Preface

The blood–gas barrier (BGB) in vertebrates is the tissue interface separating the ambient oxygen from red blood cells within the capillaries of the gas-exchanging organs. The BGB allows acquisition of O_2 from the ambience in exchange for CO_2 from respiring tissues. To accomplish this, the BGB has a unique tripartite structure which can be remodelled to accomplish specific diffusion needs. Although the scope of vertebrates is very diverse in terms of zoogeography and even physiology, the structure of the BGB has been well preserved through evolution. This book broadly covers the entire BGB in 10 chapters; from aspects of diffusion, structure, embryological development, injury and remodelling, to preservation during tissue transportation. The book would therefore be interesting to students, teachers, researchers and even clinicians dealing with respiratory biology.

Passage of gases via the BGB occurs through simple diffusion because diffusion is an 'economical process'. Diffusion is an almost unavoidable phenomenon built in the energy of the universe. At temperatures above the absolute zero, all particles have some thermal energy responsible for various forms of interactions, which allows atoms to disperse spontaneously within a crystal of their own species (Piiper et al. 1971). The thermodynamic activity is responsible for intermolecular reactions and the solubility of gas molecules into liquids. Most importantly, thermodynamic activity is the source of the pressure responsible for *diffusion*, that is, the passive displacement of particles from regions of high activity to regions of low activity; no additional energy is required other than the original thermodynamic activity. This activity enables diffusion of gases across the BGB. The first chapter (Jacopo Mortola) comprehensively captures principles of gas diffusion where gas laws are adequately elucidated.

The pulmonary BGB is exceptional by its remarkable thinness and vast surface area (Weibel 1984). Its diffusing capacity of oxygen correlates directly with the surface area and inversely with the thickness. Structurally, the pulmonary BGB comprises an epithelial cell, an interstitial space and an endothelial cell. Along and across the evolutionary continuum, the thin, essentially three-ply laminated architecture of the BGB has been widely and greatly conserved in lungs of animals that remarkably differ morphologically, phylogenetically, behaviourally and ecologically. On the transition from aquatic to terrestrial life, and with it, preponderance

of air-breathing as means of acquiring oxygen (O_2), the 'layered' design appears to have been the only practical structural solution to supporting efficient movement of O_2 from air to blood by means of simple passive diffusion. The second chapter (John Maina) describes the BGB from a bioengineering perspective with details on functional capacities.

During embryological development, the vertebrate lung inaugurates as a primitive endodermal bud from the ventral aspect of the primitive foregut (Bellairs and Osmond 1998). The bud divides into primitive airways that form gas-exchanging chambers, where a thin BGB is accomplished. The development of the BGB in the compliant mammalian lung entails conversion of columnar cells of the migrating tubes to primitive type II cells and lowering of the apical intercellular tight junctions so that the gaps between the cells enlarge. The latter cells give rise to the definitive alveolar type II (AT-II) and type I (AT-I) cells. Extrusion of the lamellar bodies and thinning and stretching of the cells attains the squamous phenotype, characteristic of AT-I cells. Diminution of interstitial tissue, fusion of capillaries and apposition of capillaries to the alveolar epithelium results in formation of a thin BGB. In contrast, in the non-compliant avian lung I, attenuation proceeds through cell-cutting processes, referred to as secarecytosis (Makanya et al. 2006). Several morphoregulatory molecules including transcription factors such as Nkx2.1, GATA, HNF-3, WNT5a, signaling molecules including FGF, BMP-4, Shh and TFG-β and extracellular matrix proteins and their receptors have been implicated (Waburton et al. 2005; Makanya et al. 2013). In the postnatal period, alterations in the BGB may occur during late phases of alveolarization or as repair subsequent to lung injury. The third chapter (Andrew Makanya and Valentin Djonov) describes BGB formation in both mammals and birds, both in the prenatal and perinatal period.

The fourth chapter (David Budd, Victoria Burton and Alan Holmes) details the factors that come into play in maintenance of a healthy BGB. Besides formation of an efficient BGB, it is important that it remains healthy for optimal function. Disruption of the BGB is an early pathological event in a number of acute and chronic life-threatening pulmonary disorders. Thus, understanding the molecular processes that modulate the barrier function of the BGB is vital to aid in the development of new treatment paradigms. Airborne and blood-borne environmental challenges modulate signaling pathways that can severely compromise the ability of the BGB to maintain an effective barrier function. Successful rapid reconstitution of pulmonary epithelial and endothelial monolayers and restoration of junctional complexes following injury is essential to limit lung tissue damage, permit effective gas exchange and to preserve normal tissue architecture (Vandenbroucke et al. 2008). An inability to withstand these environmental challenges and efficiently affect endogenous reparative processes predisposes susceptible individuals to the development of lung diseases.

In Chap. 5, the authors (Panfeng Fu and Viswanathan Natarajan) discuss the signaling pathways that enhance barrier function. The endothelium and epithelium of the BGB form the size-selective barrier that controls the exchange of fluid from blood. Therefore, the integrity of vascular endothelium and epithelium is critical for lung function preservation and normal gas exchange. Movement of trans-

endothelial fluid and leukocyte flux occurs through paracellular gaps, which are formed at sites of active inflammation between vascular endothelial cells. Paracellular gap formation is regulated by the balance of competing contractile forces that generate centripetal tension and adhesive cell–cell and cell–matrix tethering forces intimately linked to the actin- and myosin-based endothelial cytoskeleton. Actin and myosin microfilaments, critically involved in endothelial barrier regulation, are physically coupled to multiple membrane-spanning target proteins found in intercellular junctions and focal adhesion complexes. Intercellular contacts along the endothelial monolayer consist primarily of adherens and tight junctions, which link to the cytoskeleton to provide both mechanical stability and transduction of extracellular signals into the cell. In addition, dynamic actin polymerization at the endothelial cell periphery produces cortical structures that are essential to barrier enhancement by barrier-enhancing agonists. Maturation of adherens and tight junctions not only forms a tight connection between cells and their surrounding environment, but also initiates signaling pathways regulating cytoskeletal remodelling. Contrarily, these junctions are targets for various intracellular signaling pathways activated by barrier-protective factors. Net movement of solute across the alveolar epithelium plays an especially important role in lung fluid homeostasis and appropriate oxygenation of the body. Apically located epithelial sodium channels, alongside the coordinated action of basolateral Na/K ATPase pumps play a critical role in generating and sustaining the osmotic gradient needed for net fluid reabsorption across lung epithelia (Eaton et al. 2009). In Chap. 6 (Charles A. Downs and My N. Helms), the dynamics of trans-barrier fluid and ion transport have been presented with an emphasis on the role of ion channel transporters, pumps that are important in maintaining alveolar fluid homeostasis and biophysical changes to the cell membrane that can occur under pathological conditions.

The lung epithelium is also uniquely exposed to an oxidizing environment, and therefore, the role of oxidants and antioxidants must be taken into careful consideration when evaluating the pathogenesis of trans-barrier dysfunction(s), which lead to lung disorders. Severe disruption to the barrier properties of the alveolar capillary membrane occurs in acute respiratory distress syndrome, whereas dysfunction in ion channels and transporters are the root cause of cystic fibrosis and chronic obstructive pulmonary disease.

Over and above disruption by disease, the BGB can undergo stress failure since it must be exceedingly thin to allow adequate transfer of gases across it by diffusion (Maina and West 2005; West et al. 1991). In Chap. 7 (John B. West), the causes and consequences of stress failure of the BGB have been documented. Under some physiological conditions, humans develop arterial hypoxemia because the diffusion rate of oxygen through the barrier is insufficient. Next, the barrier must be immensely strong to prevent bleeding into the alveoli. However, again this occurs in humans under some physiological conditions, and it is particularly striking in animals such as thoroughbred racehorses that are capable of very high aerobic activity. Mechanical failure of the barrier can occur when it is exposed to high stresses. Failure is seen if the capillary transmural pressure is greatly increased, the lung is inflated to very high volumes or the type IV collagen that is responsible for strength

becomes abnormal in disease. Remodelling of the barrier is seen if the stresses increase over a period of time.

In addition to its physiological function, the BGB also provides a barrier to protect against inhaled particles and pathogens. Chapter 8 (Holger C. Müller-Redetzky, Jasmin Lienau and Martin Witzenrath) describes the events and effects that characterize the endothelial component of the BGB. Following infectious or sterile inflammatory conditions, strictly controlled endothelial leakiness is required for leukocyte transmigration. However, increased permeability caused by host-dependent inflammatory mechanisms or pathogen-induced endothelial injury may lead to uncontrolled protein-rich fluid extravasation, lung edema and finally, acute respiratory distress syndrome (ARDS) (Bhattacharya and Matthay 2013), which still carries an unacceptably high mortality rate. A detailed overview of the major mechanisms underlying pulmonary endothelial barrier regulation and disruption, focusing on the role of specific cell populations, complement and coagulation systems and mediators including angiopoietins, sphingolipids, adrenomedullin as well as reactive oxygen and nitrogen species in the regulation of pulmonary vascular permeability is also provided in Chapter 8.

Preservation of the structural and functional status of the BGB is pivotal in successful lung transplantation. The BGB is subjected to a variety of stressors during all phases of lung transplantation. These result in ischemia-reperfusion (IR) injury and can manifest clinically as primary graft dysfunction (PGD). IR injury affects the epithelium, interstitium and endothelium of the alveolar septa as well as the pulmonary surfactant system. It leads to functional and morphological damage and death of pulmonary cells largely due to an inflammatory response by activated resident cells as well as inflammatory cell infiltration, which is governed by a large number of mediators (Yeung and Keshavjee 2014). Since PGD is the major cause of early morbidity and mortality after lung transplantation, much effort is undertaken from organ procurement, to preservation and implantation to prevent or ameliorate IR injury including surgical management procedures and pharmacological additives to perfusion solutions or ventilation gas. Particularly to increase the rate of transplantable donor organs, very promising results are achieved by the new technique of ex vivo lung perfusion (EVLP). Beyond the immediate transplantation period, the BGB is jeopardized in certain forms of acute rejection and chronic lung allograft dysfunction. Chapter 9 (Anke Schannaper and Matthias Ochs) in this book explores this subject in good detail.

Gas exchange during fetal/embryological development occurs through specialized structures, namely, the chorioallantoic membranes in oviparous vertebrates and the placenta in eutherians. The avian egg and mammalian placenta are transient structures, which are discarded after hatching or parturition but, during their lifespan, must adapt to the changing needs of the growing embryo/fetus. The embryo/fetus exerts demands on its environment whether it be the impersonal one in which an egg is laid, or the nurturing one within the body of the mother. In the case of the avian egg, nutrients are obtained internally but respiratory oxygen (O_2) must be obtained from the environment (Bissonnette and Metcalfe 1978). In eutherian

mammals, nutrients and O_2 are obtained from the mother via the placenta. The capacity of the egg and placenta to transfer O_2 to the embryo/fetus is expressed as a diffusive conductance (DO_2 in the units $cm^3O_2.min^{-1}.kPa^{-1}$). For these and other gas exchangers, a morphometric estimate of DO_2 can be obtained by combining stereological estimates of relevant microstructural quantities (vascular volumes, exchange surface areas and harmonic mean diffusion distances) with physiological data (O_2-haemoglobin reaction rates and Krogh's permeability coefficients). In Chap. 10, the avian egg and human placenta are taken as models for gas exchangers and their structures and functional capacities are compared. Particular focus is accorded to the human haemochorial placenta and its ability to serve the growing needs of the fetus is illustrated using results from normal and compromised pregnancies.

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