They also provide evidence to support their model *in vitro*.

Genome-wide association study identifies five new schizophrenia loci
The Schizophrenia Psychiatric GWAS Consortium. *Nat. Genet.* doi:10.1038/ng.940 (18 September).

Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near *ODZ4*
Psychiatric GWAS Consortium Bipolar Disorder Working Group. *Nat. Genet.* doi:10.1038/ng.943 (18 September).
Two studies identify new genetic variants associated with the psychiatric disorders schizophrenia and bipolar disorder. In the first, the authors perform a meta-analysis to identify five new loci associated with schizophrenia, and, in a second study, a genome-wide association study approach is used to identify a bipolar-associated variant in the *ODZ4* gene.

Proteomic and phosphoproteomic comparison of human ES and iPS cells
Phanstiel, D.H. *et al. Nat. Meth.* doi:10.1038/nmeth.1699 (11 September).
The authors use a high-resolution mass spectrometry approach to compare the proteomes of four human embryonic stem cell lines and four induced pluripotent cell lines and show small differences in the protein expression between the two types of cells, further supporting the idea that iPS cells might 'remember' features of the original cells that they were derived from.

The antiviral factor APOBEC3G enhances the recognition of HIV-infected primary T cells by natural killer cells
Norman, J.M. *et al. Nat. Immunol.* doi:10.1038/ni.2087 (28 August).
An intrinsic antiviral mechanism is characterized in which the cytidine deaminase APOBEC3G leads to upregulation of ligands recognized by the natural killer (NK) cell-activating receptor NKG2D in HIV-infected cells, thus stimulating destruction of the infected cells by NK cells.