Indeed, magnetic fluctuations are thought to be involved in mediating electron pairing in cuprates[6], and such a mechanism might be a recurring theme among unconventional superconductors.

In support of this idea, the 2019 discovery[10] of superconductivity in the nickel-based compound $Nd_{0.8}Sr_{0.2}NiO_2$ (Nd, neodymium; Sr, strontium) garnered considerable interest. The crystal structure of this material is said to be infinitely layered, because it consists of a periodic repetition of planes of nickel and oxygen, mirroring the building blocks in the structure of cuprates. The magnetic fluctuations in the material are also reminiscent of those in cuprates. Yet there are clear distinctions between superconductors containing copper, iron and nickel[11]. And with a relatively modest T_c of about 20 K, the infinite-layer nickelates do not qualify as high-temperature superconductors, although pressure can enhance their T_c to around 31 K (ref. 12).

In light of this, Sun and co-workers' report of a T_c of 80 K in $La_3Ni_2O_7$ stands out – the material seems to be edging into the realm of cuprates, with unconventional superconductivity above the 77 K benchmark set by the point at which nitrogen liquefies. Moreover, $La_3Ni_2O_7$ comprises bilayers of nickel and oxygen arranged in octahedra (Fig. 1). This structure is noteworthy because it differs from that of the infinite-layer nickelate superconductors, which closely resembles the structure of cuprates.

Sun and colleagues' calculations reveal that coupling between the double layers is enhanced by a pressure-induced reorientation of the octahedral geometry, which could give rise to electronic states similar to those of cuprates. Whether $La_3Ni_2O_7$ indeed features cuprate-like electronic states, with a similar pairing mechanism, remains a tantalizing question for complementary theoretical studies. Either way, it is worth noting that $La_3Ni_2O_7$ shows magnetic and charge instabilities[4], which are suppressed with the onset of superconductivity. This suggests once more a theme among unconventional superconductors.

In future experimental investigations, it will be crucial to address the sample-to-sample variation reported by the authors, who found that certain single crystals lacked a superconducting transition. This discrepancy might be related to potential variations in the oxygen content of $La_3Ni_2O_7$, and could also shed light on the origin of the absence of superconductivity in previously studied powder samples[2,3].

The discovery of superconductivity in $La_3Ni_2O_7$ markedly diversifies the landscape of high-temperature superconductors. Exploring other multilayer nickelates similar to the bilayer compound $La_3Ni_2O_7$ offers an exciting prospect for uncovering new superconductors, perhaps even with a T_c surpassing 80 K. This would initiate a serious challenge to the current dominance of cuprates in research on superconductors.

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Medical research

Immune treatment tackles a lung disease in smokers

John V. Fahy & Richard M. Locksley

Smoking causes chronic obstructive pulmonary disease. Some people with this disease have high levels of eosinophil cells, which is typical of the type 2 category of inflammation, and blocking such inflammation improves their lung health.

Chronic obstructive pulmonary disease (COPD) is a common lung disease caused by tobacco smoke and other airborne pollutants, and it can be fatal. COPD exacerbations – defined as acute difficulties in breathing – can be triggered by viral or bacterial infections, or by changes in air quality[1]. Exacerbations are associated with diminished lung function, which can lead to respiratory failure. This increases the risk of death and requires treatment in hospital. Because chronic lung inflammation in COPD persists between exacerbations and even after cessation of smoking, a major goal is to reduce persistent inflammation to decrease the frequency and severity of exacerbations.

Writing in the *New England Journal of Medicine*, Bhatt *et al.*[2] report the results of a clinical trial for COPD that tested an antibody called dupilumab. The antibody broadly blocks a category of inflammation (type 2) that is associated with high numbers of white blood cells called eosinophils. The authors found that treatment with dupilumab decreased the rate of exacerbations and improved lung function in a subset of individuals with COPD who had high numbers of eosinophil in their blood.

Inflammation occurs when groupings of key molecules called cytokines and chemokines are secreted by immune cells to communicate with other cells and orchestrate the resulting immune response. Inflammation is divided into three categories: chronic or type 1 inflammation (associated with the cytokine IFN-γ); allergic or type 2 inflammation (associated with the cytokines IL-4, IL-5 and IL-13); and acute or type 3 inflammation (associated with the cytokine IL-17). Knowledge of these distinct immune responses has guided the use of anti-cytokine interventions in precision-medicine approaches to treat diseases associated with inflammation[3]. IL-4 and IL-13 are produced by subsets of immune cells, and dupilumab blocks the receptor required for signalling by these molecules (Fig. 1).

Bhatt and colleagues' dupilumab trial for COPD was prompted by the success of cytokine-targeting antibodies that block type 2 inflammation in people who have asthma[4]. Between 20% and 25% of people with COPD have higher-than-normal numbers of eosinophils, which is often associated with type 2 inflammation and is a potential risk factor for COPD exacerbations[5]. The authors tested whether dupilumab decreases exacerbations in this particular subset of individuals.

Examining data for almost 1,000 individuals who had COPD with high levels of blood eosinophils, the authors found that dupilumab lowered the annualized rate of moderate or severe exacerbations by nearly one-third and improved lung function and quality of life compared with those who did not receive the antibody. This result is important because current treatments for people with COPD have limited efficacy, and improved therapies could decrease the personal and economic costs of COPD exacerbations.

Besides dupilumab, other cytokine-targeting antibodies that are effective in

people with asthma and type 2 inflammation include mepolizumab, reslizumab and benralizumab[4]. These antibodies target IL-5 or its receptor to decrease eosinophil differentiation and survival. Curiously, in previous research[5], mepolizumab had only modest efficacy in reducing exacerbations in people with COPD and high eosinophil levels, and benralizumab was ineffective, suggesting that effects on eosinophil cells alone do not explain how dupilumab decreases exacerbations. Compared with drugs that block IL-5 or its receptor, the ability of dupilumab to block the IL-4 receptor alpha subunit (IL-4Rα) means that it can suppress a larger number of inflammatory pathways because the IL-4 receptor is expressed on a wider range of immune and tissue cells than the IL-5 receptor is.

IL-4Rα is a component of the type I IL-4 receptor (expressed primarily on immune cells) and of the type II IL-4 receptor (expressed more broadly, and mainly on tissue cells). Activation of IL-4 receptors on B cells — a type of white blood cell that makes antibodies — is needed to produce IgE antibodies, which bind to receptors found on immune cells called mast cells and basophils. Allergens inhaled from the environment can bind to IgE antibodies on these cells and trigger the release of inflammatory molecules.

The activation of type II IL-4 receptors on lung cells (fibroblasts, epithelial cells and endothelial cells) results in the secretion of cytokines and chemokines that promote the entry of eosinophils and other cells from the blood, thereby amplifying the production of IL-4 and IL-13. These cytokines alter the composition of mucin molecules in the airways and increase the contraction of airway smooth muscles, creating a feed-forward cycle that contributes to impaired lung function.

The clinical efficacy of anti-cytokine antibody treatments for people with asthma supports a multi-step cascade of type 2 cytokines as a key molecular mechanism of lung disease. The cascade is initiated by environmental triggers that turn on local signals, including 'cytokine alarmins', molecules that activate IL-4, IL-13 and IL-5 from lung-resident immune cells. Next, lung structural cells, including epithelial cells, fibroblasts and endothelial cells, respond to these cytokines by producing chemokines and adhesion molecules that facilitate the entry of blood-borne immune cells, including eosinophils. Finally, newly recruited cells and IgE antibodies amplify local type 2 inflammation, resulting in structural alterations involving airway mucins and smooth-muscle contraction that compromise lung function[6].

Bhatt and colleagues provide evidence that dupilumab decreases the rate of exacerbations and improves lung function in people with COPD by interrupting a type 2 inflammation cascade. Specifically, the dupilumab treatment decreased exhaled-breath levels of nitric oxide (a sign of IL-13-induced activation of epithelial cells) and lowered blood levels of IgE and chemokines, which recruit eosinophils into tissue. Deeper analysis of the signalling pathways in dupilumab-responsive individuals with COPD who have high eosinophil levels might reveal other mechanisms that could have therapeutic benefits and thus guide further study.

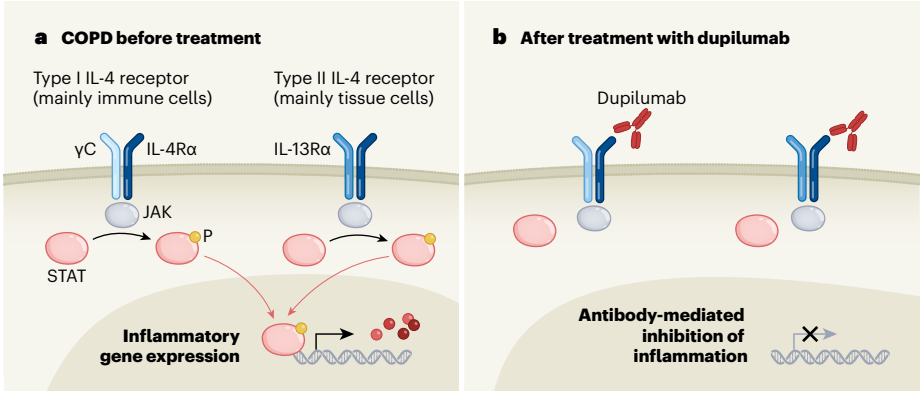

Figure 1 | Therapy for a chronic lung disease. The airways of people with a condition called chronic obstructive pulmonary disease (COPD) can become inflammed and constricted. **a**, A subset of individuals with COPD have signs of a category of inflammation called type 2. Such inflammation can arise from signalling through the type I and type II IL-4 receptor. The type I IL-4 receptor has two subunits, termed γC and IL-4Rα, and is predominantly found on immune cells, as well as on some other cells in lung tissue. The type II IL-4 receptor has two subunits, IL-4Rα and IL-13Rα, and is predominantly found on lung-tissue cells and on some immune cells. Signalling by these receptors is mediated by proteins called JAKs and STATs (STAT activation requires the addition of a phosphate (P) group), and it drives the expression of molecules associated with inflammation; these molecules include chemokines, cytokines and mucin. **b**, Bhatt *et al.*[2] report the results of a clinical trial that tested an antibody called dupilumab in individuals with COPD and a particular hallmark of type 2 inflammation. Dupilumab targets IL-4Rα, and the treatment improved lung health.

People who have a chronic upper-airway disease associated with type 2 inflammation, called chronic rhinosinusitis with nasal polyps (CRSwNP), have persistent changes in gene expression in the epithelial cells associated with IL-4 and IL-13 signalling[7]. Dupilumab treatment improves disease control in people with CRSwNP by decreasing the numbers of mast cells[8] and immune cells called regulatory and cytotoxic T_H2 cells[9]. The success of dupilumab in reducing type 2 inflammation in both CRSwNP and COPD with elevated eosinophils suggests a common mode of action for treating upper- and lower-airway diseases.

Both smoking and older age increase the risk of mutations and are associated not only with COPD but also with a type of abnormality in blood-cell production called clonal haematopoiesis (CH)[10]. CH reflects the formation of blood cells from stem cells that contain accumulated mutations, some of which confer cell-survival advantages[10]. Indeed, CH might explain why otherwise-healthy individuals can show increases in the unusual regulatory and cytotoxic T_H2 cells found in the lungs of some individuals who have COPD[9].

Among the mutations associated with CH are those in JAK2 (a cytokine-signalling molecule), which is associated with hypereosinophilia (a condition in which people have high levels of eosinophils, similar to that found in type 2 inflammation), and with other inflammatory diseases, including atherosclerosis and possibly COPD[10]. The successful use of JAK inhibitors to treat type 2 and other inflammatory diseases[11] suggests that the exploration of such pathways might be warranted for some individuals with COPD.

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