Chapter 8

Systems Medicine for Lung Diseases: Phenotypes and Precision Medicine in Cancer, Infection, and Allergy

Bernd Schmeck, Wilhelm Bertrams, Xin Lai, and Julio Vera

Abstract

Lung diseases cause an enormous socioeconomic burden. Four of them are among the ten most important causes of deaths worldwide: Pneumonia has the highest death toll of all infectious diseases, lung cancer kills the most people of all malignant proliferative disorders, chronic obstructive pulmonary disease (COPD) ranks third in mortality among the chronic noncommunicable diseases, and tuberculosis is still one of the most important chronic infectious diseases. Despite all efforts, for example, by the World Health Organization and clinical and experimental researchers, these diseases are still highly prevalent and harmful. This is in part due to the specific organization of tissue homeostasis, architecture, and immunity of the lung. Recently, several consortia have formed and aim to bring together clinical and molecular data from big cohorts of patients with lung diseases with novel experimental setups, biostatistics, bioinformatics, and mathematical modeling. This "systems medicine" concept will help to match the different disease modalities with adequate therapeutic and possibly preventive strategies for individual patients in the sense of precision medicine.

Key words Asthma, Allergy, Infection, Pneumonia, Mycobacteria, Immunology, Transplantation, Model organisms, Gas exchange, Personalized medicine

1 Introduction

Among the ten most common causes of death worldwide, there are four pulmonary diseases, killing 9.5 million people per year (Fig. 1) [1]. In addition, pneumonia, COPD, tuberculosis, and lung cancer are also among the ten most common causes of disability-adjusted life years (DALYs) lost worldwide. Pneumonia alone is the single most important cause of DALYs lost, more important than HIV/AIDS, ischemic heart disease, cerebrovascular disease, or diarrhea [2]. The total cost of lung diseases in the European Union amounts to more than €380 billion annually. In addition to the abovementioned diseases, asthma alone causes costs of over €72 billion, consisting of €19.5 billion for direct medical costs, €14.4 billion for lost productivity (work absence, early

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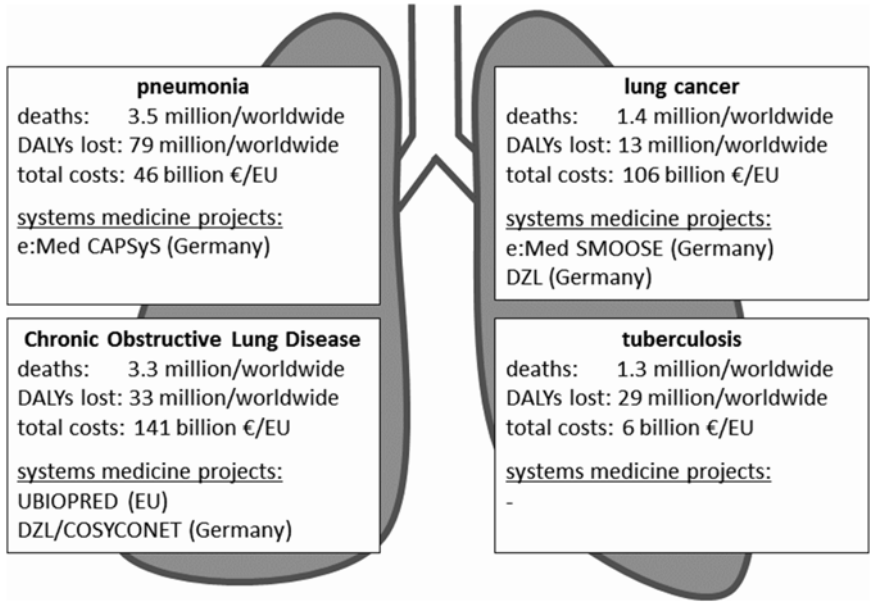

Fig. 1 Frequent lung diseases and related systems medicine consortia. Depicted are the four lung diseases with the highest mortality worldwide, including death worldwide 2011, disability-adjusted life-years (DALYs) lost 2008, aggregated annual total (direct and indirect) costs and the value of DALYs lost for EU countries 2011, and related systems medicine projects according to internet and database research [1, 2]

retirement, etc.), and €38.3 billion for monetized value of DALYs. Lung cancer causes the greatest socioeconomical loss from disability and premature mortality. Because of late diagnosis and limited treatment options, most treatment costs are concentrated within the year of the diagnosis. Therefore, the total annual costs per case are calculated as €364,000 for lung cancer [2].

The lung and airways provide many unique features in terms of anatomy, physiology, and immunology. This paves the way for manifold pathologies and presents challenges for pulmonary clinicians and researchers. The lung is the body's largest organ, but contains about four liters of air and only about half a liter of tissue and the same amount of blood [3]. Therefore, the organ tissue has to be organized in a sophisticated and delicate way. The main function of the lung is the exchange of two gases, O_2 and CO_2, between the air that we breathe and the bloodstream. Three main processes are involved in this: ventilation of air along the bronchial tree, passive diffusion of gases, and perfusion of blood through the alveolar capillaries [4]. These processes are tightly regulated, and not every part of the lung is equally ventilated and perfused. Every day, about 10,000 l of air—containing pollutants, allergens, pathogens, etc.—is ventilated through the about 23 generations of dichotomically dividing airways and over a lung surface of about 130 m^2 that is condensed mainly in over 300 million alveoli. The capillary surface has about the same size. Diffusion of oxygen critically depends on

a short diffusion distance over the air–blood barrier [3]. In healthy lungs, the mean thickness of this tissue barrier is about 0.6 μm, consisting of very thin parts of alveolar epithelial type I cells and capillary endothelial cells sharing one single layer of basement membrane [5]. This delicate architecture is only possible due to the surfactant layer that lines the alveolar surface, reduces its surface tension, and is released by alveolar epithelial type II cells.

2 Clinical Challenges

2.1 Acute Infection: Pneumonia

Community-acquired pneumonia is a high incidence disease which results in more hospital admissions per year in some industrialized countries than myocardial infarction [6, 7]. It has the highest mortality rate worldwide of all infectious diseases. Its lethality ranges from 1 % in outpatient settings to 35 % in high-risk patients [8]. UNICEF (the United Nations Children's Fund) data suggest that pneumonia kills more children under the age of 5 than malaria, AIDS, and measles together [9]. Notorious problems are emerging new pathogens that may combine a high mortality with an easy transmission, e.g., the SARS and MERS coronaviruses or certain pandemic influenza strains [10]. Severe pneumonia can lead to sepsis and septic shock requiring intensive care treatment with artificial organ support, causing extremely high costs [11]. Recently, it has been observed that pneumonia patients face an increased death risk for several months after the acute infection [8].

2.2 Chronic Inflammation: Asthma

Asthma is classically defined as an inflammatory chronic airway disease characterized by reversible airway obstruction and airway hyperresponsiveness [12]. This disease affects 200–300 million people worldwide, and its prevalence has been increasing over the last decades [13]. Up to 10 % of asthmatics are considered as severe cases. Typically, the inflammation in asthma is described to be allergic, eosinophilic, IgE dependent, and Th2 driven [14]. Therefore, therapy besides bronchodilation targets mainly this eosinophilic inflammation, either unspecific with topical or systemic glucocorticoids, with antileukotriene drugs, or with "biological therapies" specifically addressing IgE, or probably in the future IL-13, IL-5, and others [15]. However, sufficient control of asthma symptoms is impossible in many patients, in part due to more than 50 % of asthma patients that do not show a persistent eosinophilic inflammation [16], and this seriously challenges the classical pathophysiological concepts. Systems-based approaches can help to stratify patients to their phenotypes and respective available therapies and to identify new targets for the treatment of patients that are unresponsive to existing drugs [17].

2.3 Chronic Inflammation: COPD

Chronic obstructive pulmonary disease (COPD) is the third most common noncommunicable disease with a very high prevalence worldwide. It causes significant disability, mortality, and healthcare costs, e.g., for lifelong medication, lung transplantation, or mechanical ventilation. The most common causes for the development of COPD are long-term exposure to primary or secondary tobacco smoke, combustion of biomass, e.g., by open-fire cooking in developing countries, or genetic predisposition. Increasing evidence indicates that COPD is rather a syndrome than a solitary disease. The pathophysiological hallmarks are (1) chronic, cortisone-insensitive inflammation which causes mucus hypersecretion and fixed bronchoconstriction and remodeling as well as (2) irreversible tissue destruction in terms of bronchiectasis and emphysema [18]. They result in respiratory and ventilatory failure. An aggravating aspect is the vicious circle of impaired innate immunity, chronic bacterial colonization, and recurrent viral or bacterial infections called exacerbations and often resulting in hospitalization [19]. Besides substance avoidance and exercise training, COPD symptoms are typically treated by long-acting airway dilators on a lifelong basis. The underlying pathophysiology of chronic airway inflammation can be targeted by either topic or systemic glucocorticoids or phosphodiesterase inhibitors. However, these treatments are hampered by side effects and low effectivity. Increasing numbers of patients with severe ventilatory insufficiency receive lifelong mechanical ventilation, which is expensive and requires special infrastructure. On the other hand, the chances of COPD patients to receive lung transplantation are decreasing due to high risk of, e.g., cardiovascular or metabolic comorbidities.

2.4 Pulmonary Hypertension

Pulmonary hypertension is a disease of the lung vasculature. Hallmarks are a deregulated proliferation of different vascular cell types and a progressive obliteration of vessels [20]. This often results in an increased pulmonary vascular resistance, increased right heart afterload, and *cor pulmonale*. Pulmonary hypertension is caused by a combination of genetic and environmental factors. It occurs in a variety of clinical situations and heterogeneous phenotypes. Several histological patterns of abnormalities have been described. Despite significant progress that has been made in understanding the pathogenesis and the development of new methods for delaying the progression of the disease, there is still no cure for it [21].

2.5 Cancer

Lung cancer displays the highest neoplasia-related mortality in man. Over the last years, its mortality is also increasing in women. Cure rates and prognosis are generally poor due to late diagnosis. Therefore, a major focus lies on screening and early diagnosis [22]. Another important challenge is the correct molecular diagnosis for a targeted therapy. Up to now, lung cancer is subdivided in

so-called small cell lung cancer (SCLC, of neuroendocrine origin) and non-small cell lung cancer (NSCLC, e.g., squamous cell cancer, adenocarcinoma). Recently, certain mutations have been found to be predictive for the sensitivity to new targeted therapies [23]. Therefore, cancer might be the first entity of lung diseases matching the concept of precision medicine [24]. Lung cancer is mainly caused by exposure to primary or secondary tobacco smoke, biomass combustion, or naturally occurring radon [25].

3 Methodological Challenges: "The Mouse Trap"

The basic aim of systems medicine is to model human pathophysiology and disease to advance our understanding and to improve clinical diagnosis and treatment. Therefore, it is a logical and straightforward strategy to establish big and well-characterized patient cohorts to collect as many clinical and molecular data as possible—and suitable—as a solid base for this modeling process. However, certain processes or features cannot be observed or tested neither in healthy volunteers nor in patients. This includes the early origins of disease, e.g., environmental influence on asthma predisposition that may be epigenetically transferred from mother to child, the initial pathophysiological events in the alveolus during development of an influenza virus-induced pneumonia, and many more. In part, these problems can be resolved by the use of cell culture or tissue culture models [26]. However, some aspects can only be addressed in a living organism. In the past, for academic experimental research as well as for drug candidate studies for subsequent human trials, mice have been used to model human diseases because of the practical convenience (easy handling and low costs), the possibility to generate transgenic or gene knockout animals, and the availability of molecular and immunological tools [27]. However, certain caveats have to be kept in mind: Firstly, some of the lung diseases, e.g., asthma, are unique to humans and do not occur naturally in mice. Secondly, the anatomy and (patho-) physiology may differ significantly between mice and humans. Besides the obvious size difference—the human lung has a volume of 5 l, and the murine lung has a volume of 1 ml—there are also significant anatomical and physiological differences. For instance, the human airways have 23 generations, and the murine has only 13–16, the human airway division is dichotomic, and the murine airway division is monopod; mice do not have respiratory bronchioli, and the cellular composition and vascularization of the lung are different for both species [5, 27, 28]. Moreover, mice strains differ in their likelihood to react to stressors with certain pathophysiological events. In addition, there is increasing evidence that the immune systems of mice and men differ significantly. For trauma, burns, and endotoxemia, Seok and co-workers compared

gene response patterns between human subjects and corresponding mouse models: They found that these stressors resulted in highly similar patterns in humans, whereas the responses in corresponding mouse models showed only poor correlations with human conditions and also among each other [29]. Accordingly, there are several examples where the reliance on animal models misguided the pathophysiological understanding [28], led to unsuccessful clinical trials [29], or even resulted in disastrous outcomes of clinical studies [30]. This may be in part due to differences in the molecular repertoire of immune cells in mice and humans: For example, the inherent versatility of macrophages harbors the potential for a plethora of different activation subtypes [31]. Inappropriate polarization can be detrimental to the host, as macrophages can potentiate an inapt immune response and thus aggravate a pathological condition: In rodents, alveolar macrophages have been found to play an important role for the development of airway hyperresponsiveness in allergic animals [32, 33]. In mice, solid markers for macrophage polarization are established, as is exemplified by the well-described induction of NOS2 in M1(IFNγ) and of ArgI in M2 (IL-4) macrophages. Corresponding functional markers in the human system are yet to be found, and there are notable differences between human and murine macrophage activation patterns on the transcriptional level [34]. Accordingly, a comparative study of M2 (IL-4) polarization in mouse and man shows very limited interspecies consistency, as only transglutaminase 2 (TGM2) was found to be a functional marker shared by both [35].

4 Case Studies

4.1 Modeling Lung Infection

The most frequent cause of community-acquired pneumonia is pneumococcal infection. Smith and co-workers established a mathematical model to predict the outcome of pneumococcal pneumonia with the two possible states (1) bacterial clearance, or (2) sustained bacterial growth [36]. The model is based on data of pulmonary bacterial replication from a mouse model of pneumococcal pneumonia. Using ordinary differential equations (ODEs), it describes three lines of barrier defense: First, the initial alveolar macrophage response mounts a fast but weak defense and is described by only one equation for the bacterial population. Second, the early recruitment of neutrophils consist of cytokine release by different populations of alveolar macrophages and epithelial cells, the influx of neutrophils, neutrophil apoptosis, and debris removal by alveolar macrophages. Third, a subsequent recruitment of monocyte-derived macrophages has been included that contributes to bacterial killing. This model provides some interesting insights and sufficient accuracy for certain questions,

although it is of moderate complexity and based on limited experimental data. Some more data from previously published mouse studies have been included in another effort to model pneumococcal pneumonia: Bacterial numbers in the lung and the blood and also neutrophil levels from infection experiments with four differently susceptible mouse strains [37] have been used to calibrate this ODE model. It consists of four equations describing the time evolution of the number of pathogens in the lung and in the blood, damaged lung epithelial cells, and total activated phagocytes. The model has been validated on other published data sets, and its predictions are consistent with most experimental observations. However, no study so far has modeled pneumonia dynamics in patients. Therefore, a new consortium ("Medical Systems Biology of Pulmonary Barrier Failure in Community Acquired Pneumonia; e:Med CAPSYS" [38]) aims at multiscale modeling of pulmonary barrier failure in bacterial pneumonia based on comprehensive physiological, proteomic, and transcriptomic data sets from clinical cohorts, complex mouse models, and human cell culture models (Fig. 1). It will include three cohorts: 10,000 well-phenotyped pneumonia patients of the CAPNETZ study (clinical, biochemical, and genetic data) [39], more than 1000 patients with uncomplicated or severe pneumonia or pneumogenic sepsis (several visits, data from genotyping, expression profiling, and proteomics), and a newly recruited deep-phenotyping cohort of about 100 patients that will undergo, e.g., bronchoscopy for microbiome and exosome analysis.

Several mathematical models have been developed to study and understand host immune response mechanisms in pulmonary *Mycobacterium tuberculosis* (Mtb) infection. Marino and Kirschner [40] used a two compartment model to investigate the human immune response to Mtb in the lung. By performing bifurcation analysis of the model, the authors identified key processes of cellular activation and priming that occur between the lung and the nearest draining lymph node that have the potential to determine different outcomes of the Mtb infection. To identify control mechanisms of granuloma formation during Mtb infection in the lung, Segovia-Juarez et al. [41] built a complex agent-based model which accounts for interactions between Mtb, immune effectors such as chemokines and cytokines, and immune cells like macrophages, $CD4^+$, and $CD8^+$ T cells. With the help of the model, the authors identified several issues that are crucial for granuloma formation during the course of Mtb infection, including efficiency of chemokine diffusion, prevention of macrophage overcrowding within the granuloma, arrival time, location, and number of T cells within the granuloma, as well as overall host ability to activate macrophages. To investigate the contribution of $CD8^+$ T cells to control Mtb infection, Sud et al. [42] built an ODE model of the immune response to Mtb in the lung. Using the model, the authors

examined the importance of $CD8^+$ T cells in the control of the infection and determined putative minimum T cell levels providing effective protection following vaccination. A model of differential equations was also developed to investigate the different roles played by alternatively activated macrophages (AAM) versus classically activated macrophages (CAM) in the early stages of Mtb infection in the lung. The model described the interactions among cells, bacteria, and cytokines involved in the activation of AAM and CAM and was a useful tool to analyze strategies for reducing the switching time (i.e., when CAM become more dominant than AAM), which ensures an adequate immune response to the pathogen [43]. Similarly, Kirschner's group built two ODE models to investigate the function of macrophage (CAM)-activating cytokines (i.e., TNFα and IFNγ) in Mtb infection. One model was used to test the ability of macrophages to kill Mtb under different scenarios, in which the macrophage activation is characterized by the timing of IFNγ and TNFα signaling relative to the infection [44]. The model simulations unraveled a preferred host strategy for mycobacterial control that is implemented via the direct entry of macrophages into a granuloma site from lung vascular sources. The other model was used to predict the contribution of multiple TNFα activities to the control of Mtb infection within the granuloma, with the assumption that macrophage activation is a key effector mechanism for controlling bacterial growth in the lung. The simulation results suggested that bacterial numbers are a strong contributing factor to granuloma structure with TNF, and TNF-dependent apoptosis can reduce inflammation at the cost of impairing mycobacterial clearance [45].

One of the fundamental challenges in the control of pulmonary Mtb infection is to understand molecular mechanisms involved in the onset of latency and/or reactivation of Mtb after the initial infection. Magombedze and Mulder [46] built a mathematical model to simulate all possible Mtb latency occurrence scenarios in the lung based on the profile of differentially expressed genes. Their ODE model was used to simulate observed gene expression changes in in vitro latency models which allow for illustrating all possible latency/dormancy occurrence scenarios and latency reactivation. In a subsequent study, the same author used a systems biology approach combing both bioinformatics and mathematical modeling to identify potential drug target genes in the Mtb latency program. Boolean modeling of the data-driven regulatory network related to mycobacterial latency in the lung revealed a bistable switch between latent and actively replicating phases of Mtb [46].

4.2 Modeling Asthma

Multiscale models of the lung have been developed and applied to gain a better understanding of asthma in several aspects. These models incorporate and couple multiple spatial scales (molecules, cells, tissues, and the lung) underlying airway hyperresponsiveness

to simulate the complex physiological response to, e.g., allergens in asthma. Venegas et al. carried out a study that probed the scale of ventilation heterogeneity in asthmatic subjects using positron emission tomography imaging and that modeled complex interdependent behavior in the lung [47]. The authors found that ventilation is not uniform within bronchoconstricted regions, and within the ventilation defects themselves, there is considerable ventilation heterogeneity. Brook et al. developed an axisymmetric two-layer model of an airway wall to represent both lung slices and an intact airway in vivo, which resolves connective tissue and muscle cell properties within a composite muscle layer [48]. The model predicted that different types of airway remodeling in asthma lead to significantly different contractile responses and stress environments. For better understanding of airway hyperresponsiveness in asthmatic airways, a multiscale model of partial and ordinary differential equations was developed, which linked regulatory processes occurring at molecular and cellular level (Ca^{2+} and crossbridge dynamics) with physiological phenomena occurring at the organ level (lung deformation) [49, 50]. Chernyavsky et al. developed a mathematical model that qualitatively describes the growth dynamics of airway smooth muscle cells (ASM) over short and long terms in the normal and inflammatory environments typically observed in asthma [51]. This model allowed possible ASM accumulation scenarios to be explored and suggested possible new targets for diagnosis and prevention of ASM remodeling in asthma.

Recently, new consortia have started to apply systems biology strategies to asthma in a clinical context: Within the Innovative Medicines Initiative, a European project aims at a personalized management approach for patients with severe asthma (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome Consortium; U-BIOPRED) [52]. It involves scientists from universities, research institutes, the pharmaceutical industry, and small companies and plans to define phenotypes with respect to therapeutic efficacy by integrating -omics data from invasively and noninvasively obtained patient material and modeling of the underlying pathologies [53]. Another project aims to develop validated models that predict disease progression and response to treatment in asthma and COPD by integrating expertise in physiology, radiology, image analysis, bioengineering, data harmonization, security and ethics, computational modeling, and systems biology (Airway Disease Predicting Outcomes through Patient Specific Computational Modeling Consortium; AirPROM) [54]. This project is funded by the European Union 7th Framework Programme. Recently, the German Center for Lung Research (DZL) has established a systems biology platform [55] to integrate patient data from its cohorts for childhood wheezing and severe asthma in adults with experimental models by means of multiscale modeling.

4.3 Modeling Other Lung Diseases

To investigate airway disease resulting from inflammation and fibrosis following particulate exposure, Brown et al. used an agent-based model, which focuses on a limited number of relevant interactions, specifically those among macrophages, fibroblasts, pro-inflammatory (TNFα) and anti-inflammatory cytokines (TGFβ1), collagen deposition, and tissue damage [56]. The model predicted three distinct states of inflammation whose developments depend primarily on the degree and duration of particulate exposure. The predictions were consistent with in vivo experimental observations obtained after exposing mice lung tissue to particulate matter.

A mathematical model composed of partial differential equations that describe the interactions among immune cells and cytokines related to sarcoidosis in the lung was built by Hao et al. [57]. The model was calibrated and validated using clinical data on cytokine levels in healthy and diseased lung tissues and further used to explore the effect of potential treatments (such as anti-TNFα, anti-IL-12, anti-IFNγ, and TGFβ enhancement) that may reduce the disease activity through decreasing the size of sarcoid granulomas. Taken together, the constructed model is a step toward a more comprehensive study of sarcoidosis and its treatment.

Many end-stage respiratory diseases require lung transplantation as a last resort. However, with 27 % overall 10-year survival, this procedure shows the poorest long-term survival of all solid organ transplantations [58]. The main reason for this is the development of chronic lung allograft dysfunction (CLAD) by over 50 % of all lung transplant recipients within 5 years. Therefore, 14 lung transplantation centers teamed up to build a computational model to estimate the personal recipient risk to develop CLAD within 3 years after the transplantation (systems biology of CLAD, SysCLAD). They will analyze clinical, environmental, and immunological data, the microbiome and different -omics data both from donors and recipients [59].

One question that is still unsolved in lung cancer is how circulating tumor cells can develop at the primary site and traverse the circulatory systems. Having in mind the difficulties to generate suitable in vivo data to elucidate this question, mathematical modeling under the systems biology paradigm seems to be a good methodological option. In line with this, Kuhn's group used a Markov chain Monte Carlo model that describes cancer progression to identify and quantify the multidirectional pathways and timescales associated with metastatic spread from primary lung cancer [60, 61]. In contrast to the traditional view of cancer metastasis as a unidirectional process starting at the primary site and spreading to distant sites as time progresses, the authors quantified three types of multidirectional mechanisms of cancer progression based on large autopsy data sets: (1) self-seeding of the primary tumor, (2) reseeding of the primary tumor from a metastatic site,

and (3) reseeding of metastatic tumors [61]. By simulating the model, the authors showed that for lung cancer, the main spreaders (i.e., the distant site that has higher probability of transmitting than keeping circulating tumor cells from the primary site) are the adrenal gland and kidney, whereas the main sponges (i.e., the distant site that has lower probability of transmitting than keeping circulating tumor cells from the primary site) are regional lymph nodes, the liver, and bone.

4.4 Modeling Gas Exchange within the Lung and the Dynamics of Inhaled Pharmaceuticals for Lung Diseases

Mathematical models have been utilized not only for a system-level understanding of the whole respiratory system but also for a detailed understanding of several functions that contribute to gas exchange within the lung (reviewed by Ben-Tal and Tawhai [62]). Particularly, two studies have been carried out to investigate the effect of ventilation/perfusion mismatch on hepatopulmonary syndrome and lung inflammation, respectively. Chakraborty et al. developed a differential equation model of pulmonary oxygen uptake by considering three disparate scales, namely, micro (red blood cell), meso (capillary and alveolus), and macro (lung) [63]. The authors used the model to quantify the oxygen uptake abnormalities in patients with hepatopulmonary syndrome as a result of functional intrapulmonary right to left shunting of pulmonary blood flow, as well as spatial heterogeneity of ventilation/perfusion mismatch in the lung. Furthermore, the quantified pulmonary gas exchange abnormalities in the patients were used for stratifying them into two categories—those who are oxygen responsive and those who are oxygen nonresponsive with intractable hypoxemia. Reynolds et al. [64] developed a multi-compartment model of ODEs for gas exchange with focus on inflammation in acute lung injury. Using the model, the authors explored effects of inflammation on ventilation/perfusion distribution and the resulting pulmonary venous partial pressure oxygen level during systemic inflammatory stresses.

In the last years, a number of compartment-based pharmacokinetic (PK) models accounting for the kinetics of inhaled pharmaceuticals have been published. For instance, Sturm [65] developed a stochastic model describing mucociliary clearance in cystic fibrosis patients and its development with progressing course of the disease. The model showed that patients with cystic fibrosis have a higher risk of inhaled particle accumulation and related particle overload in specific lung compartments than healthy subjects. Markovetz et al. built a more complex model to describe the mucociliary clearance and absorption of aerosolized radiolabeled particles and small molecular probes from human subjects with and without cystic fibrosis [66]. This model captured the mucociliary clearance and liquid dynamics of the hyperabsorptive state in cystic fibrosis airways and the mitigation of that state by hypertonic saline treatment.

5 Perspectives

Despite all clinical and scientific efforts so far, lung diseases cause an enormous suffering and death toll from patients and socioeconomical costs for our societies and health-care systems, especially in the fields of infection, malignancies, chronic noncommunicable diseases, and allergy. This may be in part due to complicated, even prenatal, timelines, and heterogeneous clinical phenotypes. On the other hand, new scientific insights, e.g., in the role of the microbiome and noncoding RNA, and new technological developments, e.g., the new sequencing technologies, may help us to improve our clinical performance in future. But these tremendous amounts of clinical and molecular data require a new way of organizational, technological, and intellectual cooperation between many clinical, experimental, and theoretical disciplines, called "systems medicine." Many questions remain to be answered: What type and amount of clinical data do we need and can we afford to collect and analyze? What will be the role of animal models, human tissue models, complex cell culture models, or even artificial organs on a chip? How can we bring all these complex and multilevel data together by means of mathematics and computer science? Improving clinical practice in respiratory medicine will require enthusiasm and hard work from all participating physicians and scientists, as well as sustained support by our governments, funding agencies, and all stakeholders of our health-care systems.

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