



## Guest Editorial

## Tryptophan metabolic pathway, airway nitric oxide, and allergy



Allergic inflammation is characterized by type 2 immunity, as indicated by the presence of T-helper cell type 2 lymphocytes and allergen-specific immunoglobulin E.<sup>1</sup> The type 2 immune response promotes downregulation of type 1 immunity, including T-helper cell type 1–dependent cytokines, namely interferons.<sup>2</sup> In this regard, interferon- $\gamma$  is a strong inducer of the enzyme indoleamine 2,3-dioxygenase-1 (IDO), which degrades the essential amino acid tryptophan. This metabolic pathway acts as part of the anti-proliferative and regulatory strategy of immunocompetent cells to halt the growth of infected and malignant cells. More interestingly, the IDO pathway might play a central role in regulating allergic inflammation.<sup>3,4</sup> Indeed, IDO was initially associated with the prediction of a poor response to allergen-specific immunotherapy.<sup>5</sup> Later, tryptophan concentrations were found to be higher in patients off pollen season than in season.<sup>6</sup> Notably, serum concentrations of serotonin, another metabolite of tryptophan regulated by IDO, increased in patients with pollen allergy and related well to impaired quality of life, mainly concerning mood.<sup>7</sup> Hence, this outcome reinforces the pathophysiologic role played by the IDO pathway in the development and clinical course of allergic disorders.

In this month's *Annals*, Hu et al<sup>8</sup> report on an interesting study of a pediatric population with allergic asthma. They compared children with asthma with healthy children and evaluated IDO activity, measured in blood and in sputum, and fractional exhaled nitric oxide (FeNO). Actually, IDO activity was indirectly measured by the kynurenine-to-tryptophan ratio, a reliable index of tryptophan breakdown. This study found that the expression of IDO was significantly lower in children with allergic asthma.<sup>8</sup> This study adds to the literature evidence that IDO activity is significantly decreased in airways of children with asthma consistent with blood IDO activity. Unfortunately, IDO activity did not correlate with age, sex, peripheral eosinophils, or asthma severity.

However, specific interactions between IDO and nitric oxide (NO) could be important because enhanced formation of NO has been reported in patients with asthma and allergic rhinitis.<sup>9</sup> In particular, FeNO could be considered a convincing biomarker for type 2 bronchial inflammation. To consolidate the close link between FeNO and IDO, it has been reported that serum nitrite concentrations are higher in patients with allergy out of pollen season than in season.<sup>10</sup> Likewise, it is well documented that NO slows down the expression and activity of the heme enzyme IDO.<sup>4</sup> These observations are explainable because tryptophan concentrations increase from the suppression of IDO activity by NO. As a result, inhibitors of inducible NO synthase could be candidates for

antiallergic therapy that might decrease the production of NO and thus abrogate the arrest of IDO. In this context, Hu et al confirmed that IDO activity negatively correlates with FeNO. In other words, IDO activity decreases as FeNO increases. This outcome highlights the potential role of the tryptophan metabolic pathway as a pivotal actor in the scenario of the regulation of type 2 immunity in allergic disorders. From this view, Hu et al tested combined IDO activity and FeNO as ancillary biomarkers in asthma management. However, some caveats remain to be defined. First, IDO might be considered a reliable biomarker of asthma only if some requirements are well evidenced, including a clear relation between IDO and clinical outcomes at baseline, over time, and after treatments. Second, it has to well define specificity, sensibility, reproducibility, and measurability by an analytically validated assay. Third, IDO measurement should be easily performed and everywhere available. Fourth, a clear relation between the course of allergic inflammation and IDO expression should be documented.

This study by Hu et al, even with some limitations, mainly the very limited number of patients, is clinically relevant because it provides evidence that IDO activity is closely associated with type 2 immunity and confirms its potential pathogenic role in allergic asthma.

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