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In This Issue

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Post-transcriptional regulation of COX-2 in tumor cells (See article on pages 1657–1665.) Cyclooxygenase-2 (COX-2), which acts in many pathological states as the rate-limiting enzyme in prostaglandins biosynthesis, is proposed to promote tumor progression at several stages. Prostaglandins apparently not only drive the initial formation of certain pre-cancerous lesions, but also support the development of blood vessels that permit tumor growth and the phenotypic changes that result in metastasis. Much of the analysis of COX-2 regulation has focused on transcriptional control, but Dixon and coworkers now show that post-transcriptional effects may be equally important. The COX-2 mRNA, like other gene products that require rapid induction and repression, carries an A/U-rich element (ARE), a cis-acting RNA-destabilizing sequence. Dixon et al. compared the expression of this mRNA in two different human colon carcinoma cell lines, and they report here that the more aggressively tumorigenic line, HT29, expresses greatly elevated levels of the COX-2 message relative to the slower growing LoVo cell line. This difference can be ascribed to an increase in mRNA stability, not an increase in transcription rate; on the contrary, the COX2 promoter is far more active in the cells with low steady-state levels of COX-2 mRNA. Dixon et al. attribute the specific stabilization of the message to the expression of the RNA-binding protein HuR, which interacts specifically with AREs of […]

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Optimizing antiviral peptide vaccines

(See article on pages 1677–1685.)

Costimulatory receptors on T cell surface modulate the signaling pathways that activate lymphocytes against specific antigens, often with profound effects on the ultimate host response. Ahlers et al. have followed the immune cell interactions that lead to the development of antiviral immunity in animals vaccinated with an HIV peptide. These interactions, occurring between antigen-presenting dendritic cells (DCs) and antigen-specific Th cells and cytotoxic T lymphocytes (CTLs), are altered fundamentally depending on whether the co-stimulatory protein CD40L is induced on Th cells. The authors compare the effects of two, nearly identical peptide vaccines. One carries an HIV surface epitope linked to a helper peptide that binds a known Class II MHC molecule, while the other contains a single amino acid substitution in the helper peptide. This subtle change, which retains the antigenic sequence but increases the peptide's affinity for the MHC molecule, was previously shown to yield a more vigorous CTL response against the HIV sequence. Ahlers et al. now show that the tighter binding activates CD40L expression and results in a qualitatively different response to the vaccine—one in which Th cells are induced to express Th1-type cytokines, thus supporting CTL activity. The native peptide sequence, in contrast, yields a mix of Th1- and Th2-type cytokines and a weak CTL response. If such enhanced epitopes can be shown to activate costimulatory pathways and to increase Th1 polarization in other settings, this work could provide an important strategy for improving peptide vaccines.

Phenotypic variability in cystic fibrosis

(See article on pages 1705–1715.)

Cystic fibrosis (CF) is among the best studied and most common autosomal recessive disorders. Although CF is often described as a simple Mendelian trait, the clinical variability seen among patients hints at genetic or environmental modifiers. In particular, while CFTR, the chloride channel missing in affected individuals, is normally expressed in a number of epithelia in addition to the lung, not all patients with lung disease develop symptoms in the intestine or elsewhere. Some of the phenotypic variability results from the presence of different disease alleles, but, as Bronsveld and colleagues note, a great deal of variability persists even among people carrying a single allele in homozygous form. The authors worked with sets of affected twins and other sib pairs in which both siblings were homozygous for the most common *CFTR* allele, ΔF508. This mutation causes the CFTR to be retained and degraded intracellularly, but some molecules apparently reach the cell surface and may explain the "leakiness" of the phenotype in certain individuals' tissues. Electrophysiological measurements in the respiratory tract and in intestinal biopsies confirm that high residual channel activity characteristic of CFTR is a reasonable predictor of mild disease. Such residual activity is often concordant between identical twins but less so between other siblings, implying that this cellular feature is under independent genetic control and that genes other than *CFTR* influence the clinical presentation of CF.