

## In This Issue

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Function follows form in developing myocytes (See article on pages 1321–1330.) Cells undergo complex changes in morphology and gene expression as they differentiate, but the relationship between these changes has long been obscure, with hints that cell shape per se can control cellular patterns of gene expression in some cases. Yang et al. now offer a novel example of such control, as well as welcome insights into its molecular basis. Smooth muscle cell precursors become stretched as fluid accumulates in the lumen of the developing lung, and the authors show that this mechanical deformation is sufficient to induce the expression of several differentiation-dependent smooth muscle cell proteins. Stretching of cells, whether they are plated in two dimensions on an elastic membrane or maintained in three dimensions in organ culture, induces mRNAs for smooth muscle  $\alpha$ -actin and other gene products that are under control of the transcription factor serum response factor (SRF). SRF is alternatively spliced to generate an active isoform and a dominant negative isoform called SRF $\delta$ 5, both of which are expressed in smooth muscle cell precursors. Yang and colleagues show that stretch rapidly alters this splicing pattern such that only the active isoform is generated, thus inducing the expression of SRF target genes. After analyzing lung tissue from human infants that had died perinatally with hypoplastic lungs, the authors [...]

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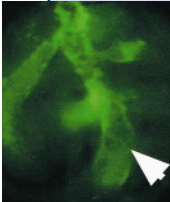


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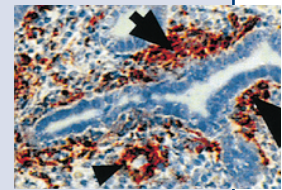
By John Ashkenas, Science Editor

## Function follows form in developing myocytes

(See article on pages 1321–1330)



Cells undergo complex changes in morphology and gene expression as they differentiate, but the relationship between these changes has long been obscure, with hints that cell shape per se can control cellular patterns of gene expression in some cases. Yang et al. now offer a novel example of such control, as well as welcome insights into its molecular basis. Smooth muscle cell precursors become stretched as fluid accumulates in the lumen of the developing lung, and the authors show that this mechanical deformation is sufficient to induce the expression of several differentiation-dependent smooth muscle cell proteins. Stretching of cells, whether they are plated in two dimensions on an elastic membrane or maintained in three dimensions in organ culture, induces mRNAs for smooth muscle  $\alpha$ -actin and other gene products that are under control of the transcription factor serum response factor (SRF). SRF is alternatively spliced to generate an active isoform and a dominant negative isoform called SRF $\Delta$ 5, both of which are expressed in smooth muscle cell precursors. Yang and colleagues show that stretch rapidly alters this splicing pattern such that only the active isoform is generated, thus inducing the expression of SRF target genes. After analyzing lung tissue from human infants that had died perinatally with hypoplastic lungs, the authors conclude that the same pathway exists in human lung development. They suggest that low intrapulmonary hydrostatic pressure, as occurs in fetuses with oligohydramnion, prevents the cellular shape change that allows for normal smooth muscle myogenesis in the lung.



## Recombinant yeast as an antifungal vaccine

(See article on pages 1381–1389)

Despite the long and successful history of vaccine use, primarily for viral diseases, fungal pathogens have only rarely been considered as targets for vaccination. To date, only one antifungal vaccine, designed to prevent ringworm in cattle, has progressed beyond the experimental stage. Wüthrich et al. now describe the use of a live attenuated strain of *Blastomyces dermatitidis* to prevent blastomycosis, an often-fatal yeast infection of the lung. Mice immunized with killed wild-type *B. dermatitidis* mount an immune response to one of its major cell surface adhesion proteins, WI-1, but they are only weakly protected when challenged with the live pathogen. Wüthrich and coworkers previously took advantage of the tractable genetics of this yeast to create a strain lacking the *WI-1* gene, showing that this strain could not propagate or cause disease in mice. Here, they report that live *WI-1*<sup>-</sup> yeast provoke a T-cell response that protects inoculated animals from infection with wild-type *B. dermatitidis*. Crucially, this protection applies not only against yeast that are isogenic to the attenuated strain, but also to several unrelated pathogenic isolates. The authors also show that fungal cell wall preparations derived from the *WI-1*<sup>-</sup> strain also protect mice from lung infections, raising the possibility that, as with the live attenuated organism, one or more purified fungal components could be used as an effective vaccine.

## Two routes to FAK activation and cancer cell migration

(See article on pages 1399–1407)

The focal adhesion kinase (FAK) is one of the first intracellular proteins to be activated when cells reorganize their cytoskeleton during adhesion, and changes in FAK distribution and activity mediate the shift of cancer cells to a migratory phenotype. Working with cultured prostrate cancer cells, Sumitomo and coworkers have now identified a dual pathway by which the cell surface transmembrane proteinase neutral endopeptidase (NEP) regulates FAK phosphorylation and cell migration. Neuropeptides such as bombesin, acting through their receptors on the surface of responsive cells, stimulate the kinase c-Src to phosphorylate FAK. NEP is known to cleave these neuropeptides, and Sumitomo et al. confirm that overexpressing NEP blocks this pathway. Surprisingly, however, a mutant form of NEP that is inactive as a proteinase still blocks FAK phosphorylation and cell migration. The authors suggest that this residual activity depends on interactions between the cytoplasmic tail of NEP and two other cytoplasmic factors that otherwise bind and phosphorylate FAK. This c-Src-independent pathway may account for other recent data indicating that catalytically inactive NEP retains some biological activity.