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In This Issue

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P. aeruginosa in the CF lung (See article on pages 317–325.) Cystic fibrosis (CF) is life-threatening primarily because the lungs of affected individuals are subject to persistent and intractable infections, typically with Pseudomonas aeruginosa. The properties of the tracheal fluids that support these infections in CF patients have been a matter of debate, which has generated considerable interest in the ionic strength and volume of airway surface liquid (ASL) in healthy and CF lungs. Surprisingly, less attention has been paid to the properties of P. aeruginosa itself as it exists within the airway epithelium. Worlitzsch and coworkers show here that these bacteria do not adhere directly to the epithelial layer but can be found within the ASL in intact lungs, as well as within the mucus layer secreted by cultured respiratory epithelia. The authors also show that the thickened ASL in the lungs of CF patients is markedly anoxic, relative to that of healthy individuals or of patients with primary ciliary dyskinesia, another condition that leads to frequent bacterial infections. Although P. aeruginosa is an aerobic bacterium, this low oxygen level is not sufficient to prevent its growth, apparently because the ASL contains nitrates or other electron acceptors that can substitute for molecular oxygen. However, hypoxia induces a stress response in the bacteria, promoting a mucoid phenotype. As has been […]

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By John Ashkenas, Science Editor

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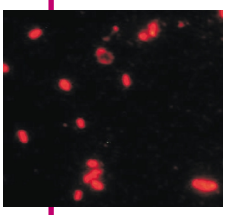
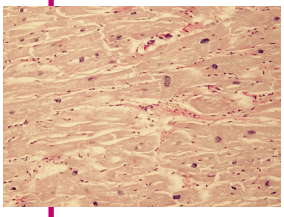
Cystic fibrosis (CF) is life-threatening primarily because the lungs of affected individuals are subject to persistent and intractable infections, typically with *Pseudomonas aeruginosa*. The properties of the tracheal fluids that support these infections in CF patients have been a matter of debate, which has generated considerable interest in the ionic strength and volume of airway surface liquid (ASL) in healthy and CF lungs. Surprisingly, less attention has been paid to the properties of *P. aeruginosa* itself as it exists within the airway epithelium. Worlitzsch and coworkers show here that these bacteria do not adhere directly to the epithelial layer but can be found within the ASL in intact lungs, as well as within the mucus layer secreted by cultured respiratory epithelia. The authors also show that the thickened ASL in the lungs of CF patients is markedly anoxic, relative to that of healthy individuals or of patients with primary ciliary dyskinesia, another condition that leads to frequent bacterial infections. Although *P. aeruginosa* is an aerobic bacterium, this low oxygen level is not sufficient to prevent its growth, apparently because the ASL contains nitrates or other electron acceptors that can substitute for molecular oxygen. However, hypoxia induces a stress response in the bacteria, promoting a mucoid phenotype. As has been seen in other bacterial species, this transition may allow the bacteria to evade host defenses and even survive exposure to antibiotics. Worlitzsch et al. suggest that the growth of hypoxia-tolerant bacteria further depletes the oxygen, thus maintaining the ASL in the hypoxic state that appears to be characteristic of the CF lung.



A novel cardiac glycogen storage disease

(See article on pages 357–362.)

Glycogen storage disorders are inborn errors of metabolism that typically affect the cellular architecture and function of the liver or kidney. However, some of these diseases manifest in skeletal or cardiac myocytes, where they lead to altered electrophysiological responses, muscle weakness, and hypertrophy. Arad et al. show here that a cardiac-specific glycogen storage disease occurs in individuals with any of 3 dominantly acting missense mutations affecting conserved residues in *PRKAG2*. This gene encodes a regulatory subunit of AMPK, the AMP-activated protein kinase. Like its yeast homolog, Snf4, PRKAG2 apparently regulates glucose metabolism by associating with AMPK's catalytic subunits. By introducing the human disease mutations into Snf4, the authors show here that the changes render the regulatory subunit constitutively active, causing it to bind to a catalytic subunit even in cells that are supplied abundant glucose. Interestingly, one of the *PRKAG2* mutations has been found previously in the related gene *PRKAG3*, where it causes a skeletal muscle-specific defect of domesticated pigs. Despite some similarities with diseases linked to sarcomere protein genes, which also present with cardiac hypertrophy, Arad et al. note that this glycogen storage disease has a different etiology and does not disrupt the structure of cardiac sarcomeres.



Fas signaling and cardiac hypertrophy

(See article on pages 373–381.)

Stimulation of Fas, the founding member of a family of dedicated cell surface "death receptors," activates one of the best-studied routes to apoptosis. Evidence for Fas activation in cardiac myocytes subjected to pressure overload is therefore not surprising, but Badorff et al. have found that this protein subserves an unexpected role in these cells. As has been noted before, cardiac overexpression of the Fas ligand (FasL) does not kill myocytes but rather leads to a metabolic and morphological transition reminiscent of the adaptive hypertrophy. Working with cultured neonatal myocytes, Badorff and colleagues show that FasL treatment activates Akt, a protein kinase that has been extensively implicated in the hypertrophic response in the heart and elsewhere. Hypothesizing that Fas participates in the adaptive hypertrophy that allows the heart to compensate for pressure overload, the authors tested the effects of aortic banding in *lpr* mice, which are deficient in Fas. As predicted, these mice failed to compensate and often died within a week of the operation. Interestingly, mice lacking FasL showed no such defect, indicating that, although FasL can induce this response, Fas can be activated by other means during adaptive hypertrophy.