Research round-up

Highlights from cystic fibrosis studies. By Liam Drew

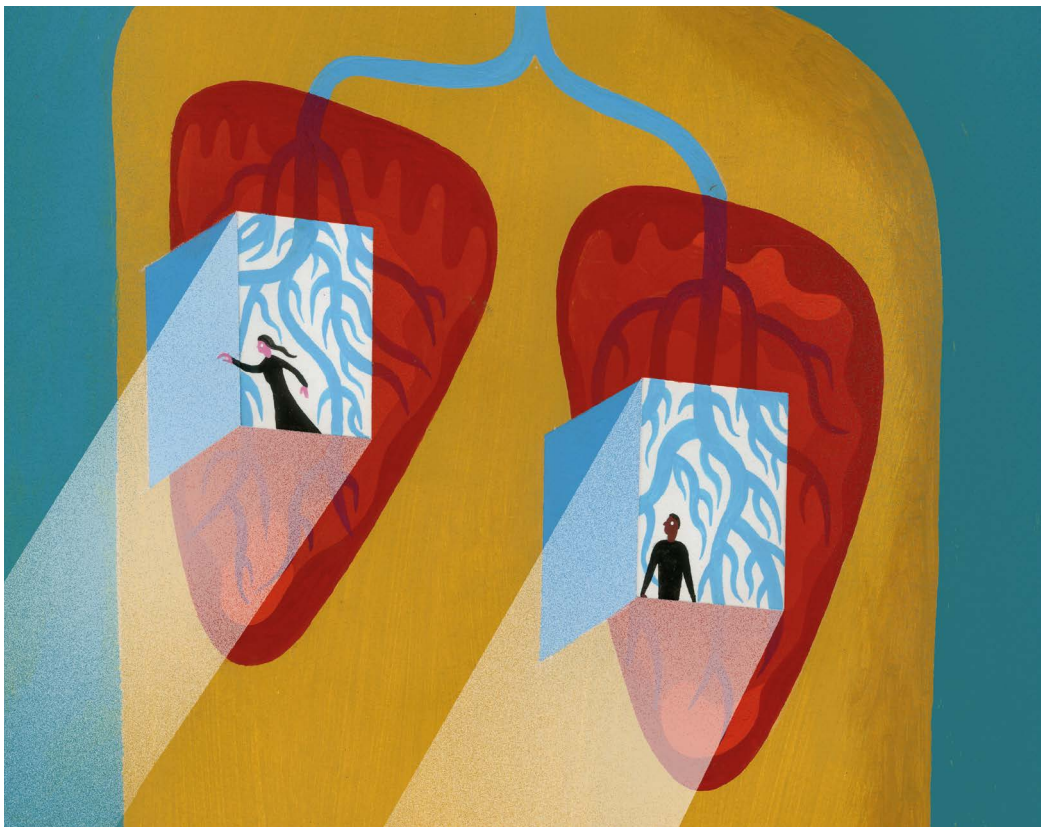

ILLUSTRATION BY RUSSELL COBB

Old drug, new tricks

Amphotericin B, which was first isolated in 1955, is an essential medicine that kills fungal cells by inserting into their cell membranes and forming a pore that is permeable to both positively and negatively charged monovalent ions. Now, research suggests that it could also treat cystic fibrosis.

The disease is caused by abnormalities in a protein called cystic fibrosis transmembrane conductance regulator (CFTR). Absence or mutation of CFTR severely disrupts lung function by reducing the release of bicarbonate ions (HCO_3^-). Martin Burke and his colleagues at the University of Illinois at Urbana-Champaign showed that HCO_3^- passes through amphotericin channels, and reasoned that the drug could be used to relieve the accumulation of HCO_3^- in cystic fibrosis.

They worked first with cell lines, then with epithelial cells taken from people with various cystic-fibrosis-causing mutations. The airway surface liquid (ASL) secreted by these cells is made more acidic, more viscous and less able to kill bacteria by these mutations. The experiments showed that amphotericin caused the release of HCO_3^-, which in turn increased the pH of the ASL, reduced its viscosity and restored its antibacterial properties. These actions persisted for at least 48 hours. They also tested amphotericin in a pig model of cystic fibrosis, in which it restored the pH of the ASL to its normal level.

This medicine is already used to treat fungal lung infections, and the authors hope it can be used to help people with cystic fibrosis. Importantly, its actions are independent of CFTR genotype, meaning it could potentially help anyone with the disease.

Nature **567**, 405–408 (2019)

Extinguishing lung inflammation

For a long time, the occlusion of airways by an excess production of viscous, hyper-concentrated mucus was considered a feature of late-stage cystic fibrosis. But research over the past decade has shown that mucus often starts to obstruct the airways of infants with cystic fibrosis within the first few years of life – sometimes even in the absence of infection.

This probably involves a positive feedback loop of chronic inflammation and constant mucus overproduction. Richard Boucher and his colleagues at the University of North Carolina at Chapel Hill have now dissected the main molecular pathways driving mucoinflammation – a discovery that offers potential therapeutic targets.

A lung secretion induces mucus production, and the researchers began by testing its individual components to see which ones upregulated the genes for the proteins mucin 5B and mucin 5AC – two major constituents of mucus. They found that the pro-inflammatory messengers interleukin-1β (IL-1β) and IL-1α had the greatest effects on these genes in both cultured epithelial cells and mice.

The authors mapped the transcription factors activated by the interleukins. Blocking IL-1 receptors stopped the inflammatory airway secretion from switching on genes for mucins and further inflammatory mediators in cells with cystic fibrosis mutations.

Finally, in post-mortem lung tissue, the interleukin, mucin and transcription factor genes were found to be highly active in people with cystic fibrosis and almost silent in control samples. Interrupting this pathway might hold promise for preventing lung disease at any stage in the progression of cystic fibrosis.

J. Clin. Invest. **129**, 4433–4450 (2019)

Carrying a risk

Cystic fibrosis occurs when a person inherits two disease-causing versions of the *CFTR* gene. It is widely thought that in carriers, the presence of one gene that encodes a functional

CFTR protein fully compensates for the pathogenic allele, and the person is healthy. There have been reports, however, that carriers might be at increased risk of developing certain cystic fibrosis-related conditions.

Now, having examined large-scale health-care data from carriers, Aaron Miller and his colleagues at the University of Iowa in Iowa City say that carriers have increased chances of developing more than 50 conditions. Using a database generated from health expense claims, the researchers identified 19,802 carriers and 23,557 people with cystic fibrosis, and matched each with five controls. They then reviewed the literature to identify 59 conditions associated with cystic fibrosis.

All but two of the 59 conditions were more prevalent in carriers than in controls. Carriers were at much lower risk for each condition than were people with cystic fibrosis. But when carriers' odds-ratios for each condition were plotted against those of people with cystic fibrosis, there was a pronounced correlation.

The findings suggest that having only one mutated *CFTR* allele predisposes people to certain illnesses. The authors stress that a carrier's individual risk of developing any condition remains low. But knowing the risks associated with being a carrier might aid disease prevention and open the way to therapies for treating certain conditions in carriers.

Proc. Natl Acad. Sci. USA **117**, 1621–1627 (2020)

Infections of infected bacteria

Chronic lung infections are a core issue in cystic fibrosis. Nearly 60% of adults with the disease have persistent *Pseudomonas aeruginosa* infections despite antibiotic treatment and pronounced immune responses. Late-stage *P. aeruginosa* infections involve a biofilm state, and chronic bronchial infection is associated with diminishing lung function, which can be fatal.

Elizabeth Burgener and her colleagues at Stanford University in California have investigated the effect of filamentous bacteriophage (Pf phage) on *P. aeruginosa*. They have shown that when this phage infects the bacterium, it promotes biofilm formation and contributes to antibiotic resistance. Their latest study shows that Pf phage is common in people with cystic fibrosis and that it contributes to sustained infections and poor outcomes.

In a Stanford cohort of 58 people with cystic fibrosis and *P. aeruginosa* infections, 21 (36%) had Pf phage. In a Danish cohort, the proportion was around 25%. Patients in the Stanford group who tested positive for Pf phage had more bacteria in their sputum, and all 21 had endured infections lasting a year or more. By contrast, only 13 of the 37 people who tested negative for Pf phage had persistent infections.

Overall, having Pf phage did not predict poorer lung function. But during periods of exacerbation, when respiratory symptoms flare, lung function decreased more dramatically in people with Pf phage infections. Also, *P. aeruginosa* isolated from people with the phage was resistant to three commonly used antibiotics.

The study indicates that Pf-phage infection is likely to contribute to chronic, treatment-resistant bacterial infections. Testing for the phage could inform treatment options, and the phage itself might be an important therapeutic target.

Sci. Transl. Med. **11**, eaau9748 (2019)

Making the gut good to grow

Gastrointestinal complications are an early manifestation of cystic fibrosis, affecting roughly 85% of infants with the condition. Typically caused by insufficient secretion of pancreatic digestive enzymes, they can lead to poor growth and short stature.

Early dietary modifications and enzyme replacement can restore normal weight gain. But therapy doesn't always correct poor linear growth, suggesting that another factor impairs this. Researchers at the University of Washington in Seattle now propose that an altered gut microbiome in early cystic fibrosis might underlie low linear growth.

Hillary Hayden and her colleagues used genomic techniques to analyse the faecal microbiomes of 207 infants with cystic fibrosis aged between 3 and 12 months. This confirmed previously found disease-associated microbiotic changes, and showed that differences were best explained by a marked lag in the development of the microbiome. The standout features of the cystic fibrosis microbiome were an overabundance of organisms in the Proteobacteria phylum and fewer in the Bacteroidetes phylum. Infants with cystic fibrosis who showed low growth had microbiomes resembling an extreme form of these changes.

The authors propose that microbiotic changes might slow growth by disrupting endocrine function, potentially by lowering bacterial production of short-chain fatty acids. The research suggests that therapies that normalize the microbiome might help infants with cystic fibrosis to achieve greater growth.

Nature Med. **26**, 215–221 (2020)

Going behind to get ahead

More than 2,000 mutations in the *CFTR* gene can lead to cystic fibrosis, so the molecular mechanisms behind the disease vary considerably. Such differences can profoundly affect responses to treatments. Notably, people with rare mutations that affect the CFTR protein in unknown ways are typically excluded from trials, and choosing treatments for them is difficult.

Personalized predictive tests would help clinicians to forecast more reliably whether a patient will benefit from a therapy. Researchers at Utrecht University in the Netherlands have shown that organoids made from stem cells taken from patients' rectums respond to drugs for cystic fibrosis in a way that correlates with those individuals' clinical responses to those drugs.

Gitte Berkers and her colleagues had previously established how to transform rectal stem cells into organoids comprised of epithelial cells, which malfunction in cystic fibrosis. Applying a drug known as forskolin to these organoids caused them to swell to a degree that varied according to which CFTR mutation was present.

Their latest study examined how organoids from 24 people with cystic fibrosis responded to the drugs these patients had been treated with. Fifteen patients had a well-characterized mutation (S1251N), which is responsive to the CFTR modulator ivacaftor. Nine with rare mutations had been given ivacaftor off-label. How drugs increased forskolin-induced organoid swelling (by boosting CFTR function) was compared to how they had affected two clinical features: lung function and change in sweat-chloride concentration (SCC).

The effect a therapy had on organoid swelling correlated with its *in vivo* effect on the patient's SCC and lung function. Organoid assays still need to be related to long-term clinical outcomes and decision points, but the authors hope that organoids will provide a cheap and simple method for predicting how an individual will respond to various drugs.

Cell Rep. **26**, 1701–1708 (2019)

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