

What's New in the Pathophysiology of Disease: Eosinophilic Esophagitis

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SCMD

Semaine canadienne des maladies digestives™

CDDW

Canadian Digestive Diseases Week™

Children's Hospital of Philadelphia




Conflict of Interest Disclosure

(Over the past 24 months)

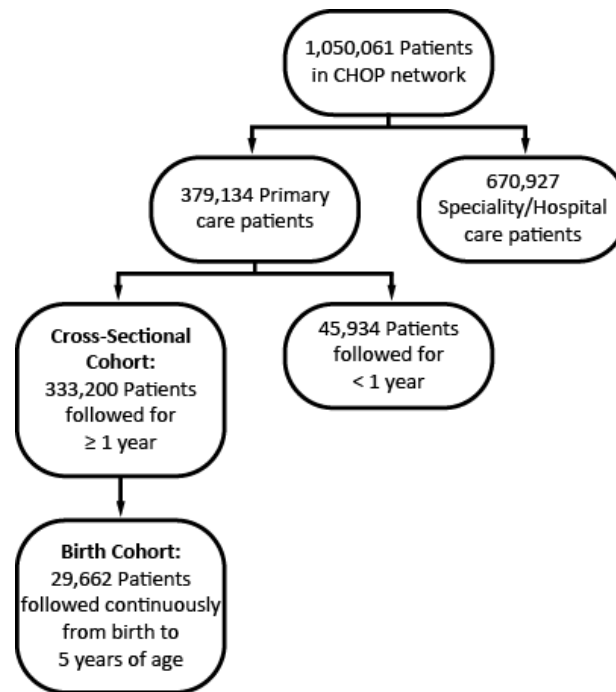
Name: Jonathan Spergel

Commercial or Non-Profit Interest	Relationship
American Academy of Allergy Asthma and Immunology	Committee Member, Chair-Division Directors
Regeneron/Sanofi, Almmune Therapeutics, NIH,	Investigator, Institutional Research Support
Kaleo, DBV Technologies, Novartis, Abbott	Consultant
Food Allergy Research Education (FARE), American Partnership For Eosinophilic Disease, IFPIES, Food Allergy & Anaphylaxis Connection Team	Medical Advisory Board

CanMEDS Roles Covered

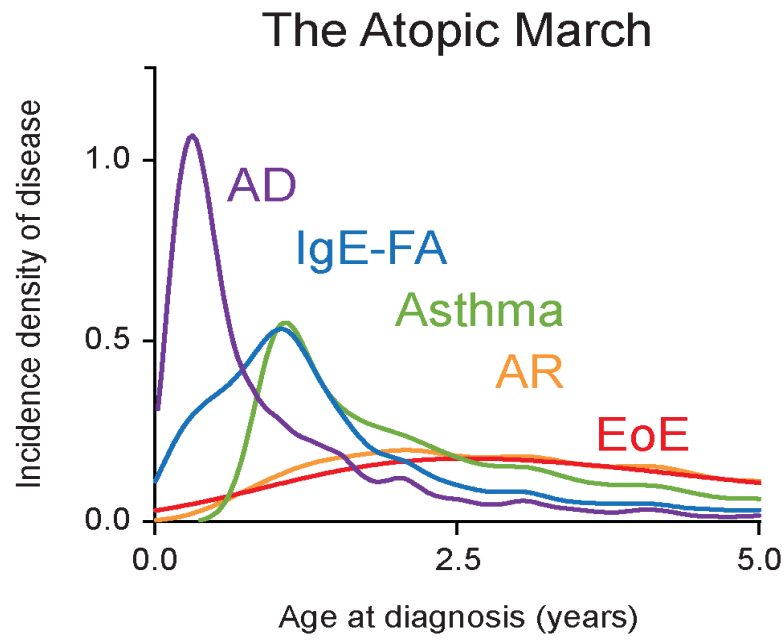
	<p>Medical Expert (as <i>Medical Experts</i>, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <i>Medical Expert</i> is the central physician Role in the CanMEDS Framework and defines the physician’s clinical scope of practice.)</p>
	<p>Communicator (as <i>Communicators</i>, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)</p>
	<p>Collaborator (as <i>Collaborators</i>, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)</p>
	<p>Leader (as <i>Leaders</i>, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)</p>
	<p>Health Advocate (as <i>Health Advocates</i>, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)</p>
	<p>Scholar (as <i>Scholars</i>, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)</p>
	<p>Professional (as <i>Professionals</i>, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)</p>

CHOP Examination of the Atopic March



Hill et al, BMC 2016

What about EoE?



Hill, Spergel JACI

		Secondary Diagnosis				
		AD	IgE-FA	Asthma	EoE	AR
Primary Diagnosis	AD	-	2.5	1.5	3.2	1.7
	IgE-FA	-	-	1.5	9.1	1.6
	Asthma	-	-	-	1.9	1.6
	EoE	-	-	-	-	2.1
	AR	-	-	-	-	-

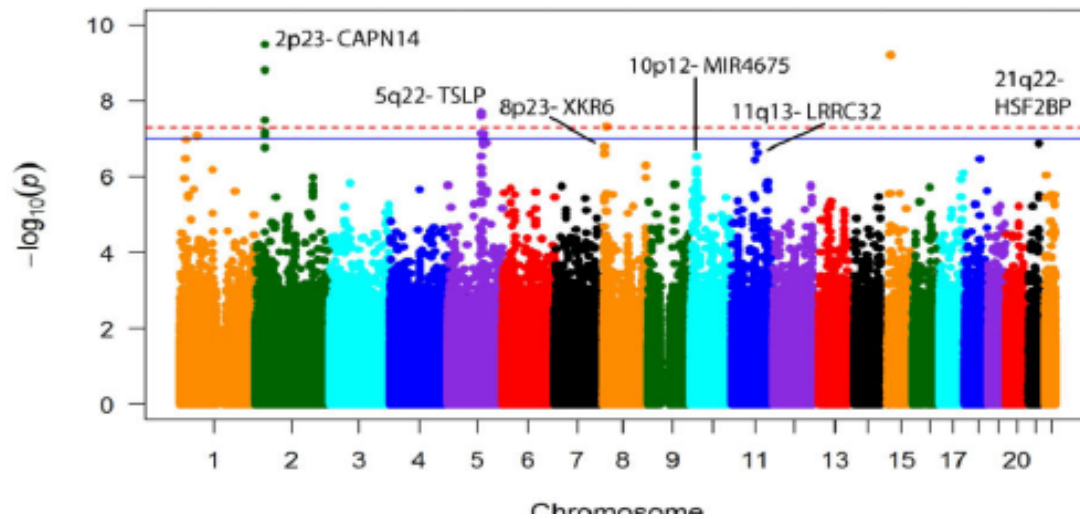
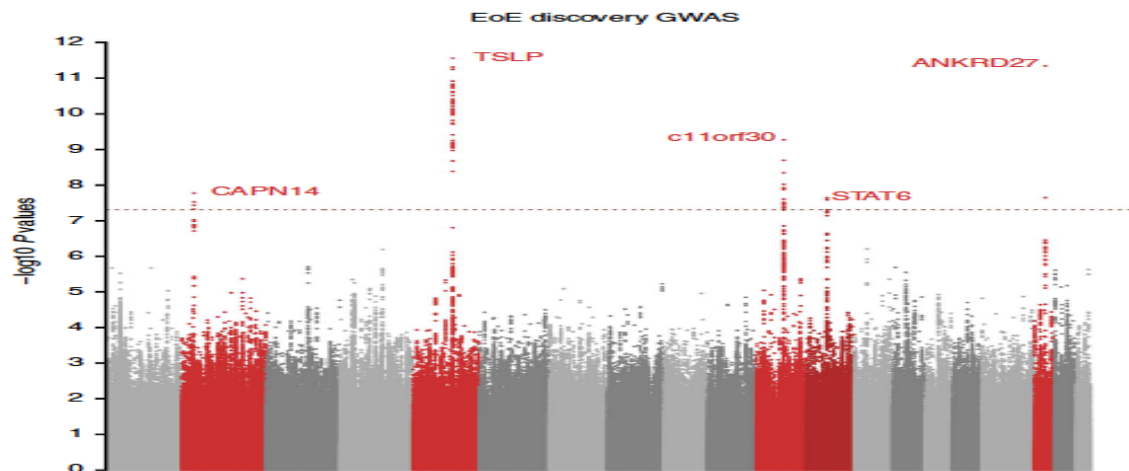
Association of Atopy with EoE

Ref	# of Pts	Age (Yrs)	Asthma	AR	AD	Food
General Population			10%	20-40%	5-20%	1-6%
Spergel	620	8m-20	50%	61%	21%	16%
Assad	89	3m-18 yr	39%	30%	19%	9%
Sugnanam	45	3m-16 yr	66%	93%	55%	24%
Guajardo	39	1m -31	38%	64%	26%	23%
Roy-Ghanata	23	18-57	26%	78%	4%	--

Pathogenesis

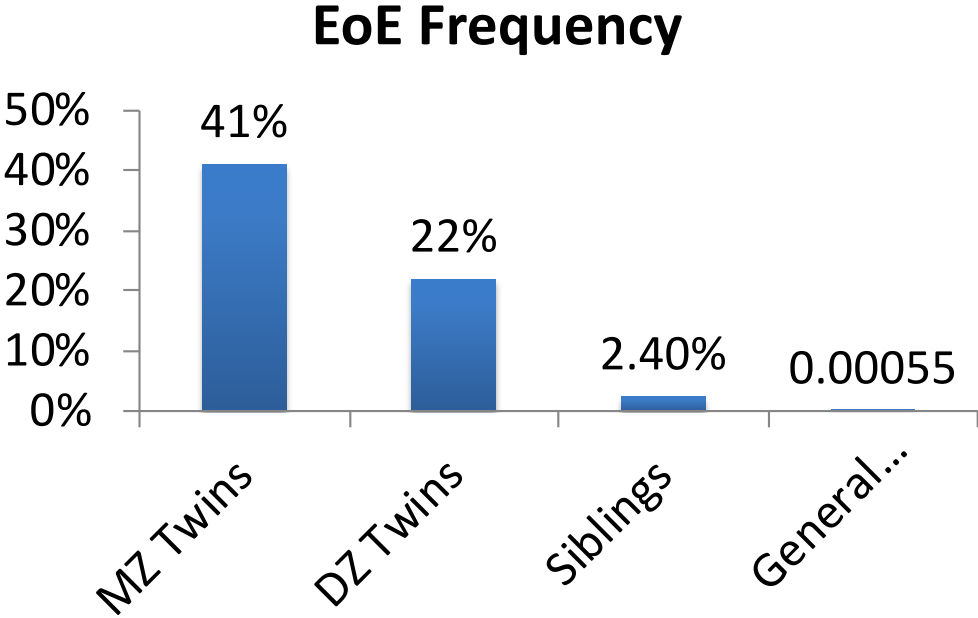
Similarities to Atopic Dermatitis and Asthma

Barrier dysfunction and systemic involvement



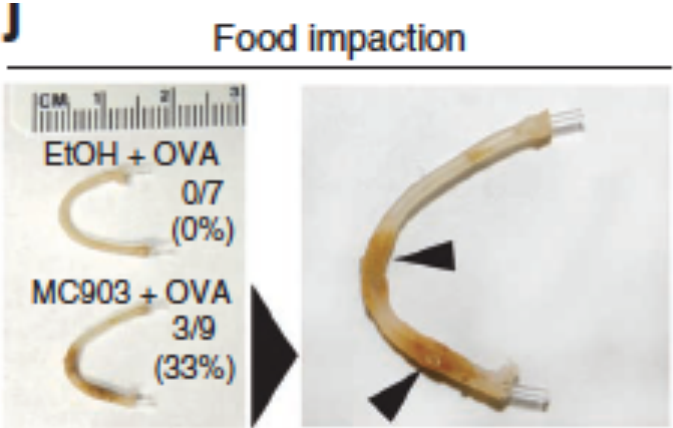
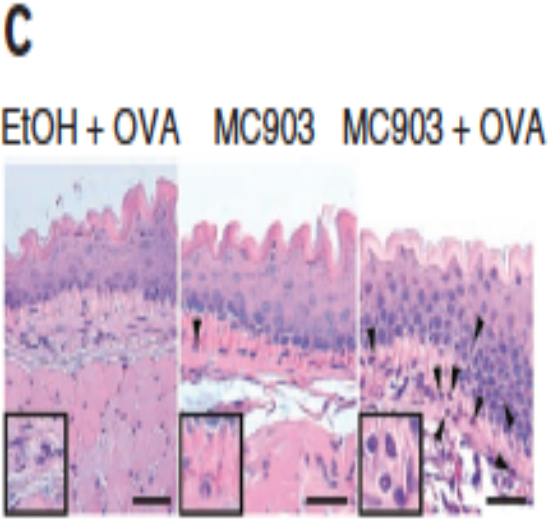
Kattyan et al. Nature Genetics 2014
 Sleiman *et al*, Nature Commun 2014

Environmental/Genetic Factors



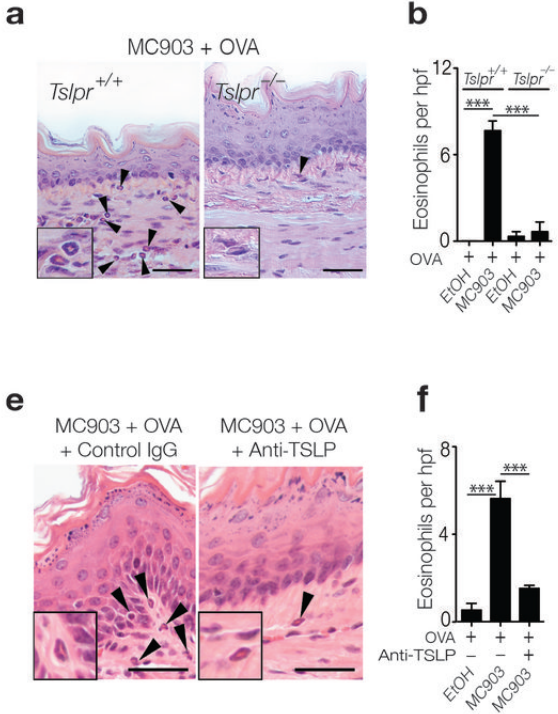
Alexander et al. J Allergy Clin Immunol 2014

Mouse Model of EoE

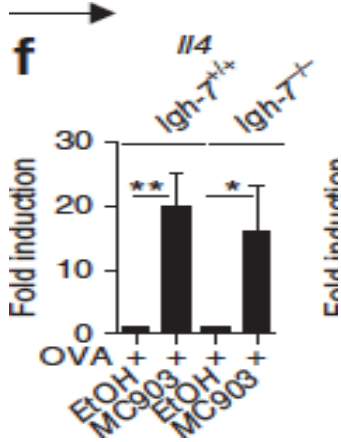


Noti et al, Nat. Medicine 2013

Mouse EoE



Not IgE dependent



Food impaction

Control IgG	Anti-TSLP	Anti-CD200R3
4/14 (29%)	0/9 (0%)	0/8 (0%)

Noti et al, Nat. Medicine 2013

TSLP induced in EoE

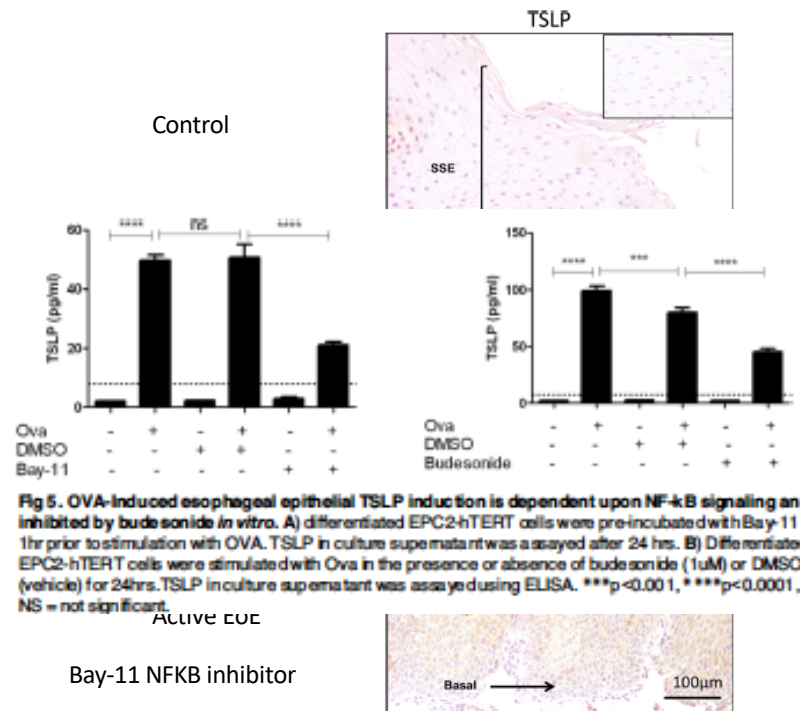
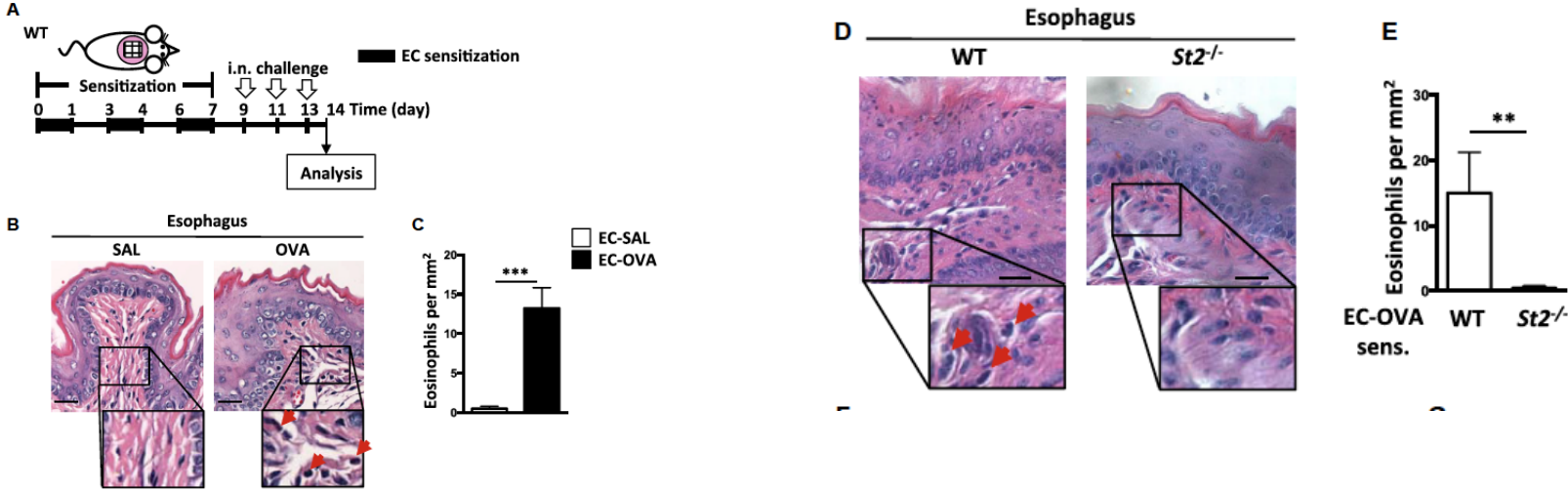
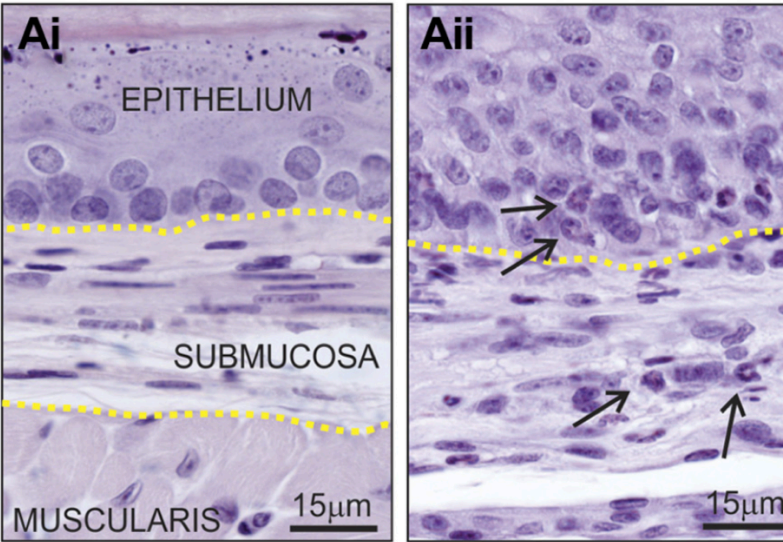


Fig 5. OVA-induced esophageal epithelial TSLP induction is dependent upon NF-κB signaling and inhibited by budesonide in vitro. A) Differentiated EPC2-hTERT cells were pre-incubated with Bay-11 for 1hr prior to stimulation with OVA. TSLP in culture supernatant was assayed after 24 hrs. B) Differentiated EPC2-hTERT cells were stimulated with Ova in the presence or absence of budesonide (1µM) or DMSO (vehicle) for 24hrs. TSLP in culture supernatant was assayed using ELISA. ***p<0.001, ****p<0.0001, NS = not significant.

Mouse Model IL33-ST2 pathway

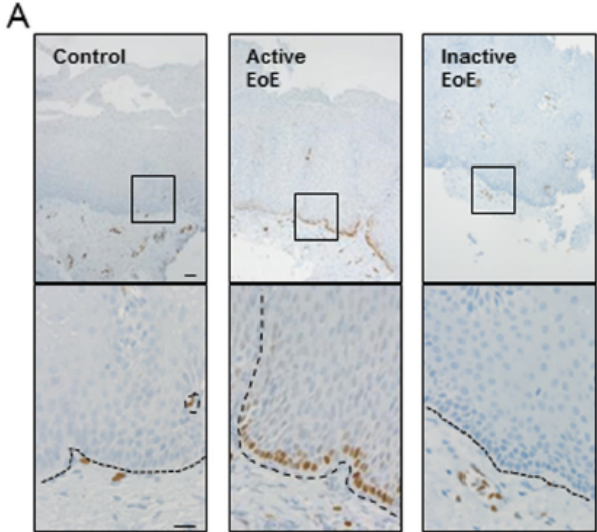


IL-33 Induces mouse EoE and increased in human disease



Di

Dii



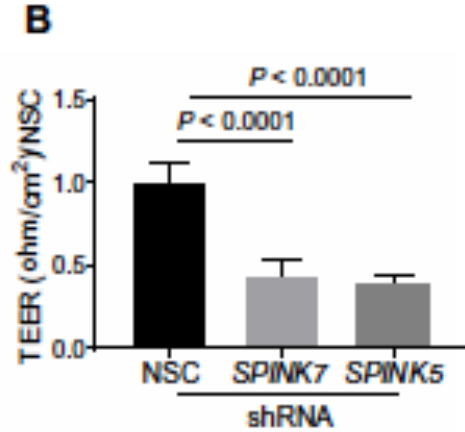
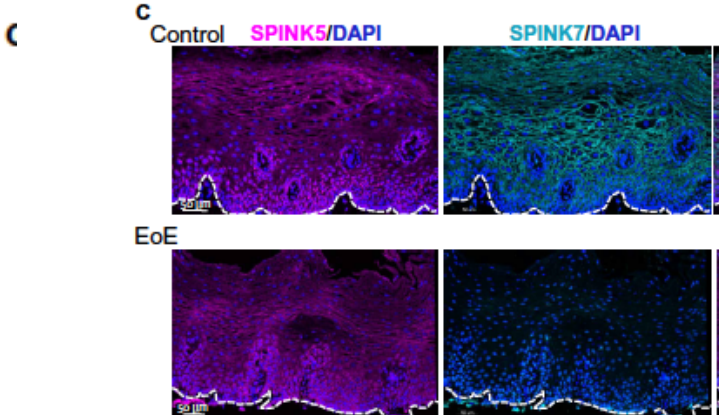
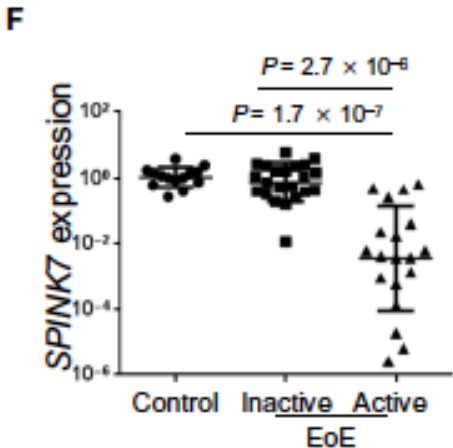
Diii

□ saline controls
 ■ IL-33 treated

Travers...Rothenberg, Scientific Reports 2017
 Judd et al. Am J Physiol Gastrointest Liver Physiol 2016

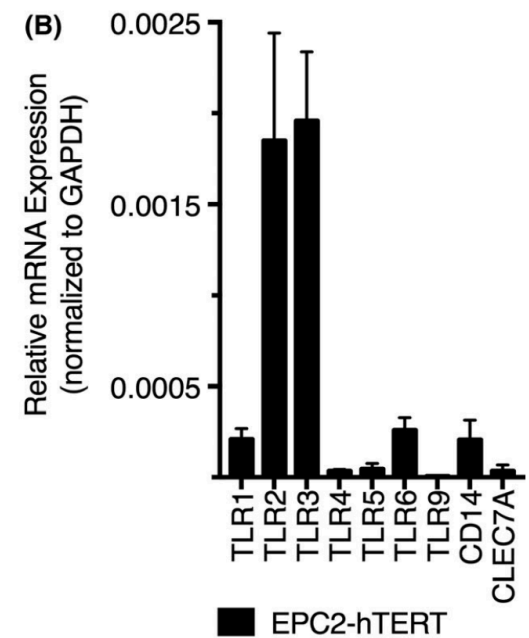
Epithelium has barrier dysfunction

Decrease in SPINK7 in active EoE

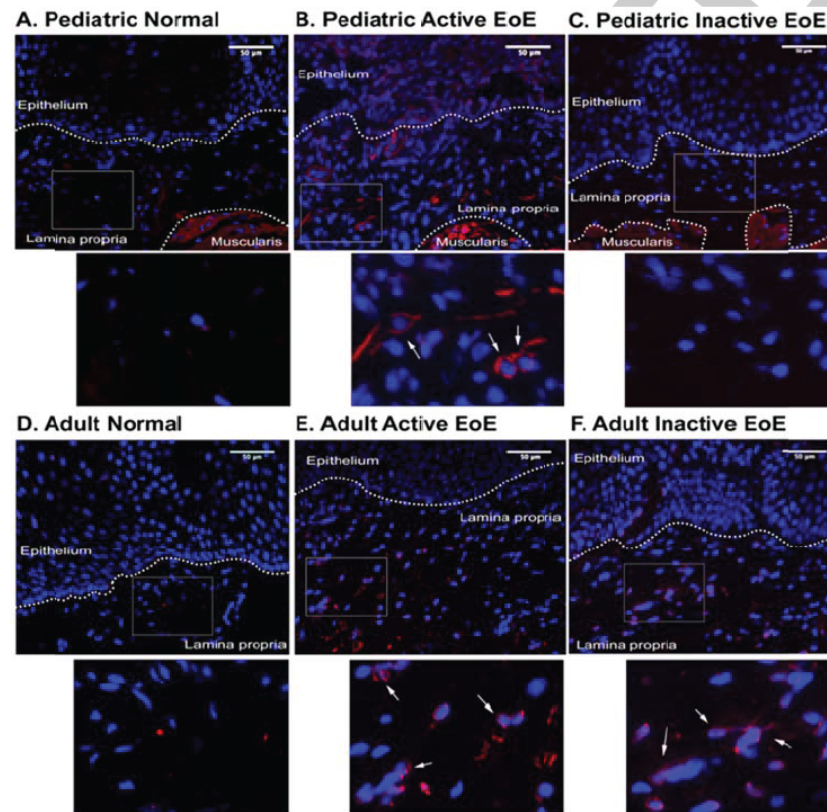


Loss of Barrier Function in EoE

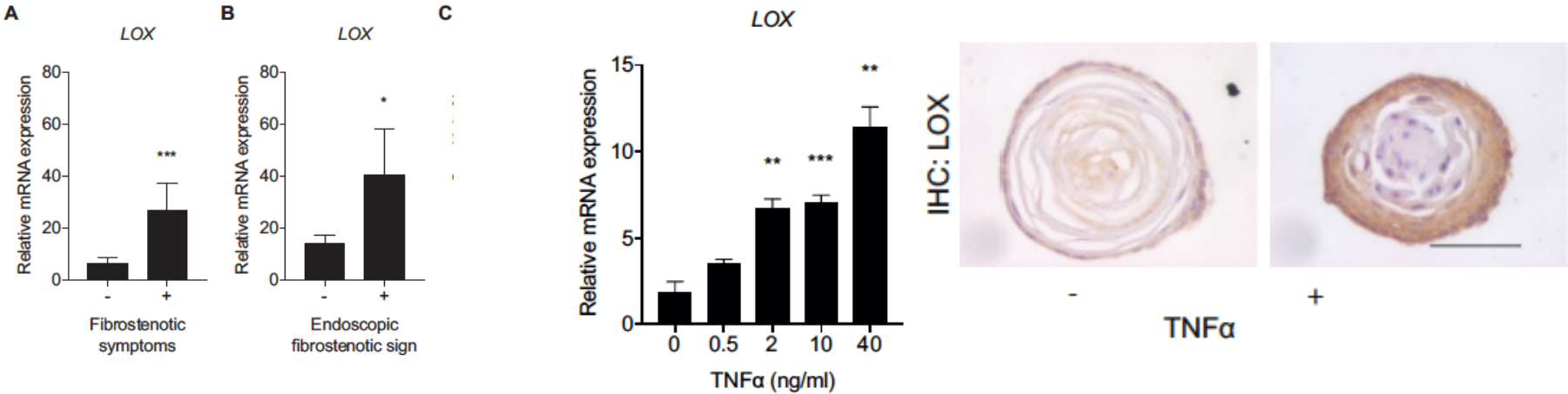
- Decreased Tight junctions in esophageal biopsies in EoE patients
 - Decreased expression of occludin and claudin 1
 - IL-13 decreases DSG-1
- High expression of TLR-2 and TLR-3 in EoE



Fibrosis in EoE: Activated Fibroblasts

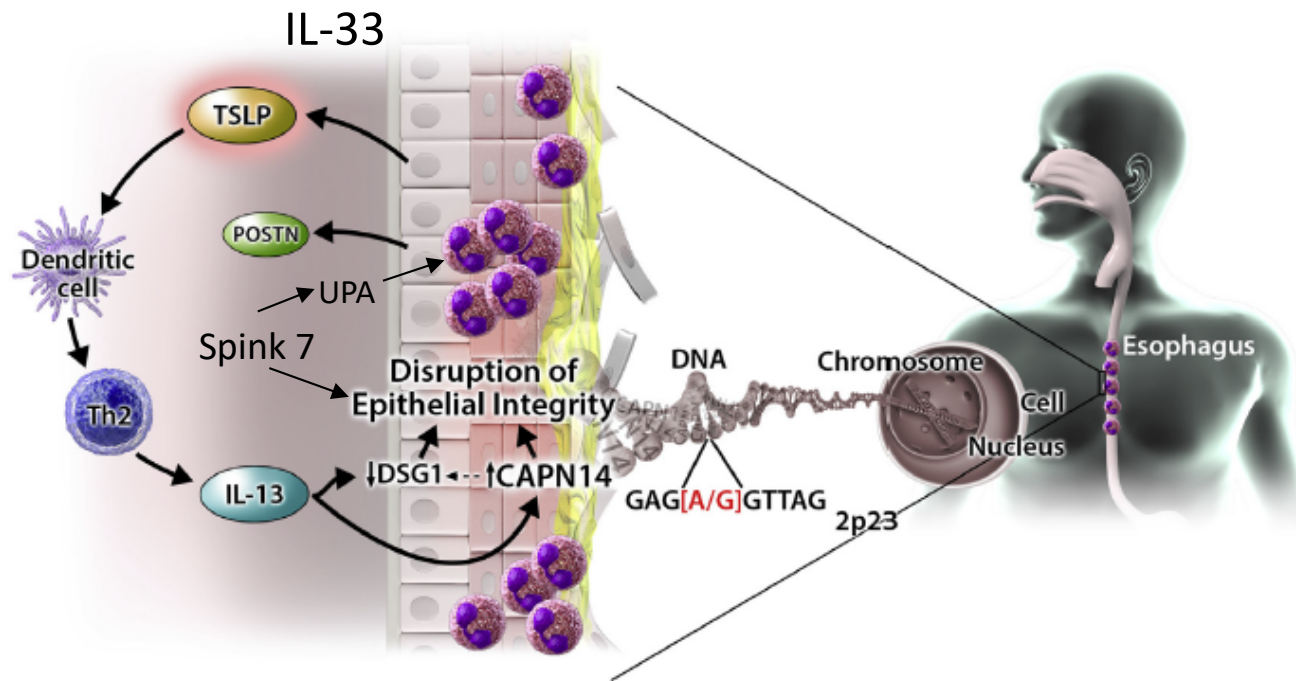


Fibrosis due to LOX and TNF- α



LOX-Lysyl oxidase enzyme that works on collagen to form cross linking

CAPN14 in EoE

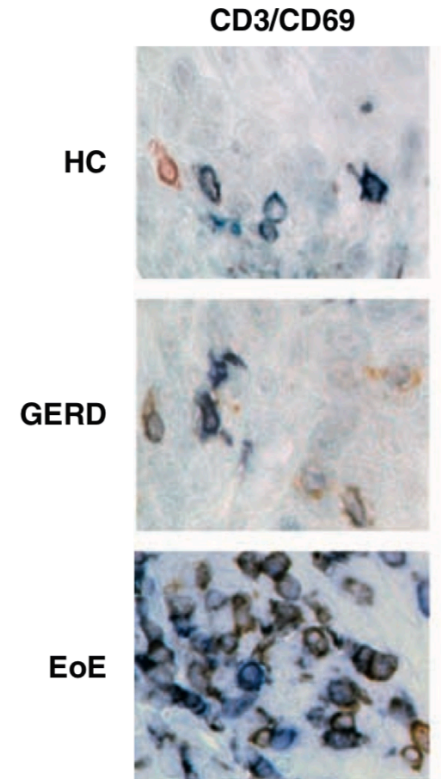
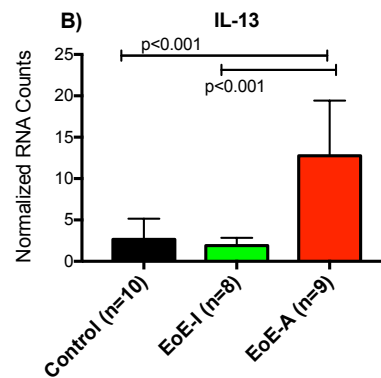
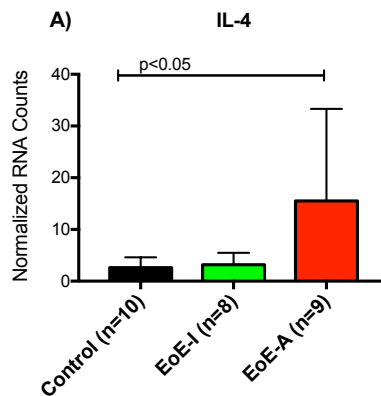


Kattyan et al. Nature Genetics 2014; Litosh et al, J Allergy Clin Immunol 2017; Modified

Role of T cells in EoE

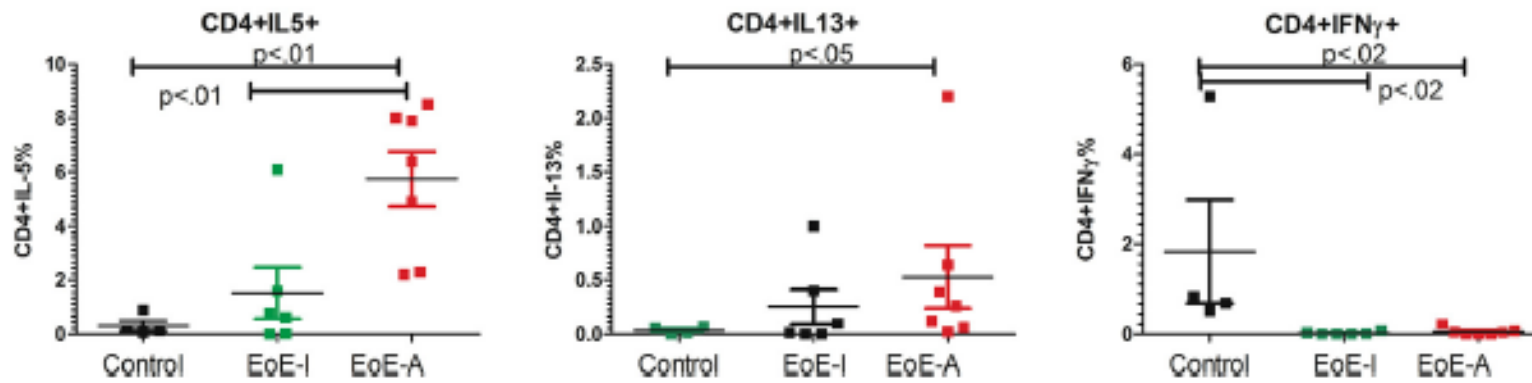
TH2 cells are identified in Esophageal Tissue

- Increase T cells compared to GERD
- Activated T cells
- Express Th2 cytokines

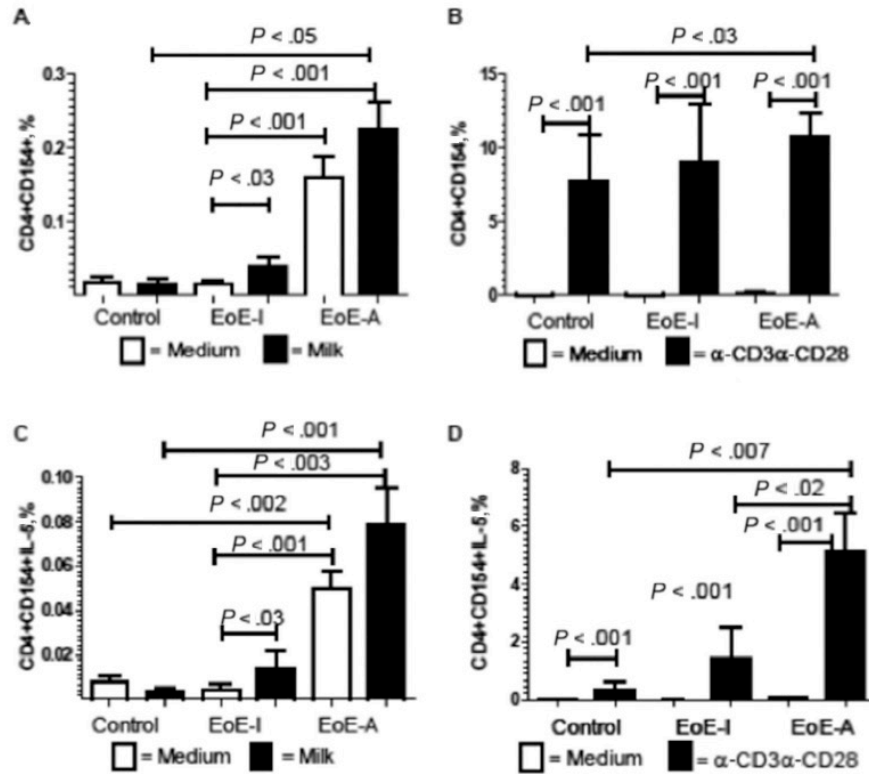


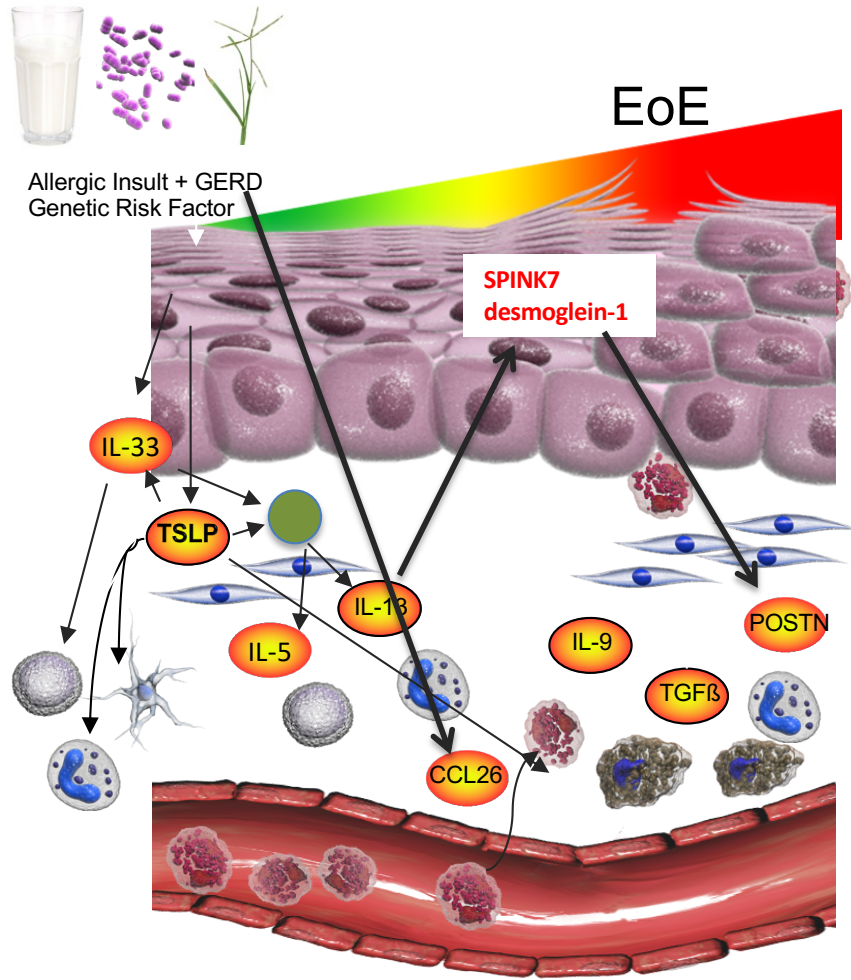
Role of Peripheral T cells in EoE-Increased Th2

- Examined T cells in milk induced EoE patients
 - On and off milk



Peripheral Th2 cells response to milk





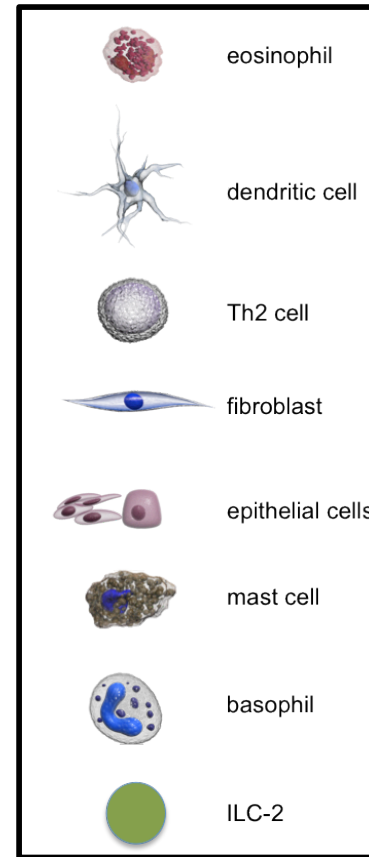
barrier function

proliferation

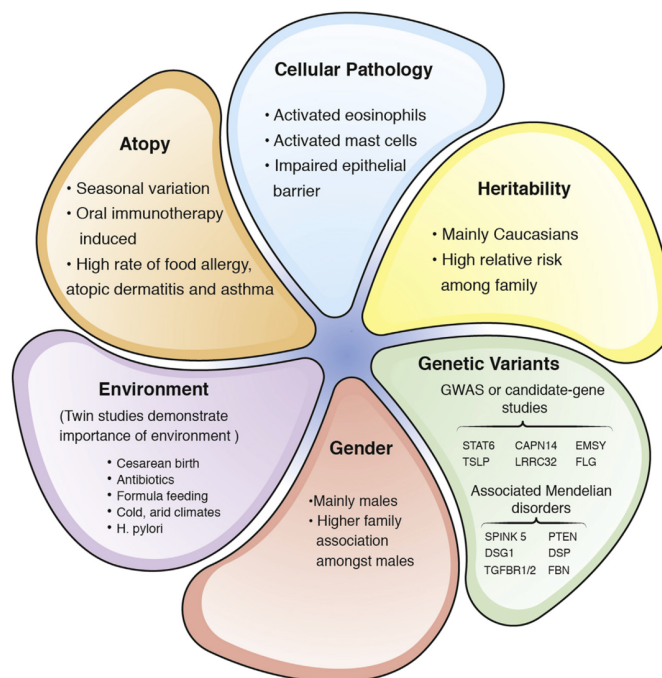
fibrosis

mastocytosis

eosinophilia



Conclusion



O'Shea Gastroenterology 2018

Acknowledgements

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