

Genes, Telomeres, Allergies and Biomarkers, Key Pathogenic Clues of Chronic Respiratory Diseases

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The first contribution of this new issue introduces a fascinating review of **the role of genetics in individual susceptibility to chronic obstructive pulmonary disease (COPD)** masterly written by *Sarah L O'Beirne* and *Ronald G Crystal*, from the prestigious *Department of Genetic Medicine and Division of Pulmonary and Critical Care Medicine, Weill Cornell Medical College, New York*. Under the senior authorship of *Ron Crystal*, a legend in respiratory research since the nineteen seventies¹, this paper focuses on the complex genetic architecture in COPD resulting from multifaceted interactions between environmental exposures, genetic susceptibility and gene-by-environment interactions. Although the most important risk factor for the development of COPD continues to be long-term cigarette smoking, environmental factors cannot be ignored. Only 15-20% of ever smokers develop COPD and not all of the patients with COPD have a history of tobacco smoking, which points to an individual susceptibility to environmental stress and/or factors independent of environment exposures, including genetic susceptibility and gene-by-environment interactions. All in all this backdrop contributes to disease development along with the familial aggregation observed in COPD and in monogenetic

conditions, such as alpha-1 antitrypsin deficiency, hence supporting a role for genetic susceptibility in disease pathogenesis. Within this context, key issues such as exome sequencing, expression quantitative trait loci, genome-wide association study (GWAS) and single nucleotide polymorphism (SNP), along with epigenetic and integrative approaches, are attractively exposed to provide a more thorough picture of COPD heritability.

The next paper features information in regard to the **Mechanisms of Development of Allergy (MeDALL) study**, disentangled through a complex systems medicine approach to improve the understanding of allergic diseases. This review is elaborately structured and well-paced by two senior scholars with a brilliant long-term trajectory in respiratory epidemiology research: *Josep M Antó*, from the *Institute for Global Health (ISGlobal), Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona*, and *Jean Bousquet*, from the *University Hospital, Montpellier*, and the *INSERM Unit 1168, Paris* and *Charité, Berlin*.

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The MeDALL study emerged as a proposal to the important call of the *European Union Seventh Framework Programme (FP7) for Research and Technological Development*, aimed to adopt systems medicine to improve the understanding of the mechanisms of allergic diseases. The authors, who coordinated this research project, highlight the main essences of this programme-project with special emphasis on its novel methodological tools and the advances reached out in the understanding of the multi-morbidities of allergic disease. The review also includes an update of the main findings involving genetic and molecular mechanisms. Of note that the MeDALL project pioneered a systems medicine approach to understand allergic diseases from early childhood to young adulthood while critically linking epidemiologic, clinical, and basic research tools in birth cohorts, including GWAS studies together with transcriptomic, epigenetic, and targeted proteomic investigations. This approach was possible due to the multidisciplinary nature of the MeDALL study which included 21 partner institutions within a vast expert networking.

The third contribution refers to **the role of the regulation of telomere length and telomerase activity in lung diseases**. This is a fascinating review written by a combined team of three basic and clinical researchers: *Leandro Sastre, Maria Molina-Molina and Rosario Perona*. While all three are part of the *Biomedical Research Networking Centre on Respiratory Diseases (CIBERES), Madrid*, the first and the last authors work at the *Instituto de Investigaciones Biomédicas, Hospital de la Paz, Madrid*, and the second is based at the *Respiratory Diseases Service and Biomedical Research Institute, Bellvitge Hospital, Barcelona*. They write about

eukaryotic chromosomes that are capped at their ends by specialised nucleo-protein structures so-called telomeres that protect them from degradation. Human telomeres are composed of thousands of repetitions of the TTAGGG hexanucleotide. A protein complex, named shelterin, associates to this deoxyribonucleic acid (DNA) region to form the telomere-specific chromatin structure. Telomeres protect the chromosomal ends from degradation, being essential for chromosomal and genome stability. The review highlights detailed basic information regarding these chromosome structures with further critical details on the implications in prevalent respiratory conditions, such as idiopathic pulmonary fibrosis, emphysema, pulmonary fibrosis-emphysema and lung cancer.

The fourth review is devoted to a very timely field, **the role of biological clusters potentially related to COPD**, authored by *Andreas Halner and Mona Bafadhel*, from the *Respiratory Medicine Unit, Nuffield Department of Medicine, University of Oxford*, under the scientific leadership of the latter author, a talented scholar who has compellingly emerged in respiratory medicine research over the last years. The need to identify subgroups of COPD patients for whom the limited benefits of existing treatment significantly outweigh the risks, while targeting disease mechanisms specific to particular subsets of patients, constitutes the background of this review. In a way, this negative feedback has prompted the identification of different COPD phenotypes which may represent unique prognostic and therapeutic subgroups; in parallel, the search for endotypes has also emerged. However, the large number of variables to be considered for meaningful both COPD phenotypes

and endotypes has prompted the use of sophisticated tools known as cluster analysis in airways disease heterogeneity. Ultimately, this intellectually rigorous review focuses precisely on the assessment of approaches to identify COPD clusters and how these interfere with disease prognosis, biopathology and pathophysiology to facilitate optimisation of treatment outcomes. The authors suggest that the unravelling of COPD heterogeneity should now focus on COPD inflammatory profiles, so the reproducibility of these inflammatory profile COPD clusters over time and between different studies must then be assessed.

The last paper concentrates on **the interplay between physical activity and underlying muscle biology in COPD**, written by *Leandro Cruz Mantoani, Humberto Silva, and Roberto A Rabinovich*, from *ELEGI and COLT Laboratories, Queen's Medical Research Institute, University of Edinburgh*, and the *Department of Respiratory Medicine, Royal Infirmary of Edinburgh, Edinburgh*. The senior author, *Roberto Rabinovich*, is a creative research scholar with a long-standing career in the area of pathophysiology and biopathology of muscles in patients with COPD. This review comprehensively ponders the underlying muscle biology and its effect on physical activity in the COPD population. The authors rightly underline the concept of muscle dysfunction, as one of the most relevant systemic effects in patients with COPD that can be caused by muscle underuse-induced sedentary life which in turn can become a predictor of mortality in this

sick population. Conversely, muscle wasting and muscle dysfunction also contribute to inactivity in COPD. The molecular mechanisms leading to skeletal muscle wasting and/or dysfunction are likely to be multifactorial. Pulmonary rehabilitation through the different modalities of exercise training can contribute to ameliorate muscle function with a positive impact on exercise capacity in these patients. The transformation of these effects into increments in physical activity still remains a challenge with longer and more intense programmes. As psychological and behavioural factors seem to influence the predisposition of patients towards a more active lifestyle, strategies aiming at helping patients to change their likelihood towards activity level can play a role in treating the inactivity of patients with COPD.

We invite the readers to enjoy this new issue of *BRN Reviews* with inspiring topics and first-rate authors to enrich their knowledge. Needless to say that this can make your summer or winter vacations (depending on your geographic location) much more congenial!

REFERENCES

1. Crystal RG, Fulmer JD, Roberts WC, Moss ML, Line BR, Reynolds HY. Idiopathic pulmonary fibrosis. Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. *Ann Intern Med.* 1976;85:769-88.

