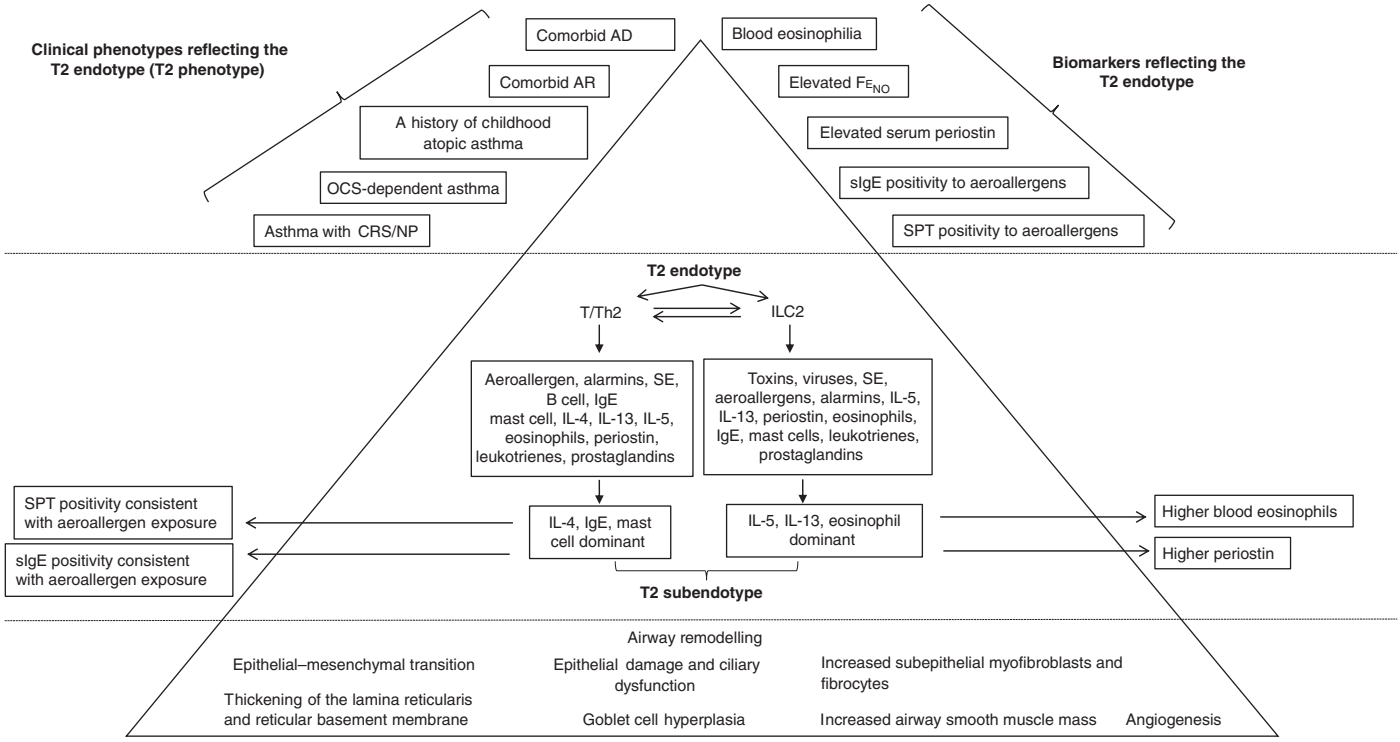

Figure 1. T2 asthma phenotype/endotype and biologic markers reflecting the T2 endotype. AD = atopic dermatitis; AR = allergic rhinitis; CRS/NP = chronic rhinosinusitis/nasal polyps; F_{ENO} = fractional exhaled nitric oxide; ILC = innate lymphoid cells; OCS = oral corticosteroid; SE = *Staphylococcus aureus* enterotoxins; sIgE = specific IgE; SPT = skin prick test; T = type; Th2 = T-helper cell type 2.

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Reply to Yilmaz and Çetin

From the Author:

I am delighted by the thoughtful response to my recent article (1). I believe the overall concept of defining visible and invisible sides of the iceberg is an excellent approach. It allows us to begin to conceptualize the relationships of clinical, physiologic, and biologic characteristics, which in composite we refer to as *phenotypes*, to the underlying complex immunoinflammatory characteristics, which constitute the *molecular phenotype* and eventually lead us to *endotypes*. Combining clinical features with type 2 (T2) biomarkers has allowed us to identify a "visible" T2 asthma phenotype. Yet, even this *visibly* defined broad clinical phenotype of T2 asthma is still evolving. Incorporating clinical features such as age at onset and responses to targeted therapies allows clinicians to move beyond

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the simplistic concept of T2 asthma and begin to identify *visible* subphenotypes under this T2 asthma umbrella term (1, 2).

I am also in complete agreement that the "invisible" underlying pathobiology is complex. In fact, the two-arm mechanism for T2 asthma endotypes proposed is likely an oversimplification that does not fully explain the wide ranges of severity and responses to targeted biologic therapies. Rigorous clinical phenomics, linked with next-generation sequencing and mechanistic pathologic studies of targeted biologic therapies, continue to refine the airway disease space we know as *asthma*. This two-way information stream from clinical to mechanistic and back to clinical will clearly lead to the development of novel biomarkers better at defining smaller molecular phenotypes of T2 asthma to improve our clinical phenotyping. Continuing on with this iterative path between clinical and pathobiologic characteristics should soon allow us to identify the "*distinct* functional or pathobiological mechanisms" that then truly define endotypes. ■

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