38 Respiratory research

Introduction

Key points

- Imaging makes a major contribution to diagnosis and monitoring in respiratory medicine, so the constant improvement of imaging techniques has a significant impact on the specialty. Techniques such as real-time MRI, three-dimensional ultrasonographic computing and 'visiology' are deepening our understanding of a range of conditions.
- Genomics, proteomics and metabolomics are among the biological monitoring tools that are increasing our knowledge of diseases from cystic fibrosis to cancer. Biomarkers such as exhaled volatile organic compounds offer potential improvements in disease monitoring, while pathogen genomes are providing new insight into infectious threats.
- 'Biological' drugs are increasingly important in respiratory medicine, using antibodies and antagonists to block or modify disease mechanisms, oncogenes and metabolic pathways in asthma, COPD, idiopathic pulmonary fibrosis, cancers and pulmonary hypertension.

Respiratory diseases, whether acute or chronic, communicable or noncommunicable, impose a major global burden and affect millions of people. Despite the high prevalence of respiratory disease, only 4.3% of the health budget in the European Union's (EU) seventh Framework Programme for Research and Technological Development (FP7) was dedicated to respiratory research. Nevertheless, several large-scale local and international population studies have been and are being performed in order to gauge the prevalence and incidence of respiratory diseases and their associated risk factors. Some of these studies have been in progress for more than 20 years, among them the European Community Respiratory Health Survey (ECRHS) and its follow-up surveys. A more detailed discussion of these long-term studies is available in the online supplement.

Recently, several research areas strongly linked to the pathogenesis of respiratory disease have been identified as priorities by the EU. These areas include

1. Early origins of lung diseases
2. Lifestyle and lung health
3. Lungs and the environment
4. Lung defences and infections
5. Lung diseases in an ageing population

Table 1 – Five over-arching themes in lung research.

> *Web and smartphone applications enable patients and physicians to monitor diseases such as asthma in daily life*

tobacco, the environment, nutrition and physical activity. Lung research encompasses a wide range of diseases and can be classified according to major themes that cover both the origins and consequences of diseases in an evolving scientific environment. Five major themes have been identified by the European Respiratory Society scientific committee, relating to childhood, lifestyle consequences, environment, lung infections and ageing (table 1).

Respiratory diseases are often diagnosed at an advanced stage but hopefully, thanks to progress in investigational technologies (such as imaging and biomarkers), more patients will benefit from diagnosis and management earlier in the course of their disease. However, there is still a long way to go. Over the past 40 years, only nine new major respiratory drugs have been developed and we urgently need new medications and treatments for several respiratory diseases, as discussed later.

Fields of research

Early origins of lung diseases

The number of very premature babies who survive into childhood will continue to increase over the coming years and as a consequence, the number of children with chronic lung disease is also likely to increase. Pre-natal factors are known to influence lung health later in life and both nutritional deficiencies and maternal smoking have epigenetic influences on the developing lung. These epigenetic factors even seem to have transgenerational effects, which continue from grandmother to mother to daughter. Life expectancy for several congenital defects has also increased markedly with improved care, as infants with cystic fibrosis or neuromuscular disease benefit from early intervention with new targeted biological approaches.

Prevention of severe early infection is important, in order to reduce the incidence of life-threatening pneumonia or bronchiolitis, which can have consequences in adulthood in addition to their acute severe morbidity.

As well as impacting lung development, genetic and epigenetic factors related to the environment lead to alterations of defence mechanisms, with an undue inflammatory response to common allergens resulting in allergies in the form of rhinitis or asthma of varying severity, which often persist into adulthood. A more comprehensive understanding of these mechanisms is still needed in order to improve the treatments available.

Lifestyle and lung health

It has become increasingly apparent that lifestyle can impact lung health markedly. Nutritional deficiencies impair lung growth, favour infections and can decrease the ability to control inflammatory processes due, for instance, to a lack of antioxidative factors.

Lack of physical activity, often combined with obesity, impacts on disorders such as asthma or chronic obstructive pulmonary disease (COPD). Obesity also leads to obstructive sleep apnoea syndrome (OSAS), a condition whose prevalence has increased steadily over the past decade across all EU countries due to both better recognition of the disease and the increasing obesity of the population in general. The cardiovascular and metabolic consequences of OSAS are now recognised to be significant and will add to the overall burden of disease in Europe in the next decade.

Active and passive smoking are major factors in the aetiology of COPD and, of course, lung cancer. Asthma and COPD are the most prevalent respiratory diseases in the EU and the prevalence of both is increasing, placing a major burden on healthcare systems. There is a need to identify all contributory factors in these diseases, both intrinsic and extrinsic.

Sexual promiscuity and poverty have a major impact on the epidemiology of tuberculosis (TB), with an increase of its incidence particularly seen in the HIV-infected population. Respiratory infections in general are also frequent in such situations.

Drugs used to treat a variety of diseases can cause serious lung injury, resulting in pulmonary fibrosis or pulmonary hypertension, with possible fatal outcomes. Further research into these effects should help the relevant agencies develop prevention and management recommendations.

> *"Thanks to progress in investigational techniques, patients will benefit from earlier diagnosis"*

Lungs and the environment

The lungs are essentially wide open to the environment and have a very large surface area (approximately equal to that of a tennis court). Inspired air is separated from the blood in the pulmonary capillaries by a barrier of only about 1 µm. Inhaled particles of 2–10 µm in diameter are deposited in the airways and exposure to allergens and other particles contributes to asthma in 6–10% of the population, as well as to COPD, which is induced by exposure not only to smoking but also to indoor and outdoor pollution. The relevant indoor factors have still not all been identified. New volatile organic compounds used in construction and other industries have

been added to better-known agents, such as sulfites, chlorates, isocyanates, and many other substances already known to be potentially toxic.

Asthma is an inflammatory disease of the airways secondary to known allergens and irritants, and several occupational agents have been shown to be responsible for its development. Some professions are well known to be at risk, such as bakers and carpenters; in other occupations, such as painting, building and hairdressing, asthma is induced by mechanisms that need to be further explored so that more effective preventive measures may be taken. Common cold viruses are also a very important trigger of asthma and, to reduce the ensuing morbidity, the mechanisms involved need to be better understood.

Carcinogens are abundant in tobacco smoke but other substances known to contribute to lung cancer originate in the environment. These include the radioactive element radon, which may be released naturally from the granite below houses, or asbestos extracted from mines and used for building insulation. Such compounds need to be identified and environmental exposure to them minimised. The mechanisms involved also need to be better understood in order to improve prevention and treatment.

As the climate changes during the coming century, environmental exposures are likely to alter, as atmospheric conditions and the distribution of flora and fauna change. This climate variation can to some extent be predicted and its impact on lung health needs to be further investigated.

Lung defences and infection

Acute lower respiratory tract infections (such as bacterial and viral pneumonia, influenza and respiratory syncytial virus infections) are the third most-frequent cause of death worldwide, accounting for 4.25 million deaths each year. The state of the lungs' defences and the occurrence of infections are closely linked. A better understanding of how infections are prevented by the upper and lower airways is required; once we know how the defences function, we will have a clearer understanding of the way in which environmental factors and nutritional deficiencies may alter these defences to allow airway infections or pneumonia.

TB remains a leading cause of death worldwide, and any weakening of lung defences favours the occurrence of active disease and its propagation.

Where feasible, improvements in lung defences should be promoted – by the use of efficient vaccines, for example. The effects of immune-modulating agents, such as those used in treating malignancy and autoimmune diseases, need to be better understood in order to mitigate the effects of the resulting impairment of defences and the consequent severe secondary infections.

Early diagnosis of emerging new pathogens is crucial to allow appropriate use of new and existing therapies. New respiratory viruses appear quite frequently and rapid, reliable methods for diagnosis and typing of the viral strains need to be developed in the community. New vaccines and antiviral agents are also needed. Multidrug-resistant infectious agents and emerging fungal infections in immunocompromised patients are among other new challenges and new drugs against them need to be developed and tested.

Investigational technologies and imaging
Biological monitoring and biomarkers
New interventions and biological treatments

Table 2 – Fields where further biomedical research is needed.

Lung diseases in an ageing population

As European populations age, maintenance of good lung health will become a real challenge for current and future physicians. With age, both the upper and lower airways develop atrophic changes in the mucosa and thus the natural defences are altered. Elderly people tend to have more aspiration during swallowing and neuromuscular insufficiency may worsen their ability to cough. Humoral and cellular immunity also tend to alter with ageing. All these factors participate to varying degrees in the marked increase in lung infections that is seen with ageing, and the associated high morbidity and mortality. Physical activity, a comprehensive vaccination policy and good nutrition may help to prevent debilitating infections.

Ageing causes a reduction in the gas-exchange surface of the lungs, which may lead to a reduced capacity to oxygenate the blood. The airways become more collapsible, which contributes to obstructive lung disease. Prevention of undue inflammation related to environmental factors might decrease the effects of this natural decline in airway function.

Lung injury related to inhaled particles or to infections can produce scarring, sometimes leading to lung fibrosis and respiratory insufficiency. Some of these fibrotic processes may also be related to defects in natural repair and/or to a higher incidence of autoimmune diseases among older people. These immune processes lead not only to scarring of distal airways, but also in some patients to vascular narrowing and a higher incidence of pulmonary arterial hypertension with age.

The tissues of the body are continuously renewed by the division of progenitor cells. With ageing, dysregulation of these regeneration processes can occur, leading to various thoracic malignancies and tumours. Better knowledge of the effects of carcinogens should lead to improvement in effective prevention measures. Malignancy is also related to genetic factors and the identification of these may result in more individualised diagnostic screening and more personalised treatment.

Advances in respiratory biomedicine

Investigational technologies and imaging

Imaging methods are improving constantly. In respiratory medicine, imaging makes a major contribution to the precise diagnosis and the monitoring of therapy. Several new investigational and imaging techniques are beginning to become available, but in many cases there is still room for improvement in their application. Examples include the following.

- Real-time magnetic resonance imaging (MRI) for pathophysiological assessment, for example in pulmonary hypertension.
- Metabolic imaging with improved positron emission tomography scanning, in particular in the fields of oncology and inflammatory diseases.
- Improved analysis of three-dimensional computed tomography, applied, for example, in emphysema, fibrosis and assessment of tumour volume.
- Three-dimensional ultrasonographic computing for better assessment of pulmonary hypertension, vascular anomalies and pleural disease.
- Functional imaging using *in vivo* confocal microscopy. Such imaging allows analysis of: vasoactivity phenomena during hypoxia; ischaemia reperfusion events; or migrating ('homing') cells in pathological processes such as tumours or inflammatory diseases.
- Advances in interventional pulmonology. These techniques can be applied in the airways, the pleural space or the mediastinum. Among the more important are the superDimension endoscope, the confocal laser micro-endoscope, optical coherence bronchoscopy and auto-fluorescence bronchoscopy.
- Nanotechnology to target the *in vivo* inflammatory processes of tumoral cells for diagnostic or therapeutic purposes.
- Development of 'visiology': techniques that combine imaging with physiological measurements.
- Web and smartphone applications so that patients and physicians can monitor diseases such as asthma in daily life and facilitate the use of rescue medication or understand the role of environmental exposure for asthma control.

Biological monitoring and biomarkers

Many novel tools are now being used or are under development for improved diagnosis and better measurement of the evolution of diseases.

Several of these novel tools come under the heading of 'omics': genomics, proteomics, metabolomics and so on. Genomic analysis is already important, and will become even more so for the diagnosis of congenital conditions such as cystic fibrosis, neuromuscular diseases and some of the more severe rare diseases. Genetically determined oncological predispositions will also be more easily detectable in future. Proteomics and metabolomics in breath condensate enable monitoring of inflammatory disease before and after treatment.

Other potential biomarkers of disease include: blood microRNAs for the diagnosis of cancer, infections and rare diseases; and exhaled volatile organic compounds as a measure of lung inflammation and to detect some cancers.

Deep sequencing of the genomes of pathogens, meanwhile, will allow precise identification of new pathogens and monitoring of the appearance of resistance to available therapies.

In terms of environmental exposures, individual exposure assessments for indoor and eventually outdoor pollution, including irritants or oncogenic compounds such as radon, may improve our understanding of the health effects of these substances. Monitoring of the environment can also increase our understanding of some types of asthma and causes of COPD other than smoking. This should be coupled with epigenetic studies to unravel the influence of the environment on the expression of such diseases.

Finally, improved clinical monitoring using a telemedicine approach has the potential to greatly improve personalisation of treatment, and thus disease outcome.

> *"New approaches to personalised medicine are needed, to encourage patients to 'own' their treatment"*

New interventions and biological treatments

So-called 'biological' approaches are increasingly prominent in respiratory medicine, and new devices for ventilatory support or endoscopic procedures are constantly becoming available. New approaches to personalised medicine are also needed, in order to encourage patients to 'own' their treatment. Emerging and likely future developments include:

- New biological treatments using antibodies or antagonists against receptors in order to interfere with the inflammatory mechanisms in diseases such as asthma, COPD, idiopathic pulmonary fibrosis, pulmonary hypertension and tumour growth. Examples include CXCR2 antagonists, phosphodiesterase 4 inhibitors, endothelin-receptor antagonists and kinase inhibitors. Blocking interleukin (IL)-5 or IL-13 in severe eosinophilic asthma is already becoming a reality, a prime example of personalised medicine.
- The development of antagonists of metabolic pathways, in order to inhibit oncogenes or signalling molecules in oncological processes and inflammatory processes such as those involved in pulmonary hypertension or idiopathic pulmonary fibrosis.
- The development of novel anti-ageing drugs for treating COPD and its associated conditions.
- Targeted and customised therapies for lung malignancies.
- The advent of improved delivery systems for inhaled drugs.
- Better use of borderline donor organs and improved understanding of the causes and potential treatment of ischaemic reperfusion phenomena in lung transplantation.

Prevention of chronic graft dysfunction remains a priority.

- In tissue engineering and biotechnology, the development of lung regeneration technologies as an alternative to transplantation. The recent success of tracheal transplantation onto a scaffold has been a first step.
- Basic research on the cellular and molecular properties of stem cells, providing new insight into their homing, engraftment, differentiation and biological effects; these are positive steps on the way to future therapeutic use.
- Further development of artificial lungs for treating both acute respiratory insufficiency and end-stage lung diseases, either to allow recovery of lung function or as a bridge to lung transplantation. New extracorporeal gas-exchange devices are becoming available, with arteriovenous or venovenous devices allowing more long-term support for failing lungs.
- Development of novel endoscopic treatment strategies, such as endoscopic volume reduction and thermoplasty.
- The use of technology to increase patients' 'ownership' and management of, as well as responsibility for their disease.
- International collaboration between governments, nongovernmental organisations, academic science and the pharmaceutical industry in the development of antibiotic and antiviral drugs as well as of new vaccines.
- Increased capacity and use of rehabilitation programmes and further development of self-management approaches.

Conclusion

Respiratory medical research is vital for the future health of Europe. National and European research programmes must reflect this to a greater extent in the next decade. More translational research is needed to bring scientific advances and knowledge into clinical practice, and to this end, there is a great need to find effective ways for collaboration between research disciplines. The Alliance for Biomedical Research in Europe (www.biomedeurope.org), grouping 20 major medical and research societies, has been established in order to promote and advocate for biomedical research at the European level.

Research in the field of respiratory disease will allow us to unravel the molecular mechanisms that are the origin of major diseases. The important roles of lifestyle and the environment are becoming much clearer, and minimising their adverse effects will require political as well as research action.

We are entering an era in which many new technologies will become available for improved imaging, for more specific biomarkers and for more precise targeting of metabolic pathways. These should allow earlier and more specific diagnosis, as well as better targeted and personalised treatments. Initially, these developments might appear costly, but more personalised medicine may be cost-saving, by decreasing the number of side-effects of current therapies, improving disease outcomes and promoting more healthy ageing.

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