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In This Issue

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A detour for stalled intracellular lipid traffic (See article on pages 1541–1550.) The NPC1 protein, which is defective in the glycosphingolipid (GSL) storage disease Niemann-Pick disease type C (NP-C), resides in the cell's endosomes, Golgi stacks, and lysosomes. Defects in this protein cause free cholesterol, rather than cholesterol esters (CEs), to accumulate in these organelles and interfere with the normal routing of internalized GSLs to the Golgi apparatus. Pagano's group has found that the normal Golgi trafficking of GSLs involves caveolae or some similar specialized membrane domain and differs from the better-known mechanism involving clathrin-coated vesicles, which is used by other endocytosed lipids and proteins. How NPC1 defects affect this caveolar pathway is uncertain, but these authors have proposed that high intracellular cholesterol levels interfere with the normal flux of vesicles through the Golgi apparatus and the endosomes. The current work by Choudhury et al. demonstrates that a previously unsuspected detour can be found around this intracellular roadblock. These authors have studied the biochemical requirements for intracellular transport of fluorescent lipid analogs, and they have implicated two small GTP binding proteins, Rab7 and Rab9, in the clathrin-independent trafficking of GSLs. Overexpression of either protein not only restores their normal patterns of GSL trafficking in NP-C cells, but also reverses their abnormal accumulation of free cholesterol. These molecules thus appear to […]

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The NPC1 protein, which is defective in the glycosphingolipid (GSL) storage disease Niemann-Pick disease type C (NP-C), resides in the cell's endosomes, Golgi stacks, and lysosomes. Defects in this protein cause free cholesterol, rather than cholesterol esters (CEs), to accumulate in these organelles and interfere with the normal routing of internalized GSLs to the Golgi apparatus. Pagano's group has found that the normal Golgi trafficking of GSLs involves caveolae or some similar specialized membrane domain and differs from the better-known mechanism involving clathrin-coated vesicles, which is used by other endocytosed lipids and proteins. How NPC1 defects affect this caveolar pathway is uncertain, but these authors have proposed that high intracellular cholesterol levels interfere with the normal flux of vesicles through the Golgi apparatus and the endosomes. The current work by Choudhury et al. demonstrates that a previously unsuspected detour can be found around this intracellular roadblock. These authors have studied the biochemical requirements for intracellular transport of fluorescent lipid analogs, and they have implicated two small GTP binding proteins, Rab7 and Rab9, in the clathrin-independent trafficking of GSLs. Overexpression of either protein not only restores their normal patterns of GSL trafficking in NP-C cells, but also reverses their abnormal accumulation of free cholesterol. These molecules thus appear to be limiting for caveolar endocytosis in the mutant cells, suggesting that treatments that increase their activity could reverse the cellular phenotype in NP-C.

The MAP kinase pathway in coxsackievirus infections

(See article on pages 1561–1569.)

Heritable biochemical idiosyncrasies are thought to help explain the variable outcome when individuals in the outbred human population are exposed to pathogens. However, even in relatively tractable mouse models, there are surprisingly few clear examples of biochemical differences that can account for the characteristic sensitivity of some inbred strains to specific viruses. The coxsackievirus studied here by Opavsky et al. can infect lymphocytes and macrophages, as well as myocytes and other cell types in many organs. In some humans and in particular strains of mice, infection of the heart provokes dilated cardiomyopathy and can lead to heart failure. Earlier work showed that the MAP kinase signaling is induced by infection and suggested that this pathway might contribute to efficient viral replication. The authors have now identified signaling molecules essential for viral infection in vitro, including the kinase $p56^{Lck}$, which mediates signals from the T cell receptor, and the Erk kinases, which act downstream of $p56^{Lck}$ in T cells and activate the MAP kinase pathway in many cell types. Drugs and genetic lesions that block this signaling pathway prevent viral replication in cultured cardiomyocytes and T cell lines. Opavsky et al. show here that viral infection correlates with ERK activation in vivo as well, since a mouse strain that is insensitive to the cardiac disease shows markedly reduced ERK activation following exposure to the virus relative to another, sensitive strain. The genetic differences underlying the distinct biochemical phenotypes of these strains remain to be discovered.

Beyond Copolymer 1

(See article on pages 1635–1643.)

Copolymer 1, also called glatiramer acetate, is an unusual therapeutic compound, a heterogeneous mix of polypeptides containing the four amino acids Y, E, A, and K in definite ratios but with no uniform sequence. Although its mode of action remains controversial, this preparation clearly helps retard the progression of human multiple sclerosis (MS) and of the related autoimmune condition, studied in mice, experimental autoimmune encephalomyelitis (EAE). Copolymer 1 is presented on class II MHC molecules, including the HLA-DR2 type that is associated with increased risk of MS. This MHC molecule binds a defined auto-epitope from myelin basic protein (MBP) and presents it to CD4 T cells, initiating an immune response against myelin in the CNS. Fridkis-Hareli et al. reexamined the structure of the DR2 peptide-binding groove and concluded that the selection of amino acids used in Copolymer 1 was far from optimal if the goal was to compete against presentation of MBP peptides. Here they show that YFAK and FAK copolymers, among others, bind DR2 with higher affinity than does YEAK (Copolymer 1), allowing them to compete successfully against an endogenous autoantigenic peptide. These formulations were more effective than Copolymer 1 at suppressing the activation of T cells bearing DR2-restricted, MS patient–derived T cell receptors. Crucially, the novel copolymers were also dramatically more effective at suppressing EAE. Thus, mice injected with either a defined antigenic peptide or whole spinal cord homogenate normally initiate inflammatory and cytolytic responses in the CNS. While Copolymer 1 reduced the incidence of this disease and delayed its onset in most cases, several of the novel copolymers prevented it entirely. Given the precedent of Copolymer 1's safety and efficacy in people with MS, the use of other copolymers, perhaps optimized to target an individual's MHC haplotype, seems an attractive scenario for MS and perhaps other autoimmune diseases.