

## Editorial

### The Role of Arginase in Lung Disease

Nitric oxide synthases (NOSs) metabolize the amino acid L-arginine to form nitric oxide (NO) and L-citrulline. NO is involved in a broad spectrum of processes in the lungs and airways, including perfusion, ventilation, inflammation, infection and airway clearance. The activity of NOS can change in response to, for instance, inflammatory stimuli that can alter enzyme expression. In addition, NOS activity can be regulated post-transcriptionally by specific endogenous NOS inhibitors, such as asymmetric dimethylarginine (ADMA), but also by substrate limitation. The arginase isoenzymes decrease NO production by reducing the availability of L-arginine for NOS [1]. There is accumulating evidence that disturbances of the balance between the L-arginine metabolizing enzymes can result in both acute and chronic pathological changes. Reduced substrate availability for NOS affects the regulation of airways smooth muscle tone for instance in asthma methacholine responsiveness, and downstream products of arginase activity i.e., L-proline and the polyamines, may contribute to lung fibrosis and airway remodeling [1-3].

In this Supplement to The Open Nitric Oxide Journal, after a comprehensive introduction into the L-arginine metabolism by Racké and Warnken [1], the role or potential roles of arginase and the arginase/NOS balance is reviewed for chronic lung and airway diseases, including asthma, cystic fibrosis and sickle cell lung disease [3-5]. Evidence suggests that a shift of the arginase/NOS balance towards arginase, and thus decreased NO production, contributes to reversible airway narrowing and airflow limitation in these conditions. In addition, downstream products of arginase activity may also contribute to airway remodeling in these diseases. The role of arginase in obstructive airway disease is best studied in animal models of allergic airways inflammation that mimic the airways hyperresponsiveness and remodeling of asthma. Present animal and human studies on this topic are reviewed by North and colleagues [3]. In cystic fibrosis (CF) lung disease, the production of airway NO is reduced, when compared to healthy controls. Substrate limitation for NOS may contribute to NO deficiency and airflow limitations in CF patients, as arginase activity is increased in sputum and correlates with airway NO production and pulmonary function [4].

Vascular constriction and remodeling contributes to the development of pulmonary hypertension in sickle cell disease (SCD) and other hemolytic anemias. Hemolysis results in the release of intracellular arginase from red blood cells, which consumes circulating L-arginine and results in decreased vascular NO production. Morris, herein, reviews recent evidence suggesting that arginase-induced depletion of L-arginine may also contribute to SCD-related lung disease [5].

Lung transplantation is accepted therapy for end stage lung diseases and changes in pulmonary NO production may serve as marker of organ dysfunction. Increased arginase activity contributes to pathology after solid organ transplantation, and, in lung transplant recipients, arginase may contribute to organ dysfunction and impact on allograft perfusion, ventilation, acute rejection and graft remodeling [6].

In addition, this supplement contains two reviews focusing on the role of arginase in host defense. Moraes summarizes how modulation of arginase may alter the course of respiratory viral diseases [7]. Douda and Palaniyar review the role of arginase in innate immunity and mechanisms involved in host defense against bacterial infections [8]. Finally, Ivanecky and Belik present an original research study in which they show that pregnancy-induced systemic vasodilatation in the female rat was mediated by a decrease in arginase activity, whereas vascular tissue arginase activity was upregulated in the fetal lung [9]. While increased arginase activity in the fetal lung may contribute to maintaining a high pulmonary vascular resistance before birth [10], the observed contrasting changes in maternal and fetal arginase activities may suggest that a disturbance of this balance on the mother's side could contribute to cardio-pulmonary complications in the newborn.

Arginase and other players in the complex cardio-pulmonary L-arginine metabolome may soon become the target of specific therapeutic interventions aiming to either increase L-arginine availability for pulmonary NOS and/or modulate arginase and down-stream products of arginase activity in the lungs and airways.

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