

# Journal Pre-proof

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William W. Busse, MD



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**Asthma and Psoriasis – What do they have in common? IL-17A!**

William W. Busse, MD

Corresponding author:

William W. Busse, M.D.

Professor of Medicine

University of Wisconsin Hospital

K4/910 CSC, MC 9988

600 Highland Avenue

Madison, WI 53792

Tel: (608) 263-6183

FAX: (608) 261-1191

Email: [wwb@medicine.wisc.edu](mailto:wwb@medicine.wisc.edu)

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When I first saw the paper by Östling and colleagues, “IL-17-high asthma with features of a psoriasis immunophenotype,<sup>1</sup>” my first response was “what does psoriasis have to do with asthma?” As the authors aptly demonstrate, and I will try to highlight, they have identified a link between the immunophenotype of psoriasis and asthma. This information provides novel insights into a largely unexplored phenotype, or endotype, of asthma – the non-T2, IL-17 pathway. However, as I will discuss, their data more specifically points to the IL-17A pathway of severe asthma

Immunophenotypes of severe asthma have been arbitrarily divided into two major classes: Type (T)-2-high and T2-low, or T1.<sup>2</sup> The downstream pathways of T2 severe asthma include the generation of IL-4, IL-5 and IL-13, with well-identified airway target organ effects including eosinophilia, IgE production, polarization to a Th2 profile, mucus hypersecretion, and altered airway structure and function. The translation of the T2 profile to mechanisms of severe asthma has been instrumental to identify patient populations for T2 biologics that block IgE, IL-5, and IL-4/IL-13 pathways. Having available biomarkers that reflect the T2 pathway, e.g. eosinophils, FeNO, and IgE, provides clinical guidance to identify patients with a T2 asthma immunophenotype, where the T2 biologics are most likely to achieve clinical efficacy.<sup>2</sup>

As Östling and U-BIOPRED co-authors indicate, the role of IL-17 in asthma is far less well defined than the T2 profile, certainly important, but difficult to identify the affected asthma patient because clinical characteristics of this phenotype are not fully defined. Other investigators<sup>3,4</sup> have described the biological properties of IL-17 and its potential contributions

to the pathophysiology of asthma in subpopulations of patients, and have identified IL-17's presence in severe asthma.<sup>5</sup> For many of us, IL-17 is considered to be the prototype cytokine for non-T2 severe asthma, and characterized by neutrophilic airway inflammation, a diminished responsiveness to corticosteroids, dysbiosis, older age<sup>6</sup> and a potential contributing factor for the emergence of respiratory bacteria.<sup>3</sup> Clinical trials with biological antagonists for IL-17, specifically the IL-17RA antagonist, brodalumab, have failed to elicit a consistent pattern of efficacy thus questioning whether the IL-17 pathway plays a role in severe asthma.<sup>7</sup> The findings of Östling and coworkers<sup>1</sup> now provide insight to the clinical phenotype, or phenotypes, of IL-17-associated severe asthma and also illustrate how the use of big data that exist in U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes), provide for an informative approach to identify asthma immunophenotypes, including those associated with an over-expression of the IL-17 pathway. Given this unmet need, how did the authors link genetic markers of psoriasis to asthma and a disease pattern associated with IL-17?

A first, and initial, step to interrogate the role and contribution of IL-17 in severe asthma requires a database, which, for this study, includes transcriptomic data sets from U-BIOPRED.<sup>1</sup> U-BIOPRED has a detailed database of clinical characteristics and access to a biobank with bronchial epithelial samples and mucosal biopsies. Utilization of these bronchial samples to establish the finger prints of the immunophenotype of IL-17 was guided by findings from two previous studies in which genetic markers in T2-high and IL-17-high asthma are described.<sup>8,9</sup>

To put the investigative approach of Östling et al into perspective, a brief review of these two background studies is needed. First, to identify which novel epithelial genes were regulated by

IL-13 and reflect the Th-2 pathway, Woodruff et al<sup>8</sup> incubated bronchial brushings from normal and asthma subjects with IL-13. Three IL-13-dependent and distinct epithelial genes were identified in asthma: Serpin B2, CLCA1 and postin (periostin) and formed an identification of T2 asthma. Second, and using the same investigative approach, Choy and co-workers<sup>9</sup> incubated bronchial epithelial cells with IL-17A or IL-13, and TNF- $\alpha$ , alone or in combination with IL-17A. Their readouts identified the expression of epithelial genes associated with to IL-17A: IL-8, CXCL3, CSF3, CXCL1 and CXCL 2. They also found the expected IL-13 epithelial genetic pattern noted by Woodruff et al,<sup>8</sup> Serpin  $\beta$ 2, CLCA1 and periostin.<sup>9</sup> These studies provided a framework and approach to link epithelial gene-expression patterns to the IL-13 or IL-17 pathways in the U-BIOPRED samples.

An additional background point to more fully appreciate Östling et al's<sup>1</sup> findings is to recall that IL-17 represents a family of cytokines or isoforms: IL-17A, -17B, -17C, -17D, 17E (also called IL-25) and -17F. Although structural similarities exist between the IL-17 family of cytokines, interesting and distinct properties are found with individual members.<sup>10</sup> For example, IL-17E, or IL-25, is pathogenic in psoriasis but also has T2 generating capacities. IL-17A, however, is the focus of Östling et al<sup>1</sup> and has an important, perhaps pivotal, role in the pathophysiology of psoriasis, and therapies directed against IL-17A (e.g. secukinumab and ixekizumab or IL-17RA) lead to dramatic control of psoriasis. Moreover, in mouse models of chronic obstructive pulmonary disease, IL-17A contributes to airway neutrophilia and acute exacerbations.<sup>4</sup> Finally, when Choy et al<sup>9</sup> investigated which epithelial products follow IL-17 activation, it was IL-17A that was used for stimulation. Furthermore, IL-17A potentiates the effects of other inflammatory mediators, like tumor necrosis factor (TNF)- $\alpha$ , by stabilizing target mRNA; TNF- $\alpha$  was included

in the epithelial gene profile by Choy et al.<sup>9</sup> Not to edit the findings of Östling et al, but it is important to note that their observations likely represent the actions of IL-17A, and not all members of the IL-17 family.

Using gene expression microarrays from the endobronchial biopsies from 91 asthma subjects in U-BIOPRED, Östling et al<sup>1</sup> validated the distinct gene-expression profiles associated with IL-13 vs IL-17A activation (see Figure 2 in their article). Armed with these gene product data, the authors assessed their association with the clinical characteristics found in the U-BIOPRED cohort. Eighty-five bronchial brushings and 68 bronchial biopsy specimens were available from the 91 U-BIOPRED participants for such an analysis following activation with either IL-13 or IL-17A. Hierarchical clustering analysis was applied to the gene signatures expressed by these U-BIOPRED epithelial cells. Although the total number of patients used for analysis was small, 10 asthma patients had an IL-13 high genetic marker profile and 22 asthmatic subjects aligned with an IL-17A high pattern. Using the combined 8 gene sets identified with IL-13 and IL-17A, distinct IL-13 high (n=13) and IL-17 high (n=13) clusters emerged with neither cluster having simultaneously high expression of both signatures (**see Figure 1C**). When the IL-17A high phenotype-associated Differentially Expressed Genes (DEG) were analyzed, the canonical pathway analysis identified the “role of IL-17A in psoriasis” with the greatest overlap in the list of 797 DEGs.

How and why are these associations with the immunophenotype of psoriasis important and relevant to severe asthma? As the authors explain, they reviewed the clinical characteristics of the U-BIOPRED subjects studied, and psoriasis was not an associated finding in this small

patient population. However, associations have been noted for an increased asthma risk in the presence of co-existing psoriasis;<sup>6</sup> in addition, childhood asthma was associated with a significantly increased risk for psoriasis. Furthermore, the cutaneous debilitating features of psoriasis have been most dramatically responsive to anti-IL-17A monoclonal antibody treatment, confirming the importance of the IL-17A pathway to the pathophysiology of psoriasis.

With the wealth of clinical phenotyping in U-BIOPRED subjects, it was possible for the authors to propose a clinical profile associated with IL-17A high asthma. Fifty-nine percent of the IL-17A high patients had severe asthma, 38% had more than two exacerbations in the preceding year, 43% had nasal polyps, and 27% had been receiving regular antibiotics; oral corticosteroid use did not distinguish the IL-17A subjects from the other comparative groups. In a sub-clustering analysis, airflow obstruction was also a clinical pattern of the IL-17A expressing subjects. The IL-13 high group had sputum (49.3%) and blood (7.9%) eosinophilia and elevated FeNO (59.9 ppb). In contrast, the IL-17A-high phenotype had greater airways neutrophilia both in the sputum (63.7%) and the bronchial submucosa biopsy. Thus, Östling et al confirm an anticipated clinical phenotype of IL-17A severe asthma with distinct immuno-inflammatory characteristics and, surprisingly, a link to the genetic pattern of psoriasis.<sup>1</sup>

Another unique and possible breakthrough in recognizing IL-17A-associated severe asthma was an identification of a positive association with increased urinary 11-dehydrothromboxane B<sub>2</sub>, a degradation product of thromboxane B<sub>2</sub>. As the authors note, the expression of this urinary biomarker is also increased in both spontaneous and allergen-provoked asthma exacerbations. If this urinary biomarker is confirmed to identify the IL-17A non-T<sub>2</sub> phenotype, it represents the

fulfillment of a major unmet need to have a diagnostic biomarker to identify IL-17A-associated disease and, consequently, the most appropriate potential candidates for future anti-IL-17A treatment.

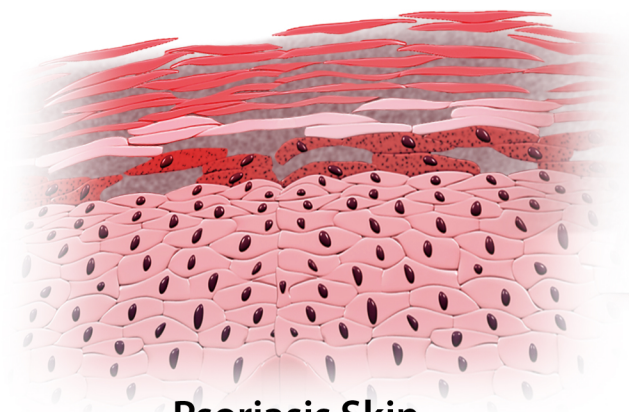
From my perspective, the research by Östling and coworkers<sup>1</sup> is noteworthy, instructive, and innovative for reasons already noted. Perhaps, most illustrative of my enthusiasm was their use of the large and comprehensive database from U-BIOPRED and their application of phenotypic links to the IL-17A molecular pathways in a relevant airway tissue – epithelium. Being able to probe a comprehensive clinical database opened doors not previously possible, and from such an approach, it will be possible to further link other molecular markers to clinical phenotypes and guide eventual applications of precise therapeutic interventions. Second, correlating clinical phenotypic features to the genetic markers linked to IL-17A substantiates and, I believe, validates the expected immunophenotype of IL-17A severe asthma, i.e. neutrophilic airway inflammation. In the face of these new data, why didn't blockage of IL-17RA with brodalumab provide a clinical signal in moderate-to-severe asthma?<sup>7</sup> Although there are no direct answers to that question, a number of possibilities exist. Choy et al<sup>9</sup> detected the epithelial genetic markers to IL-17A in the presence of TNF- $\alpha$ . Is it possible that a dual blockage of both IL-17A and TNF- $\alpha$  will be necessary for disease control in the non-T2 phenotype? More likely, patients in the IL-17A at-risk population were not identified as the initial study<sup>7</sup> with inclusive criteria and thus not a selective IL-17-family associated asthma population. The use of an apparently more specific biomarker, urinary 11-dehydrothromboxane B2, may fulfill the need to identify the correct IL-17A at-risk patients.

Finally, and fascinating to me, was the genetic association with psoriasis. Although we recognize associations of asthma with some skin diseases, like atopic dermatitis, the link of asthma to psoriasis was perhaps unexpected, but should not have been a surprise. Both psoriasis and asthma affect epithelial cell biology and barrier function. IL-17A's actions are broad and include effects on keratinocytes, anti-microbial function, neutrophils and mast cells, and may contribute to systemic manifestations, e.g. psoriatic arthritis. The parallel between psoriasis and asthma may, at this time, be insights into the complexity of the IL-17A pathway and pathobiological effects which follow its activation. Moreover, our interpretation of Östling's et al<sup>1</sup> findings should also follow the notations with psoriasis as being an IL-17A-driven disease and for us to increase the precision of IL-17's role in asthma to the IL-17A family member. Östling and colleagues' report<sup>1</sup> provides an appreciated and expanded understanding of IL-17A-associated asthma and potential clues to more effectively and accurately identify asthma populations in which the IL-17A pathway is directive of airway disease. Asthma is complex, but analyses by Östling et al<sup>1</sup> serve to demystify and identify important subpopulations for eventual improved and effective treatments.

### References

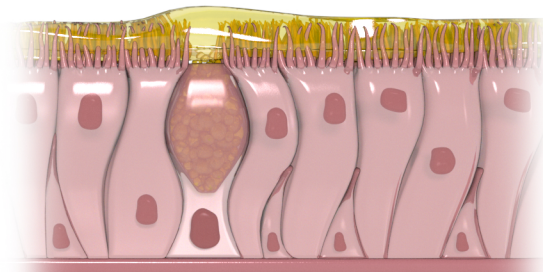
1. Ostling J, van Geest M, Schofield JPR, Jevnikar Z, Wilson S, Ward J, et al. IL-17-high asthma with features of a psoriasis immunophenotype. *J Allergy Clin Immunol* 2019.
2. Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. *N Engl J Med* 2017; 377:965-76.
3. Gurczynski SJ, Moore BB. IL-17 in the lung: the good, the bad, and the ugly. *Am J Physiol Lung Cell Mol Physiol* 2018; 314:L6-L16.
4. Roos AB, Sethi S, Nikota J, Wrona CT, Dorrington MG, Sanden C, et al. IL-17A and the Promotion of Neutrophilia in Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; 192:428-37.
5. Chakir J, Shannon J, Molet S, Fukakusa M, Elias J, Laviolette M, et al. Airway remodeling-associated mediators in moderate to severe asthma: effect of steroids on TGF-beta, IL-11, IL-17, and type I and type III collagen expression. *J Allergy Clin Immunol* 2003; 111:1293-8.
6. Wang J, Ke R, Shi W, Yan X, Wang Q, Zhang Q, et al. Association between psoriasis and asthma risk: A meta-analysis. *Allergy Asthma Proc* 2018; 39:103-9.
7. Busse WW, Holgate S, Kerwin E, Chon Y, Feng J, Lin J, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med* 2013; 188:1294-302.
8. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009; 180:388-95.

9. Choy DF, Hart KM, Borthwick LA, Shikotra A, Nagarkar DR, Siddiqui S, et al. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma. *Sci Transl Med* 2015; 7:301ra129.
10. Brembilla NC, Senra L, Boehncke WH. The IL-17 Family of Cytokines in Psoriasis: IL-17A and Beyond. *Front Immunol* 2018; 9:1682.



**Psoriasis Skin  
Epithelium**

**+IL-17A**



**Asthma Airway  
Epithelium**

**Differentially Expressed Genes**

**Psoriasis**

**Asthma**

**IL-1B, IL-6, IL-8 and  $\beta$ -defensins**

