

Can you please give us a brief overview of Type 2 Inflammation?

Type 2 inflammation is a normal part of the body's immune system and is important in fighting off certain kinds of infections.(1,2) Sometimes, as a result of genetic factors(3,4,5,6), environmental triggers (7,8,9) and a kind of overactive response of the immune system(10,11,12), excessive type 2 inflammation may lead to disease.(13)

1. Gause, William C., Thomas A. Wynn, and Judith E. Allen. Type 2 immunity and wound healing: evolutionary refinement of adaptive immunity by helminths. *Nature Reviews Immunology*. 2013;13(8):607-614.
2. McSorley, Henry J., and Rick M. Maizels. Helminth infections and host immune regulation. *Clinical Microbiology Reviews*. 2012;25(4):585-608.
3. Gandhi, Namita A., et al. Targeting key proximal drivers of type 2 inflammation in disease. *Nature Reviews Drug Discovery*. 2016;15(1):35-50
4. Oh SY, Zheng T, Kim YK, Cohn L, Homer RJ, McKenzie AN, Zhu Z. A critical role of SHP-1 in regulation of type 2 inflammation in the lung. *American Journal of Respiratory Cell and Molecular Biology*. 2009;40(5):568-74.
5. Zein, Joe, Benjamin Gaston, Peter Bazeley, Mark D. DeBoer, Robert P. Igo, Eugene R. Bleecker, Deborah Meyers et al. HSD3B1 genotype identifies glucocorticoid responsiveness in severe asthma. *Proceedings of the National Academy of Sciences*. 2020.
6. Modena, Brian D., John R. Tedrow, Jadranka Milosevic, Eugene R. Bleecker, Deborah A. Meyers, Wei Wu, Ziv Bar-Joseph et al. Gene expression in relation to exhaled nitric oxide identifies novel asthma phenotypes with unique biomolecular pathways. *American Journal of Respiratory and Critical Care Medicine*. 2014;190(12):1363-1372.
7. Wise, Sarah K., et al. Interleukin-4 and interleukin-13 compromise the sinonasal epithelial barrier and perturb intercellular junction protein expression. *International Forum of Allergy & Rhinology*. 2014;4(5).
8. Liu, Jing Nan, et al. The prevalence of serum specific IgE to superantigens in asthma and allergic rhinitis patients. *Allergy, Asthma & Immunology Research*. 2014;6(3):263-266.
9. Schleimer, Robert P., and Sergejs Berdnikovs. Etiology of epithelial barrier dysfunction in patients with type 2 inflammatory diseases. *Journal of Allergy and Clinical Immunology*. 2017;139(6):1752-1761.
10. Suárez-Fariñas M, Dhingra N, Gittler J, Shemer A, Cardinale I, de Guzman Strong C, Krueger JG, Guttman-Yassky E. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. *Journal of Allergy and Clinical Immunology*. 2013;132(2):361-70.
11. Dunican EM, Fahy JV. The role of type 2 inflammation in the pathogenesis of asthma exacerbations. *Annals of the American Thoracic Society*. 2015;12(Supplement 2):S144-9.
12. Chaaban MR, Walsh EM, Woodworth BA. Epidemiology and differential diagnosis of nasal polyps. *American Journal of Rhinology & Allergy*. 2013;27(6):473-8.
13. Gandhi NA, Bennett B, Graham NH, Pirozzi G, Stahl N, Yancopoulos G. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov*. 2016;15(1):35-50.

What diseases fall under Type 2 inflammation?

Science has shown that excessive type 2 inflammation can underlie a number of diseases which can often coexist.(1,2,3,4) These diseases are all chronic and inflammatory in nature, meaning the patients who have them suffer for a prolonged period of time if untreated, and include atopic dermatitis, or eczema, asthma, and chronic rhinosinusitis with nasal polyposis.(5,6,7) More recently type 2 inflammation has also been shown to be a component of other chronic inflammatory skin diseases including chronic spontaneous urticaria (8,9,10,11) and prurigo nodularis (12,13,14), and even a gastrointestinal disorder known as eosinophilic esophagitis (15,16). From this emerging science we can see that type 2 inflammation can occur in several parts of the body resulting in a range of diseases that may seem to be unconnected, but they actually are connected - by the underlying type 2 inflammation.

1. Gandhi NA, Bennett B, Graham NH, Pirozzi G, Stahl N, Yancopoulos G. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov*. 2016;15(1):35-50.
2. Silverberg, Jonathan I., et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. *Annals of Allergy, Asthma & Immunology*. 2018;121(5):604-612.
3. Simpson, E., et al. "Chronicity, comorbidity and life course impairment in atopic dermatitis: insights from a cross-sectional study in US adults." Poster Presented at the 25th European Academy of Dermatology and Venereology (2016).
4. Promsopa, Chakapan, et al. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. *International Forum of Allergy & Rhinology*. 2016;6(4):373-377.
5. Suárez-Fariñas M, Dhingra N, Gittler J, Shemer A, Cardinale I, de Guzman Strong C, Krueger JG, Guttman-Yassky E. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. *Journal of Allergy and Clinical Immunology*. 2013;132(2):361-70.
6. Dunican EM, Fahy JV. The role of type 2 inflammation in the pathogenesis of asthma exacerbations. *Annals of the American Thoracic Society*. 2015;12(Supplement 2):S144-9.
7. Chaaban MR, Walsh EM, Woodworth BA. Epidemiology and differential diagnosis of nasal polyps. *American Journal of Rhinology & Allergy*. 2013;27(6):473-8.
8. Bae Y et al. *Allergy Asthma Immunol Res*. 2016;8:457-460.
9. Lin W et al. *Sci Rep*. 2017;7:17797
10. Ying s et al. *J Allergy Clin Immunol*. 2002;109:694-700.
11. Caproni M et al. *J Dermatol Sci*. 2004;36:57-59.
12. Fukushi S et al. *Br J Dermatol*. 2011;165:990-996.
13. Park K et al. *Eur J Dermatol*. 2011; 21:135-136.
14. Sonkoly E et al. *J Allergy Clin Immunol*. 2006;117:411-417.
15. Muir AB et al. Epithelial-stromal crosstalk and fibrosis in eosinophilic esophagitis. *J Gastroenterol*. 2019;54(1):10-18.
16. Cheng E et al. Tissue remodeling in eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol*. 2012;303(11):G1175-G1187.

What types of treatments are available?

I would like to set this question aside for now. It is a bit complicated to answer in a holistic fashion given the breadth of diseases. If desired I could approach by discussing the common therapies which are different types of steroid treatments (topical, systemic, inhaled depending

on the disease in question), immunosuppressants (for some diseases) and biologics including dupilumab.

What are the challenges in diagnosing these patients in minority populations? (on our call you mentioned the difficulty of diagnosing this disease in darker skin color.) Would this fall under some of the challenges?

Research has shown us that there are differences in minority populations who have diseases characterized by type 2 inflammation that can lead to differences in how these diseases present as well as challenges in diagnosis and potential differences in how patients may respond to certain treatments (1,2,3,4).

For example, in addition to the overwhelming itch that is the hallmark of atopic dermatitis, patients with skin of color often present with different signs of the disease including thickened, or lichenified skin, dark circles around the eyes, and patches of hyper-pigmented skin.(5). The severity of atopic dermatitis can be underestimated in Black patients as one of the key characteristics used to assess the level of disease is the amount of erythema, or redness, that is present. Erythema is much more difficult to assess in patients with darker skin tones as it does not present the same as in patients with lighter skin tones, it appears more violet rather than red or pink. Because of this, the degree of erythema may be underestimated and may prevent early diagnosis of atopic dermatitis leading to more severe disease or delay in access to advanced therapies (5,6,7).

1. Noda S et al. *J Allergy Clin Immunol*. 2015;136:1254–1264.
2. Sanyal RD, Pavel AB, Glickman J, et al.. *Ann Allergy Asthma Immunol*. 2019 Jan;122(1):99-110.e6.
3. Brunner PM, Guttman-Yassky E. *Ann Allergy Asthma Immunol*. 2019;122(5):449-455
4. Leung DY. *J Allergy Clin Immunol*. 2015;136(5):1265
5. Kaufman B et al. *Exp Dermatol* 2018;27:340-357.
6. Ben-Gashir MA et al. *Br J Dermatol* 2002;174:920–925.
7. Vachiramou V et al. *Pediatr Dermat* 2012;29:395–402.

Other topics I can expand upon, if desired, include the immunologic and biologic differences related to atopic dermatitis in patients with skin of color; additional examples related to under-represented minorities in asthma or other type 2 diseases.