

MECCANISMI MOLECOLARI DELL'INFIAMMAZIONE DI TIPO 2 NELL'ASMA GRAVE

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S.O.D. IMMUNOALLERGOLOGIA

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**AZIENDA OSPEDALIERA UNIVERSITARIA
CAREGGI FIRENZE**

› Am J Respir Crit Care Med. 2021 Mar 17. doi: 10.1164/rccm.202102-0291LE. Online ahead of print.

The Visible and Invisible Faces of the Iceberg of Type 2 Asthma

Insu Yilmaz¹, Gülden Paçacı Çetin²

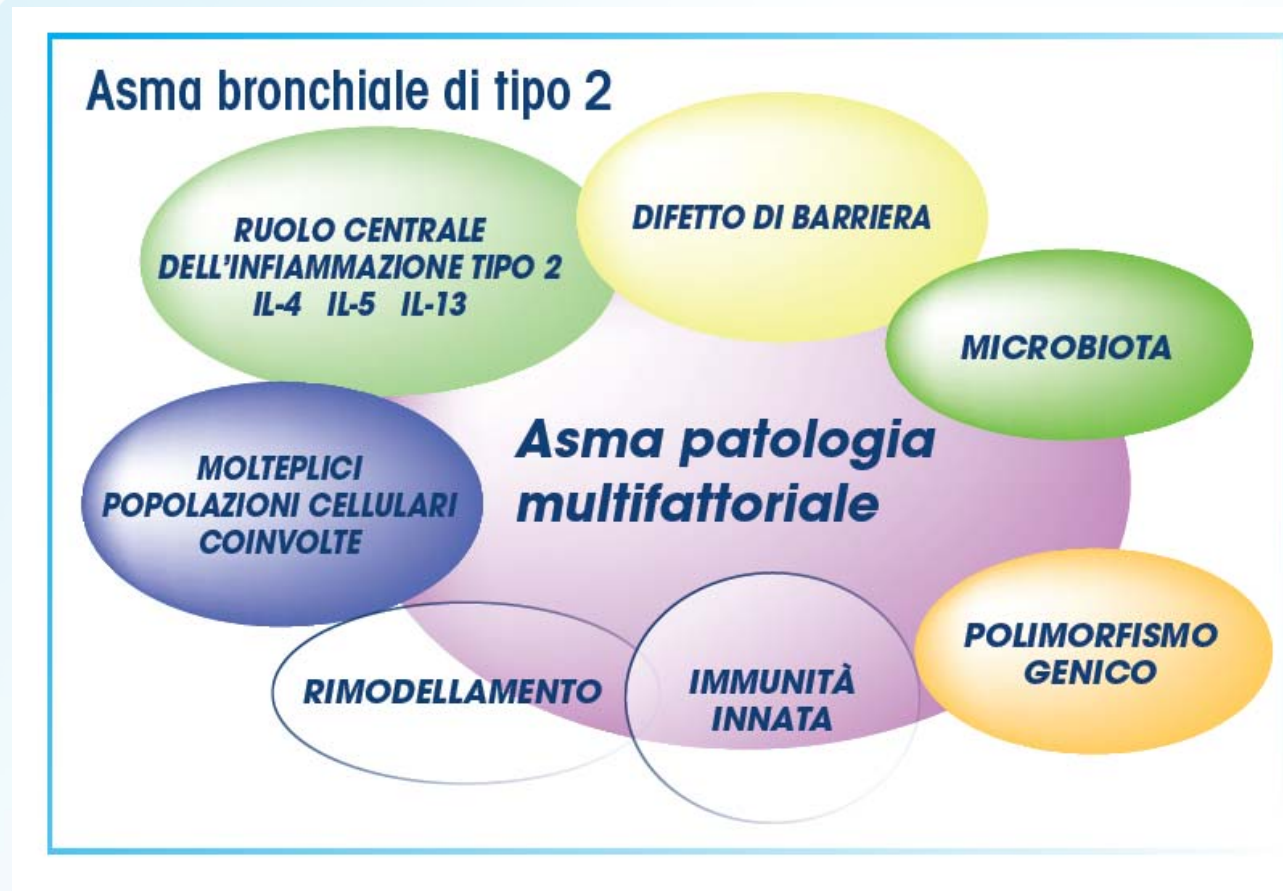
Affiliations + expand

PMID: 33730529 DOI: 10.1164/rccm.202102-0291LE

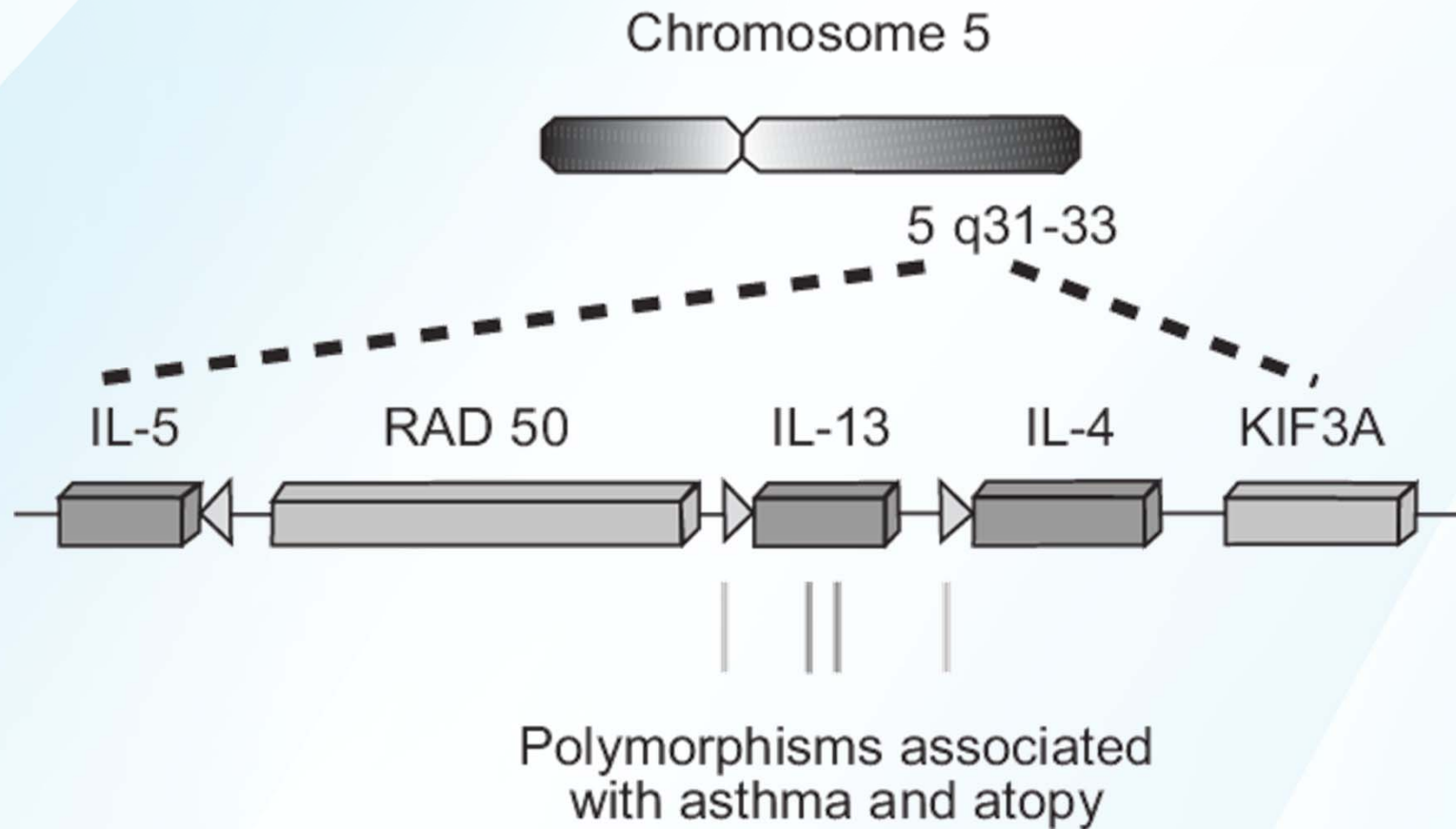
In the Global Initiative for Asthma, the T2 asthma phenotype was defined by one or more of the following features: skin prick test (SPT) against aeroallergens and / or specific IgE positivity, blood eosinophilia, sputum eosinophilia, fractionated exhaled nitric oxide (FeNO) elevation, oral corticosteroid (OCS) dependence



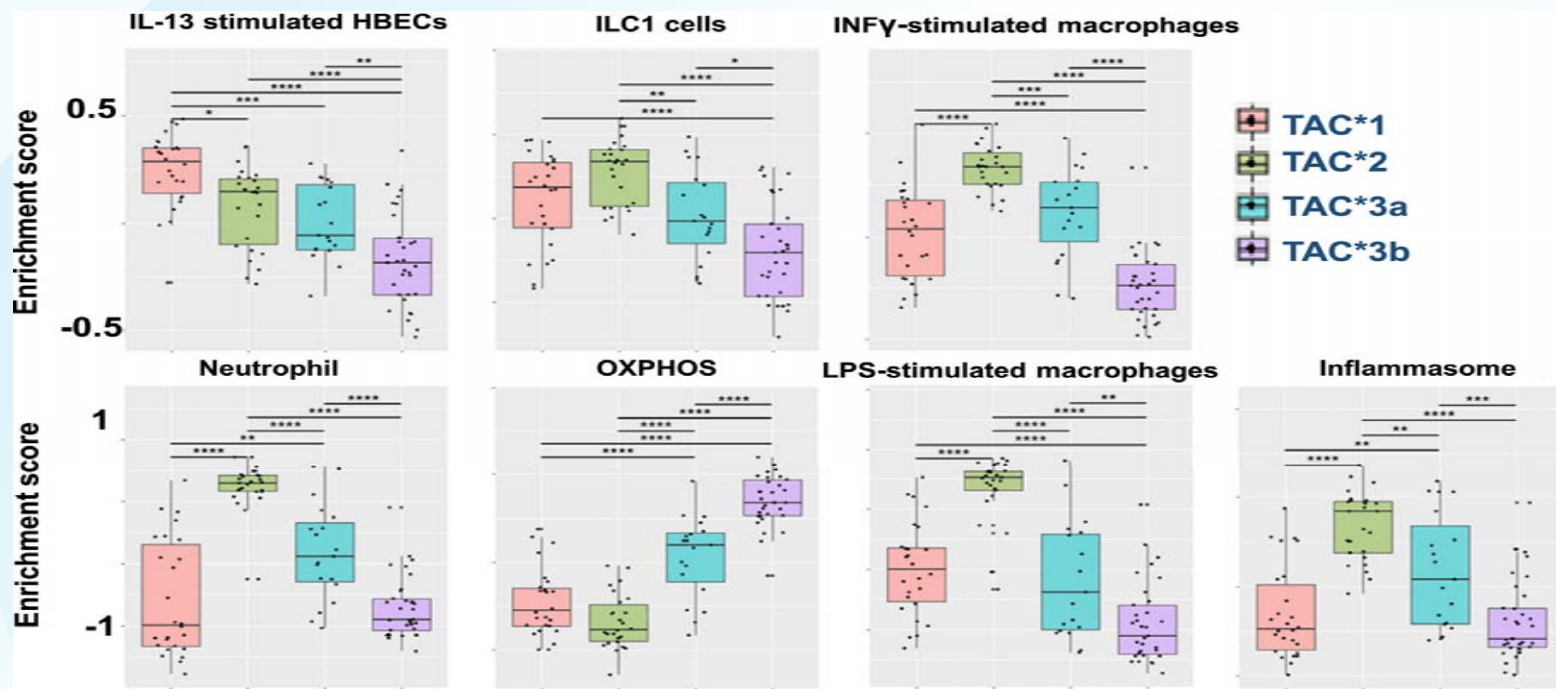
MECCANISMI MOLECOLARI DELL'INFIAMMAZIONE DI TIPO 2 NELL'ASMA GRAVE



Geni associati all'asma type 2



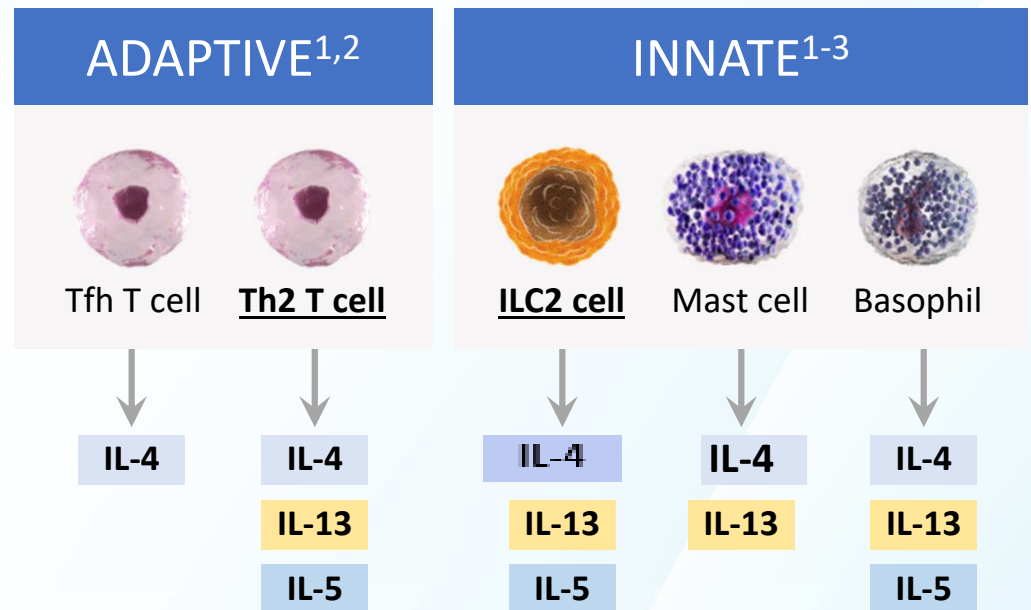
Type 2-low asthma phenotypes by integration of sputum transcriptomics and serum proteomics



TYPE 2 INFLAMMATION IS DRIVEN BY BOTH INNATE AND ADAPTIVE ARMS OF THE IMMUNE SYSTEM

Il coinvolgimento delle cellule dell'immunità innata e dell'immunità adattativa hanno ridisegnato la tradizionale patogenesi dell'asma bronchiale

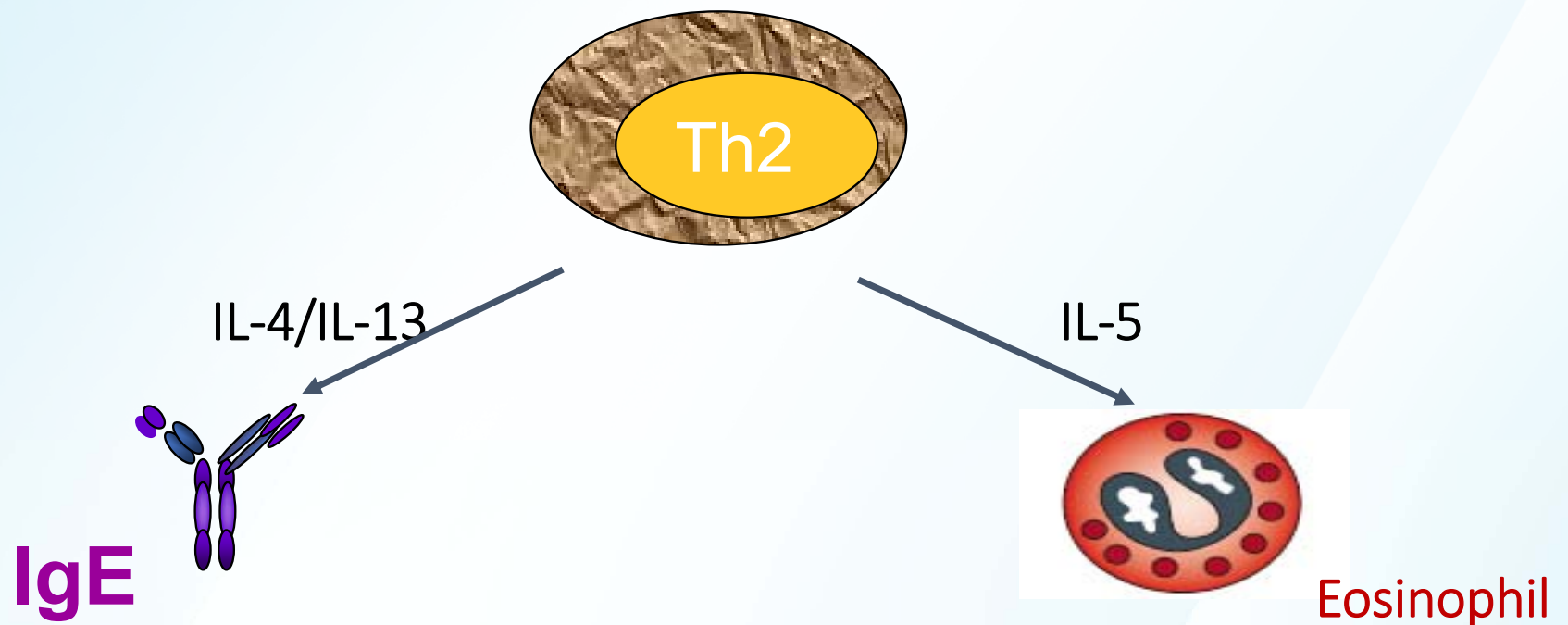
TYPE 2 INFLAMMATION



REVIEW

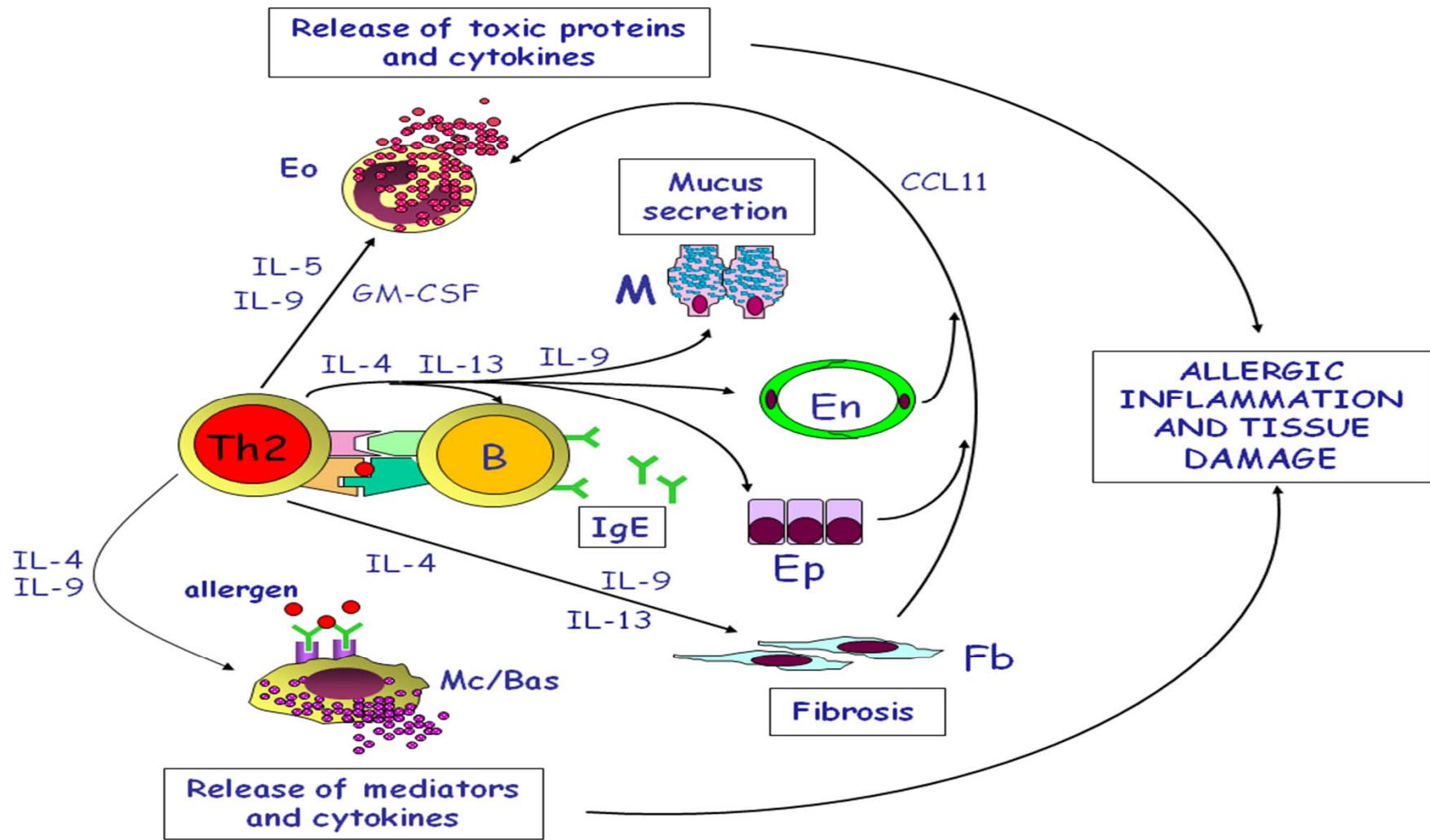
The importance of Th2-like cells in the pathogenesis of airway allergic inflammation

M. RICCI, O. ROSSI*, M. BERTONI* and A. MATUCCI*

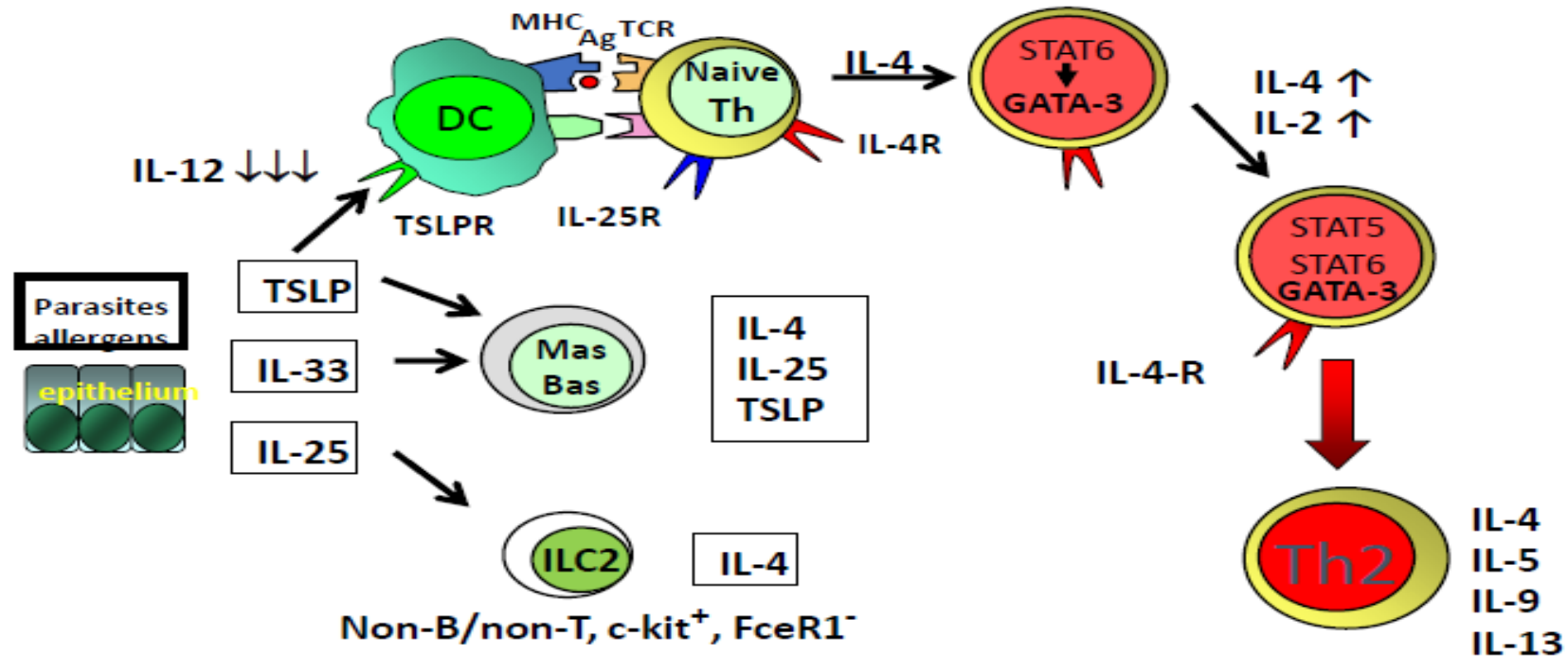


IgE = immunoglobulin E; IL = interleukin

RUOLO DEI LINFOCITI Th2 NELLA PATOGENESI DELL'ASMA BRONCHIALE



IL-4 is the cytokine that drives Th2 differentiation

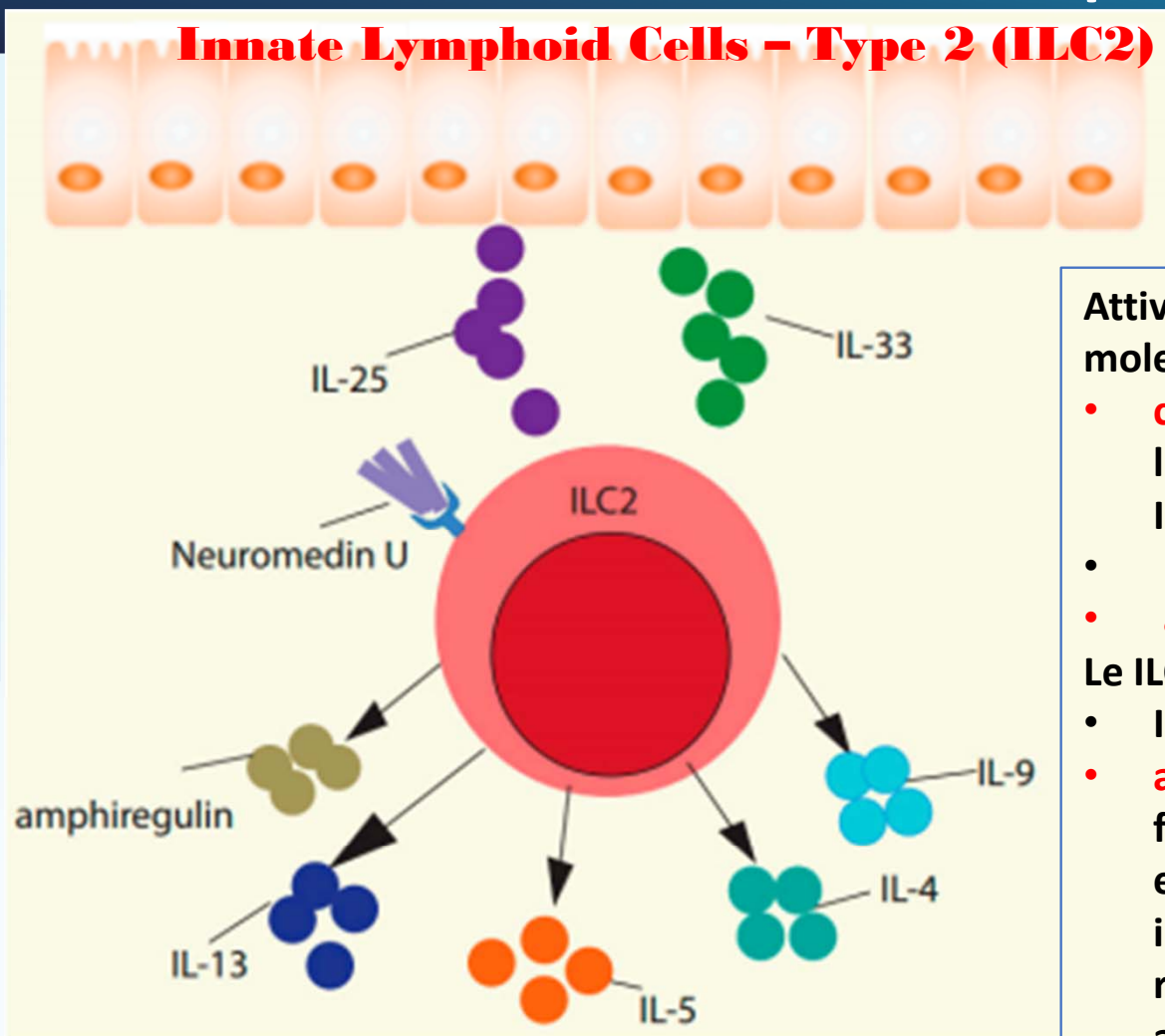


l'IL-4 e l'IL-13 contribuiscono in maniera sinergica al mantenimento e all'amplificazione del processo infiammatorio di tipo 2.

Ciò che le differenzia maggiormente è l'impossibilità dell'IL-13 di legare i linfociti T e quindi l'IL-4 è l'unica in grado di promuovere la differenziazione e lo sviluppo dei Th2

Ruolo delle ILC-2 nell'«infiammazione di tipo 2»

Innate Lymphoid Cells - Type 2 (ILC2)



- Non presentano recettori per l'antigene
- sono presenti nei siti di interfaccia con l'ambiente esterno, come la sottomucosa polmonare o il derma.

Attivate da diversi tipi di molecole :

- **citochine** prodotte dai linfociti T (IL-2, IL-4, IL-7 e IL-9)
- **mediatori lipidici**
- **allarmine.**

Le ILC2 producono :

- IL-4, IL-13, IL-5
- **amfiregulina** simile al fattore di crescita epidermico, che è implicata nel processo di rimodellamento delle vie aeree

Ruolo delle ILC2 nell'«infiammazione di tipo 2»

Human circulating group 2 innate lymphoid cells can express CD154 and promote IgE production



Laura Maggi, PhD,^a Gianni Montaini, BSc,^a Alessio Mazzone, PhD,^a Beatrice Rossetini, BSc,^a Manuela Capone, PhD,^a Maria Caterina Rossi, PhD,^a Veronica Santarlasci, MD,^a Francesco Liotta, MD,^{a,c} Oliviero Rossi, MD,^c Oreste Gallo, MD,^d Raffaele De Palma, MD,^b Enrico Maggi, MD,^{a,c} Lorenzo Cosmi, MD,^{a,c} Sergio Romagnani, MD,^a and Francesco Annunziato, PhD^{a,c} *Florence and Naples, Italy*

ILC2 promote IgE production

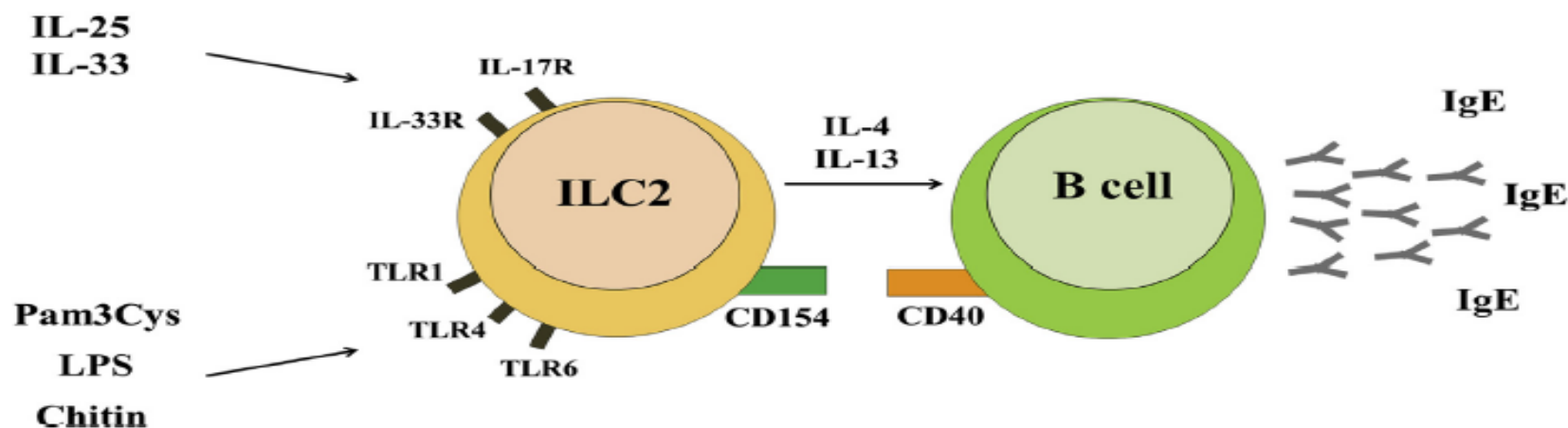
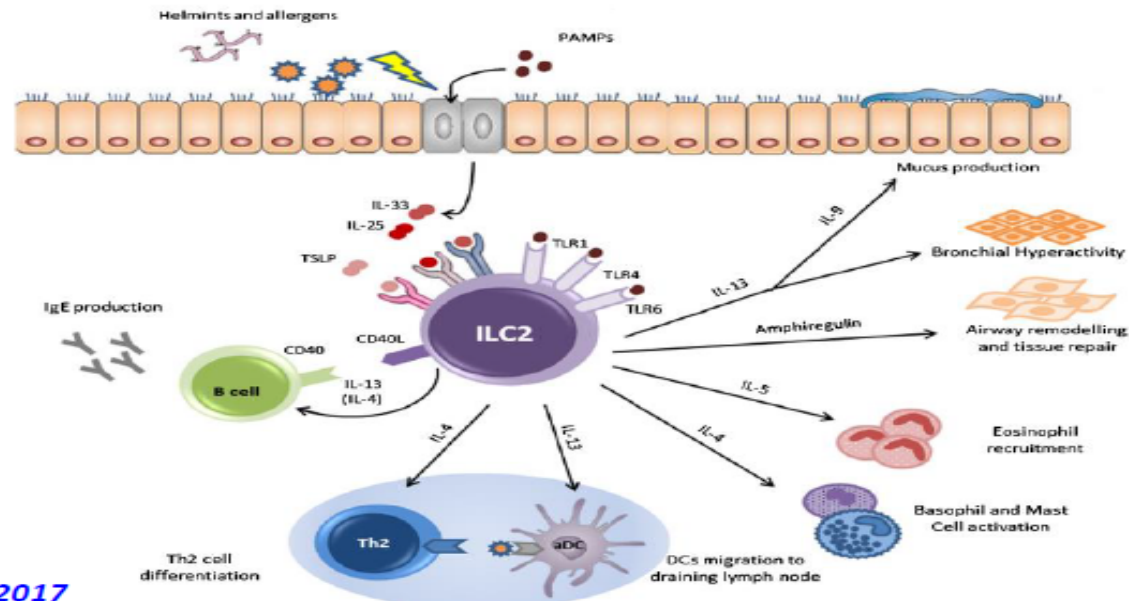


FIG 7. Activated ILC2s are able to induce IgE production by B cells. Human circulating ILC2s can express CD154 and type 2 cytokines after IL-25/IL-33 stimulation or triggering of TLR1, TLR4, and TLR6 and are able to induce IgE production by autologous B cells.

Ruolo delle ILC2 nell'«infiammazione di tipo 2»

Role of type 2 Innate Lymphoid Cells in allergic diseases



Cosmi L et al Curr Allergy Asthma Rep 2017

ILC2 are present also within the skin and suggest that they may play a role in AD pathogenesis.

ILC2 work like a bridge between epithelial cells and the immune system.

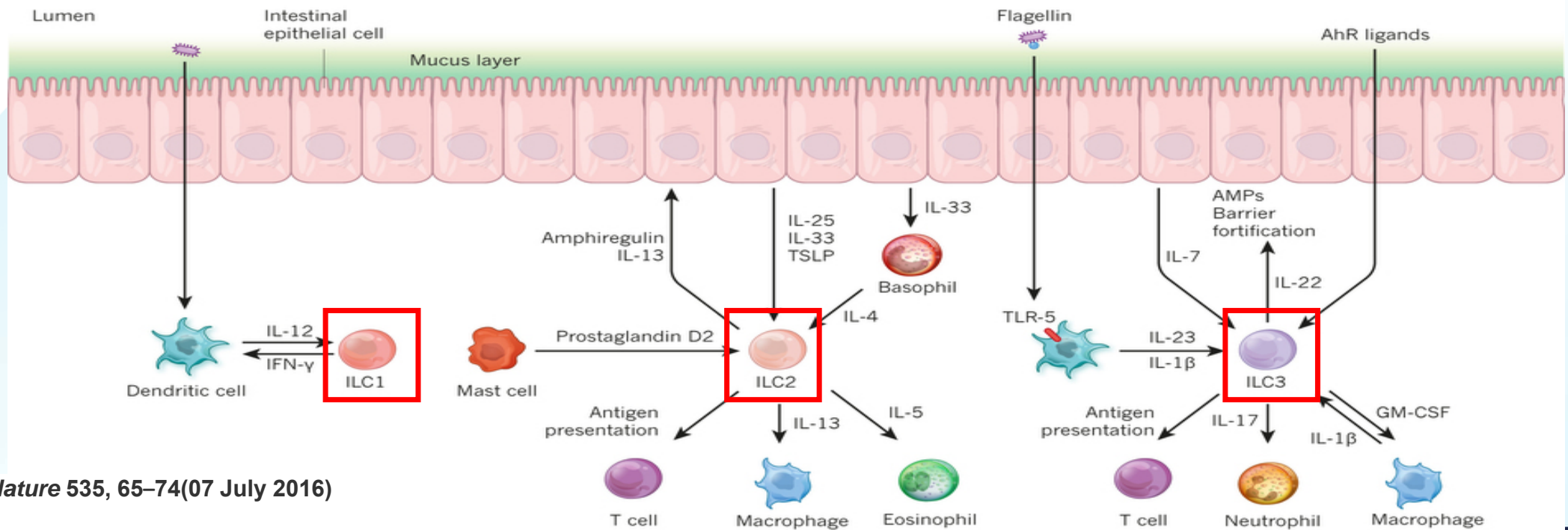
Microbioma e immunità innata

REVIEW

doi:10.1038/nature18847

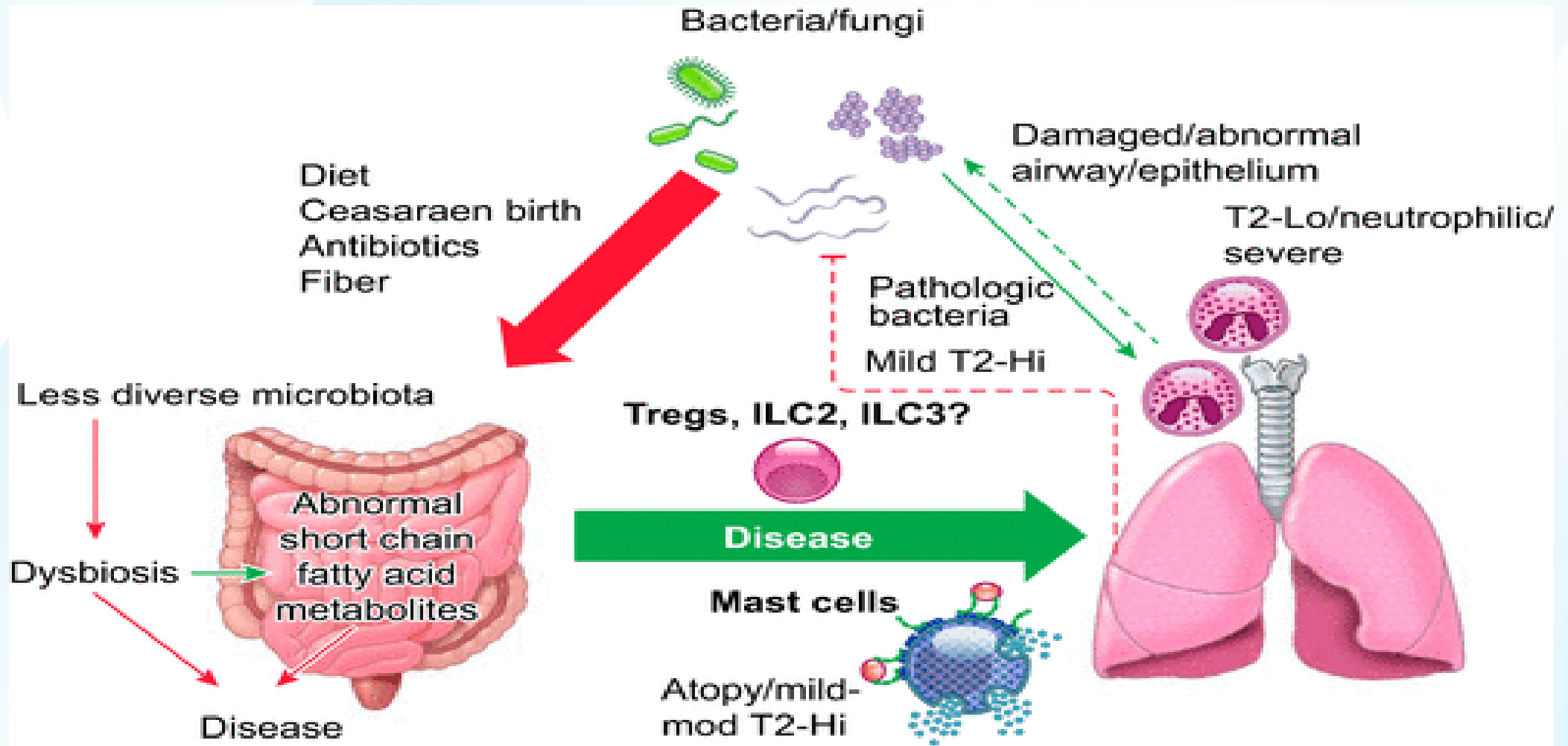
The microbiome and innate immunity

Christoph A. Thaiss^{1*}, Niv Zmora^{1,2,3*}, Maayan Levy^{1*} & Eran Elinav¹

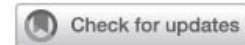


Nature 535, 65–74(07 July 2016)

Microbiome and type 2 inflammation



Type 2-high asthma is associated with a specific indoor mycobiome and microbiome



Louise-Eva Vandenberght, PhD,^{a,b,c} Raphaël Enaud, MD,^{a,b,d} Charlotte Urien, PhD,^c Noémie Coron, MD,^d Pierre-Olivier Girodet, MD, PhD,^{a,b,d} Stéphanie Ferreira, PhD,^c Patrick Berger, MD, PhD,^{a,b,d} and Laurence Delhaes, MD, PhD^{a,b,d} *Bordeaux, Lille, and Pessac, France*

(J Allergy Clin Immunol 2021;147:1296- 1305.

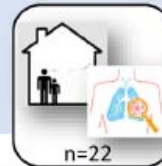
GRAPHICAL ABSTRACT



Patients with type 2-high severe asthma revealed a specific indoor microbial environment

Microbiome and Mycobiome analysis of induced sputum samples (Respiratory samples (R)) and electrostatic dust collector located at patient's bedroom (Indoor samples (I))

The analysis were based on bacterial (V3-V4 locus of 16S gene) and fungal (ITS2 region of rDNA) amplification using a 250-bp paired-end technology on MiSeq (Illumina) platform.

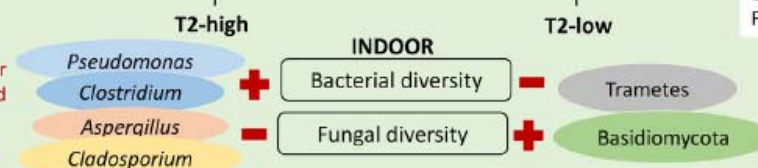


Main findings

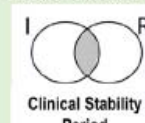
(1) FeNO level is correlated with indoor fungal Chao1 indexes

(2) Beta-diversity of indoor fungal communities is clustered according to T2 endotypes

(3) Indoor and Respiratory mycobiomes: More fungal taxa are significantly shared with indoor mycobiome during exacerbation periods, compared to clinical stability periods



INDOOR (I) + RESPIRATORY (R)

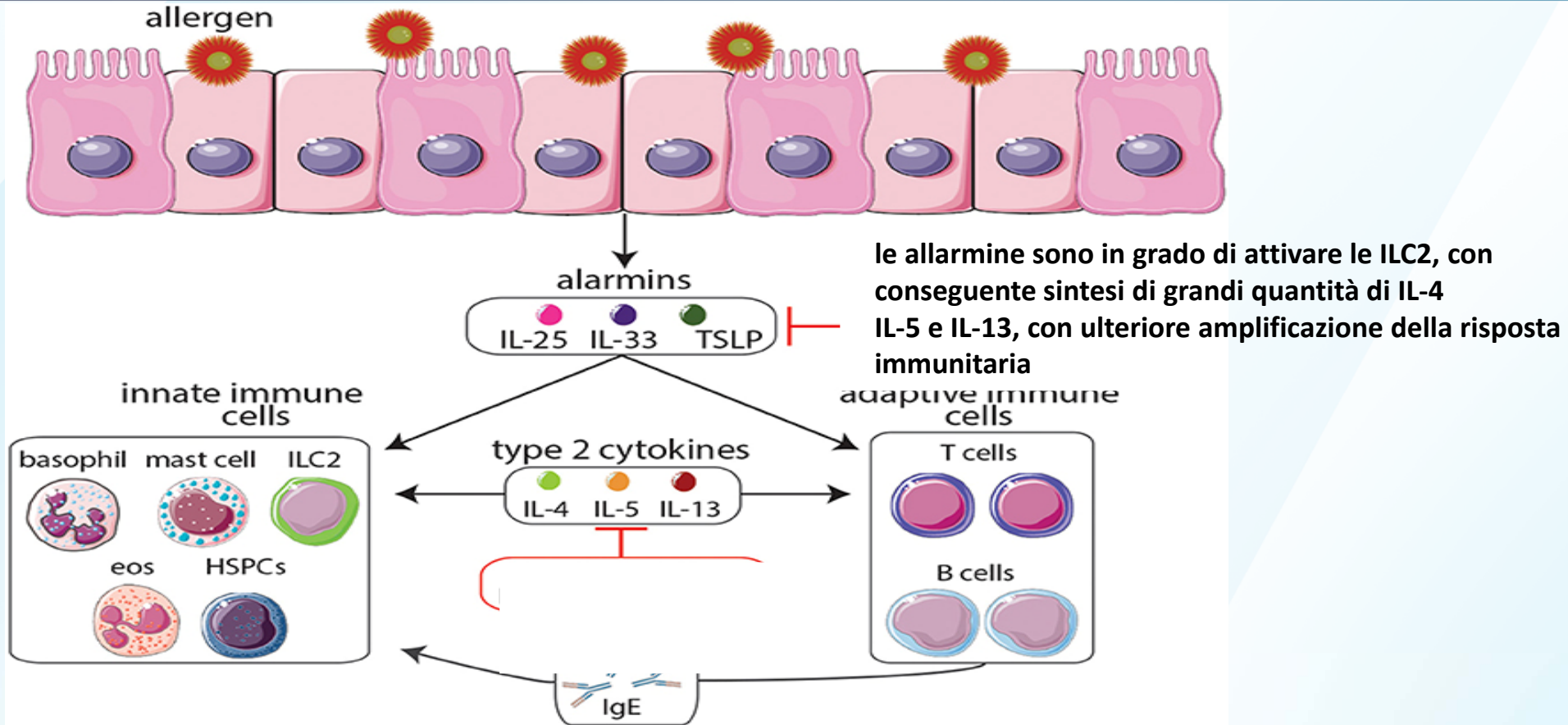


Abbreviations:

Chao1 index: Alpha-diversity index estimating the number of species in a community
FeNO: Fraction of exhaled nitric oxide



Infiemmazione di tipo 2 : ruolo delle cellule epiteliali e delle allarmine



L'epitelio delle vie aeree non è solo la sede finale del danno prodotto dall'infiammazione, ma svolge anche un ruolo attivo nel suo inizio e mantenimento

ASMA BRONCHIALE INFIAMMAZIONE «TYPE 2» : disfunzione di barriera

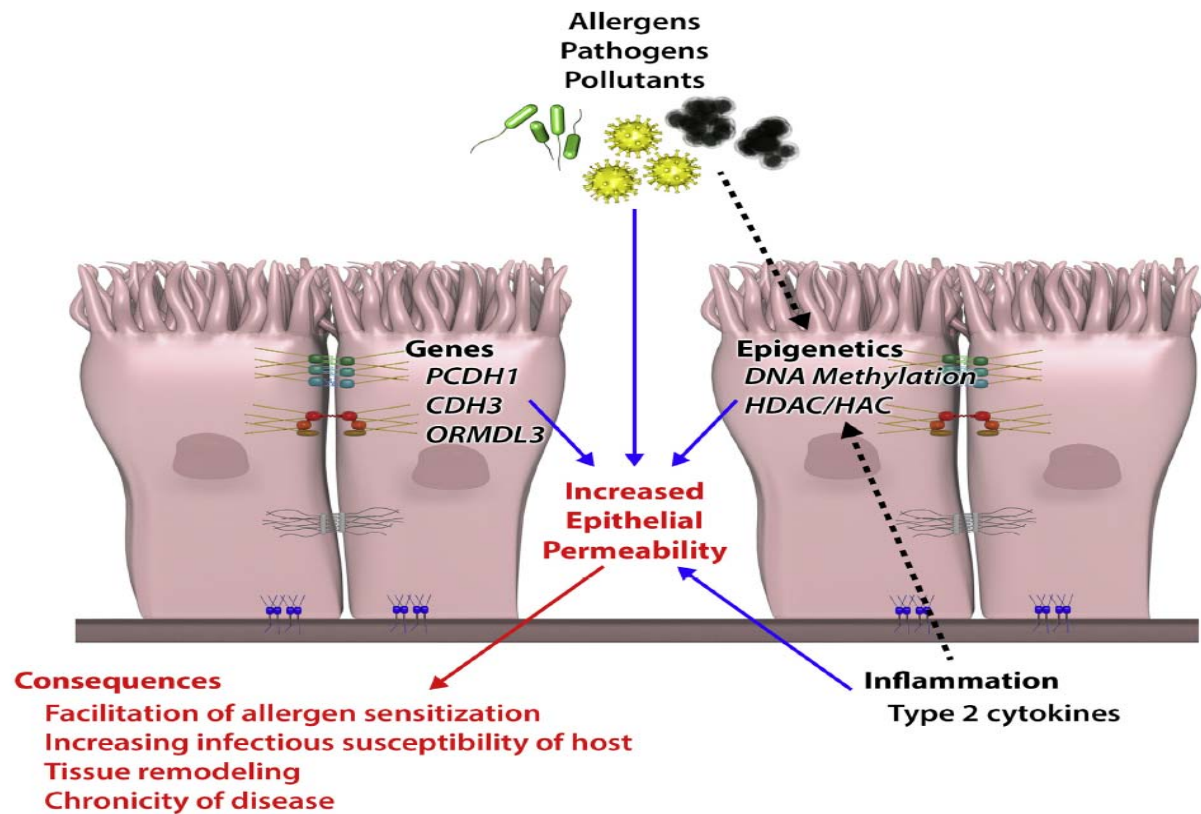
Mechanisms of allergic diseases

Epithelial barriers in allergy and asthma

Check for updates

Peter W. Hellings, MD, PhD,^{a,b,c,d} and Brecht Steelant, PhD^{c,e} *Leuven and Ghent, Belgium; Amsterdam, The Netherlands; and Crete, Greece*

The airway epithelium in asthma and upper airway diseases is dysfunctional due to disturbed tight junction



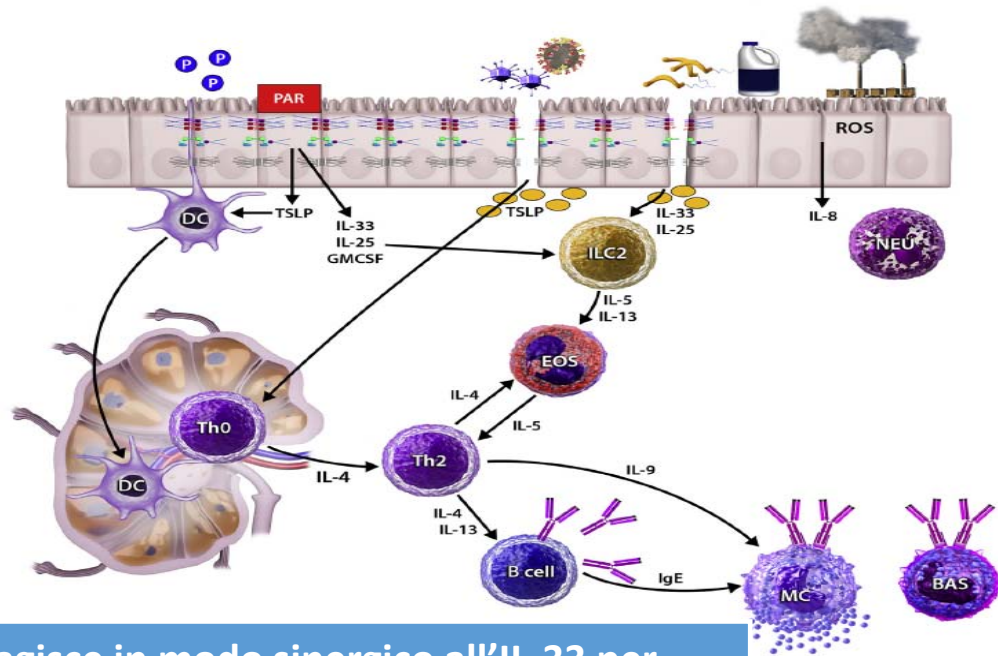
Una disfunzione di barriera è tipica di tutte le malattie caratterizzate da **infiammazione «type 2»**

Rostra

Environmental factors in epithelial barrier dysfunction

Check for updates

Zeynep Celebi Sözen, MD,^{a,b,*} Lacin Cevhertas, MSc,^{a,c,d,*} Kari Nadeau, MD, PhD,^e Mübeccel Akdis, MD, PhD,^a and Cezmi A. Akdis, MD^{a,d} Davos, Switzerland, Ankara and Bursa, Turkey, and Stanford, Calif



IL-4 and IL-13 decrease epithelial junctional integrity and increase epithelial permeability^{1,2}

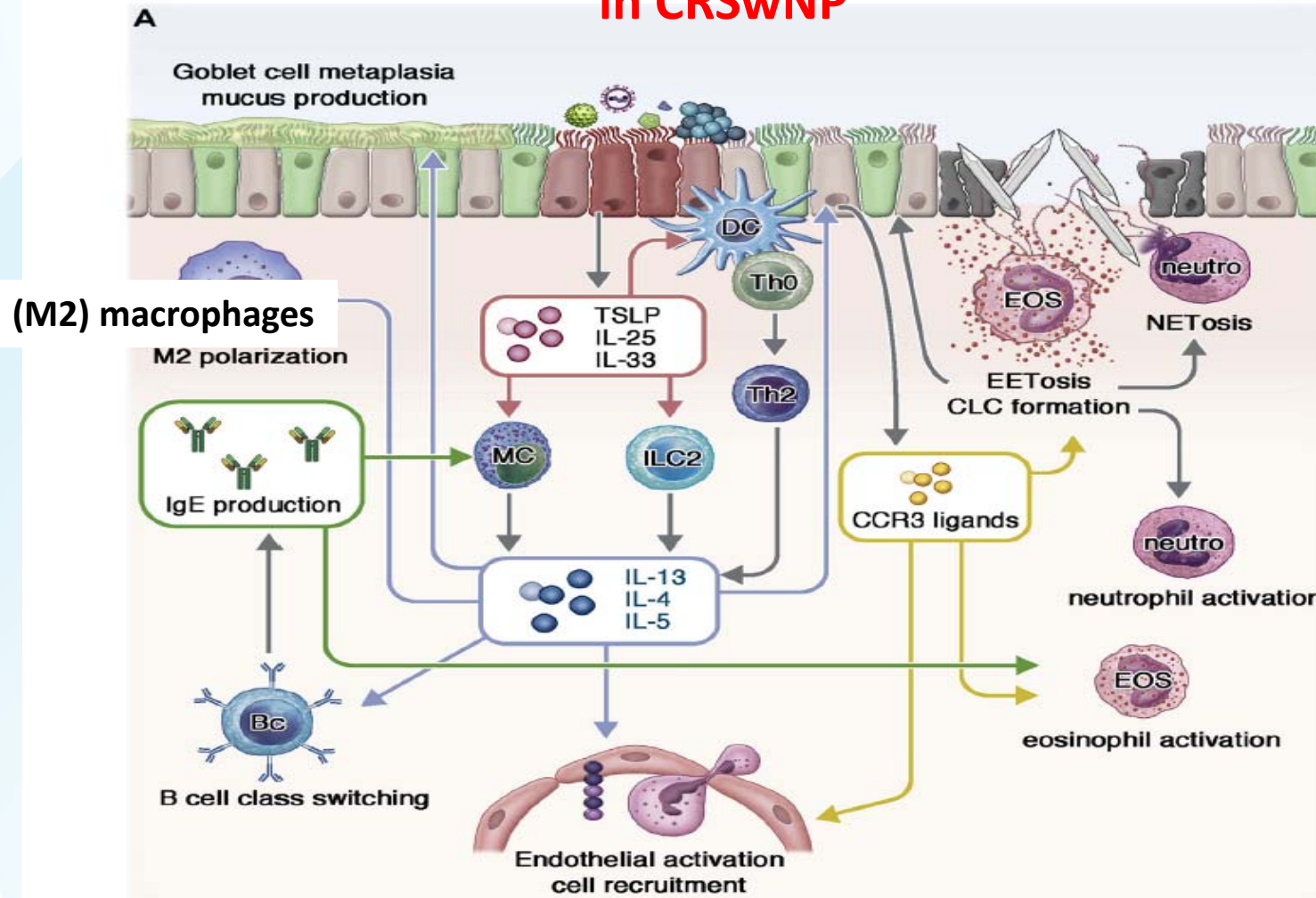
Le allarmine, promuovono la migrazione delle cellule presentanti l'antigene (APC) dalla periferia alle stazioni linfonodali secondarie, dove entrano in contatto con i linfociti T helper naïve (Th0) e, principalmente attraverso la secrezione di IL-4, ne promuovono la differenziazione verso il fenotipo Th2.

L'IL-25 agisce in modo sinergico all'IL-33 per la produzione di IL-5 e IL-13 da parte delle ILC2. In generale, mentre la TSLP promuove la sopravvivenza delle ILC2

(J Allergy Clin Immunol 2020;145:1517-28.)

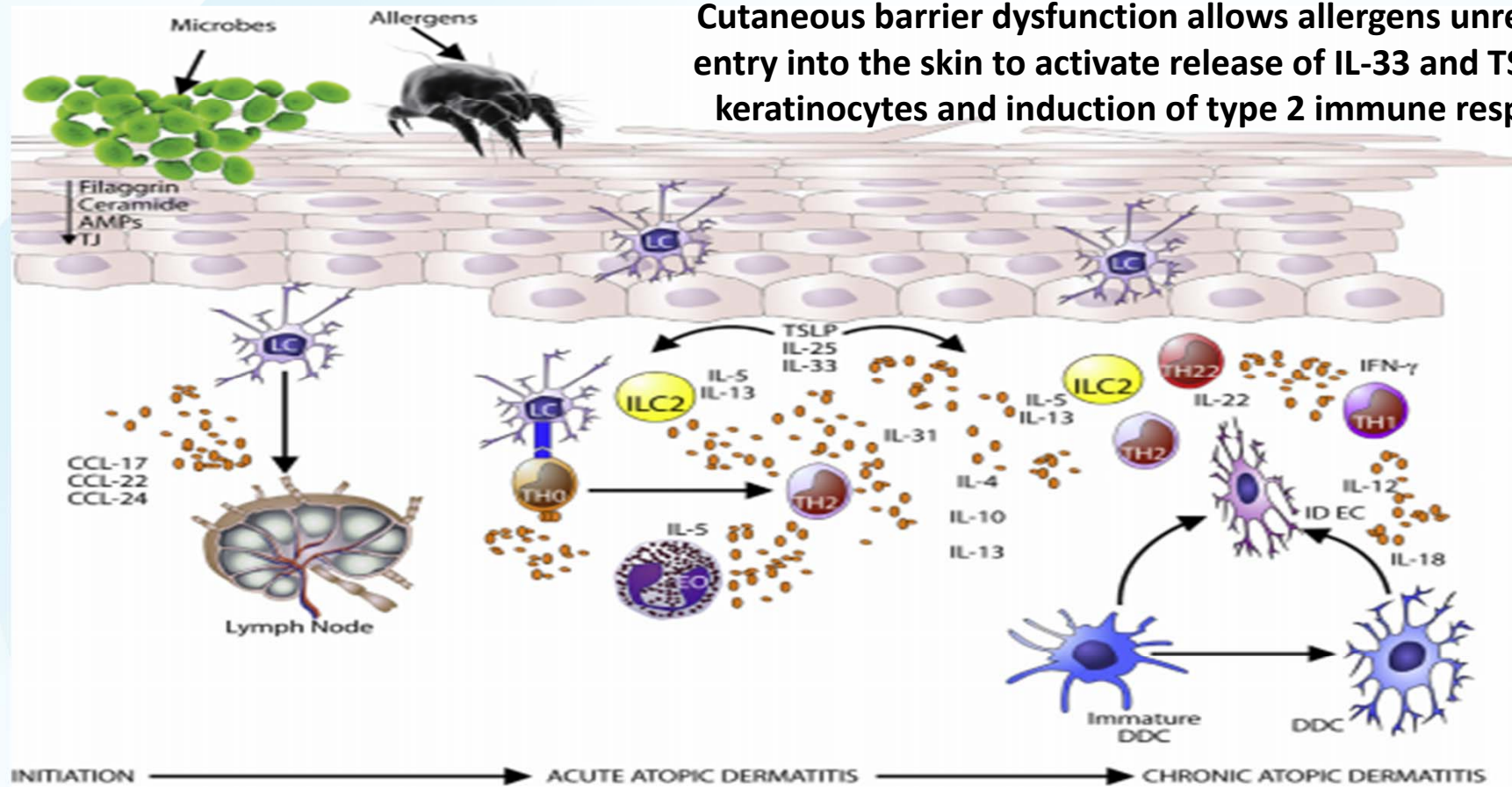
Epithelial Barrier Disruption and Remodeling and the Formation of Nasal Polyps

in CRSwNP



Atopic dermatitis: defective skin barrier

Cutaneous barrier dysfunction allows allergens unrestricted entry into the skin to activate release of IL-33 and TSLP from keratinocytes and induction of type 2 immune responses.



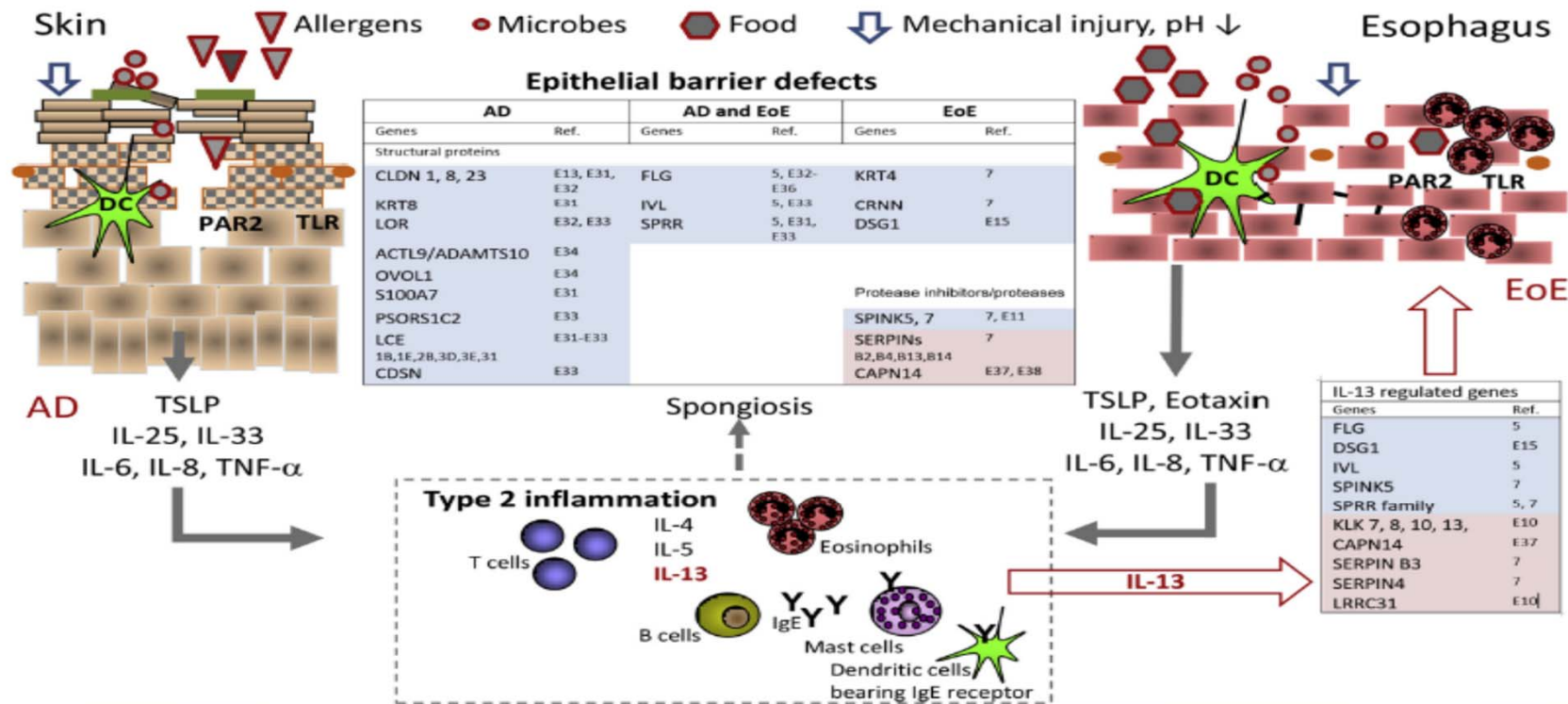
DERMATITE ATOPICA/ESOPHAGITE EOSINOFILA

Paradigms and perspectives

Relationship of skin barrier breakdown and eosinophilic esophagitis

Check for updates

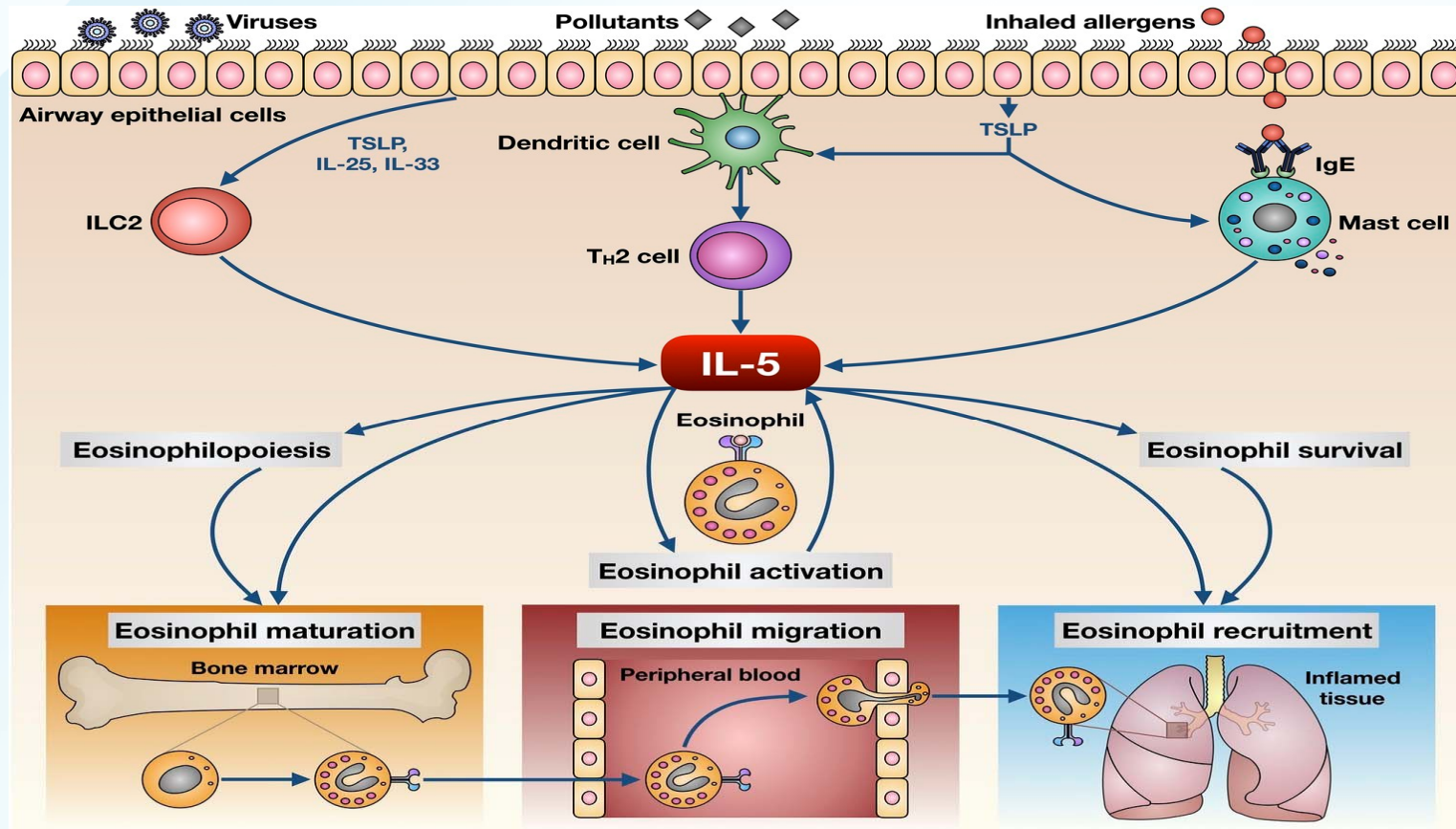
Dagmar Simon, MD,^a and Hans-Uwe Simon, MD, PhD^{b,c} Bern, Switzerland, and Moscow, Russia



15/06/2021

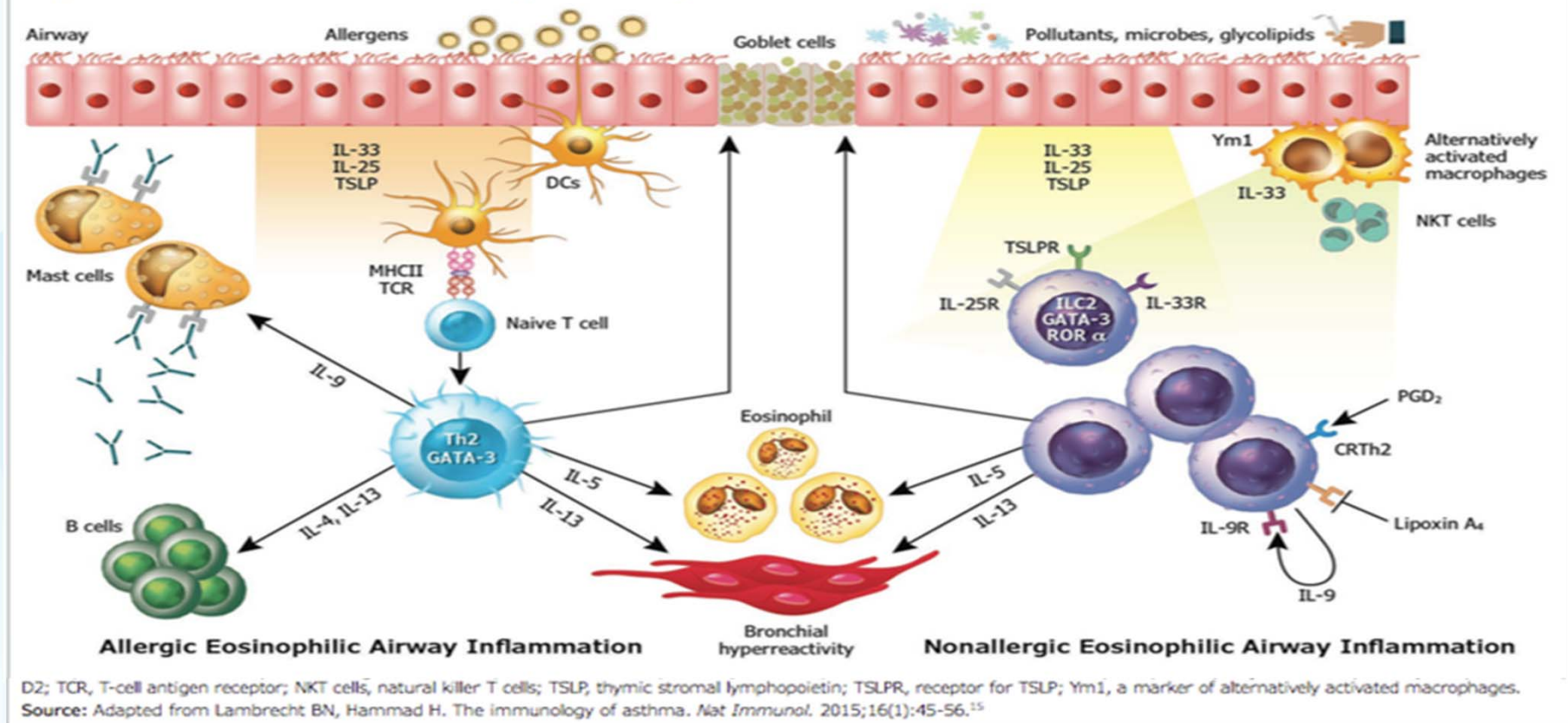
J Allergy Clin Immunol 2020;145:90-2.

IL-5 ED EOSINOFILI RUOLO CENTRALE NELL'INFIAMMAZIONE DI TIPO 2



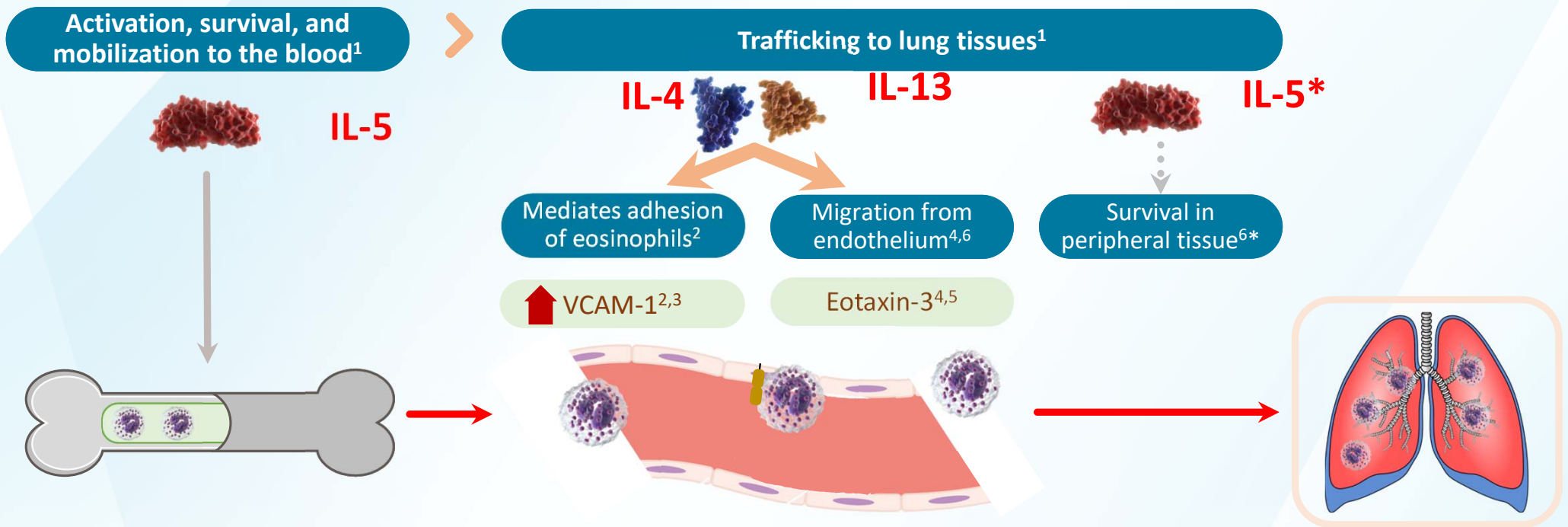
Type 2 asthma and eosinophils

Figure 1. Postulated Mechanism of Type 2 Eosinophilic Inflammation in Asthma



INFIAMMAZIONE EOSINOFILICA : RUOLO NON SOLO DELL' IL 5

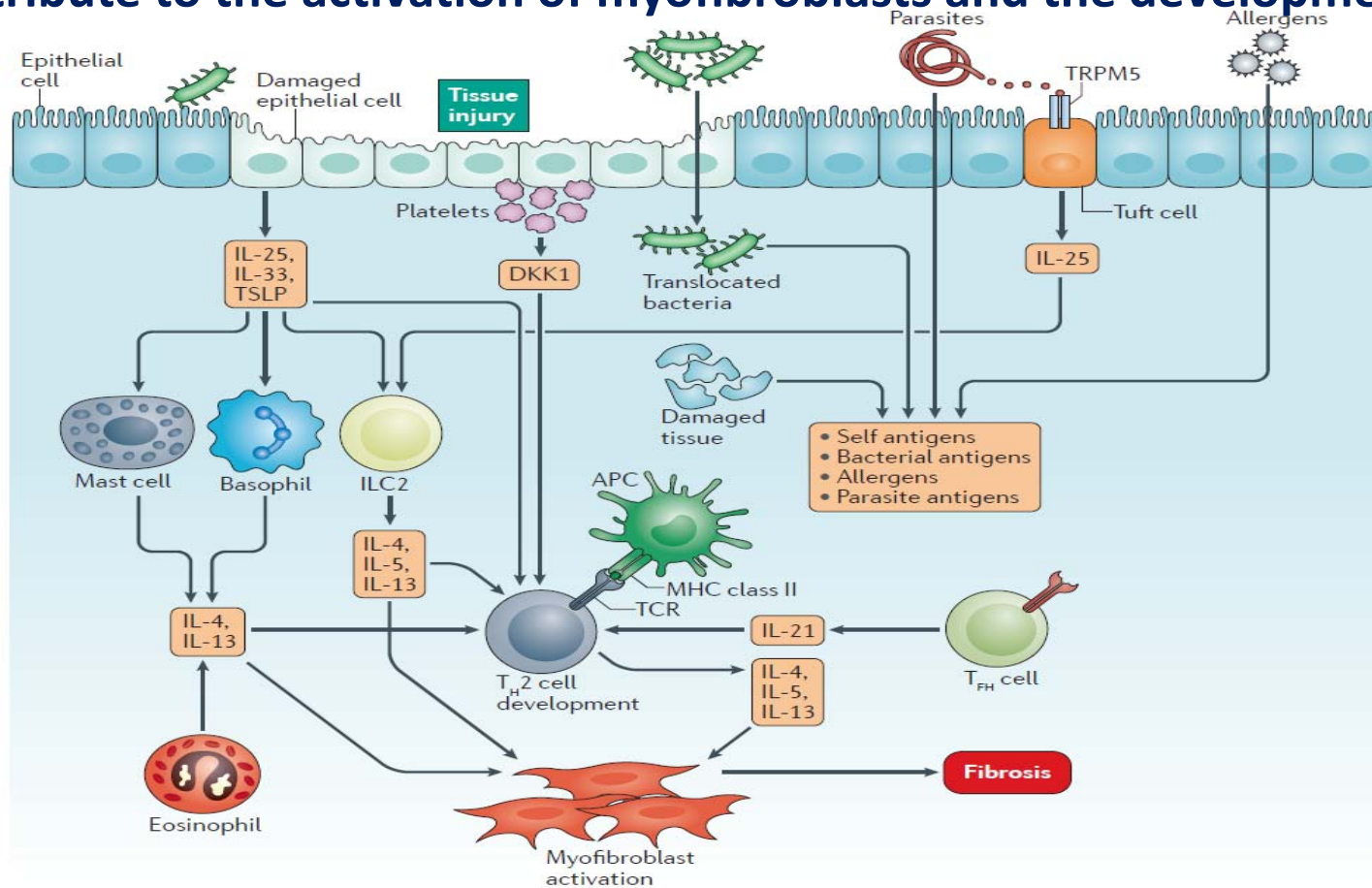
IL-4, IL-13 e IL-5 promuovono la maturazione, attivazione e il trafficking degli eosinofili



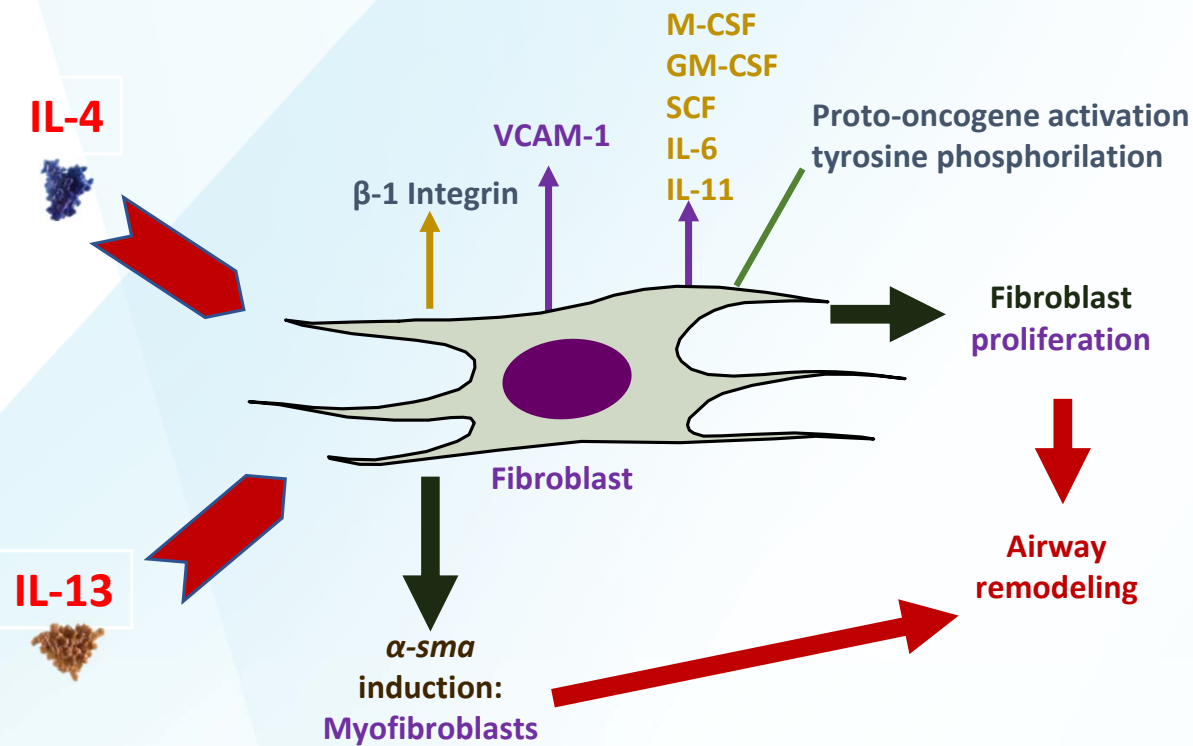
- IL-5 promuove la maturazione, attivazione e sopravvivenza degli eosinofili
- IL-4 e IL-13 aumentano l'espressione sia di VCAM-1, che favorisce l'adesione degli eosinofili all'endotelio, inducono chemochine quali l'eotassina-1 e l'eotassina-3, che favoriscono il trafficking degli eosinofili verso il tessuto polmonare

IL-4/IL-13 E RIMODELLAMENTO

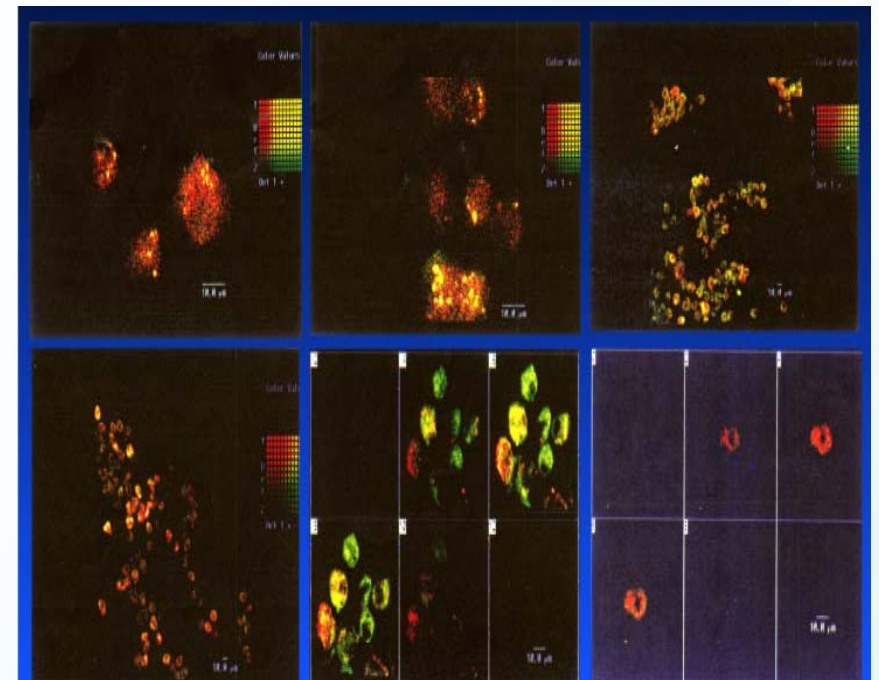
IL-4 and IL-13 secreted from Th2, basophils, mast cells, eosinophils and ILC2s also directly contribute to the activation of myofibroblasts and the development of fibrosis.



IL-4/IL-13 activate subsets of lung fibroblasts, which may act as effector cells in lung remodeling in the pathogenesis of asthma

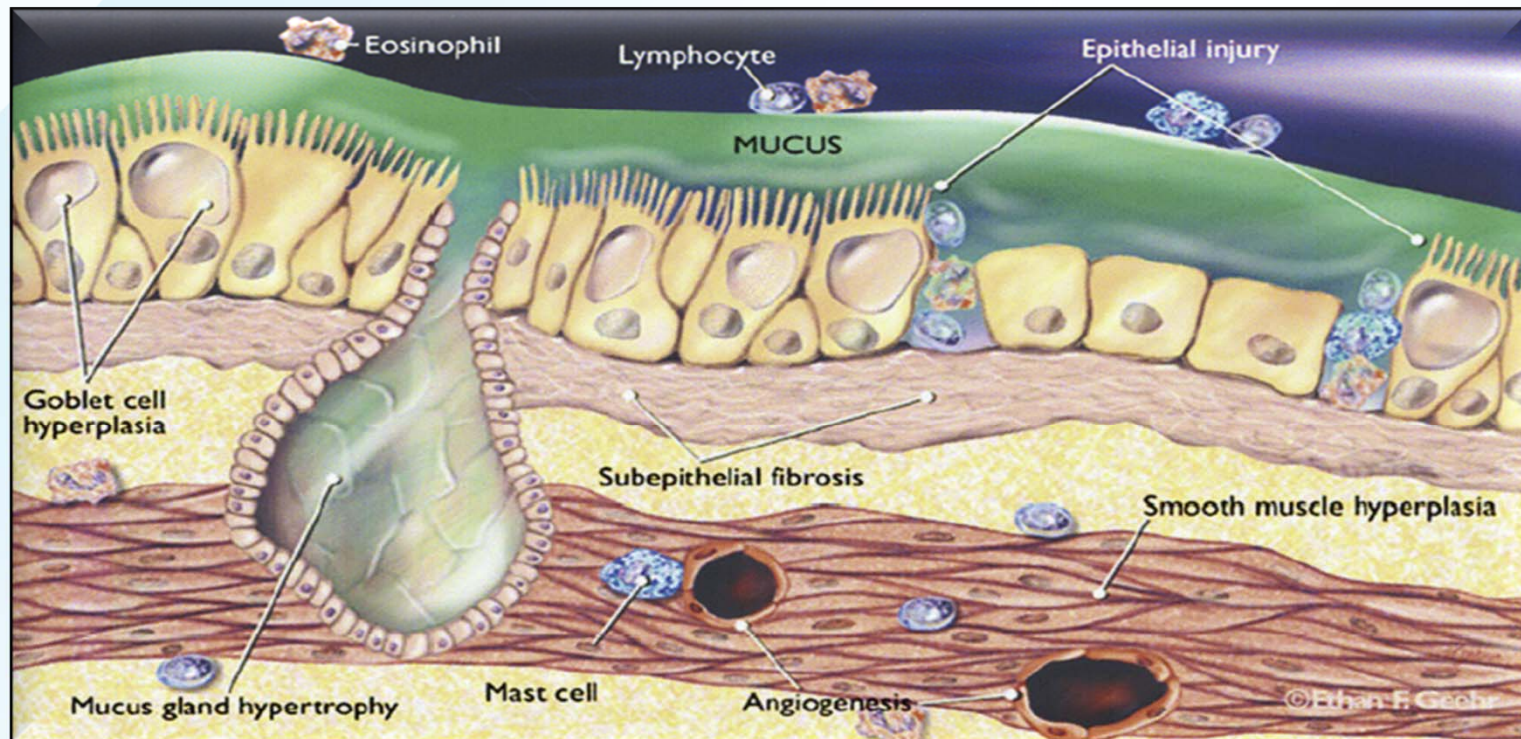


Analysis of intracellular localization of the IL-4/IL-4R α complex in lung fibroblasts stimulated with IL-4 or IL-13



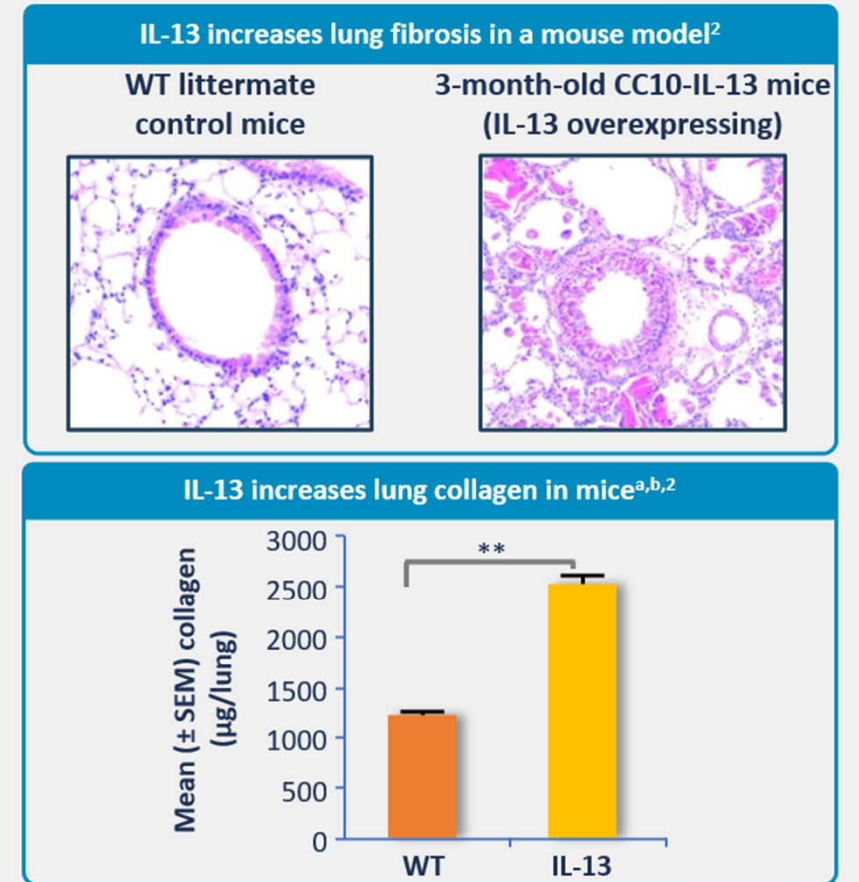
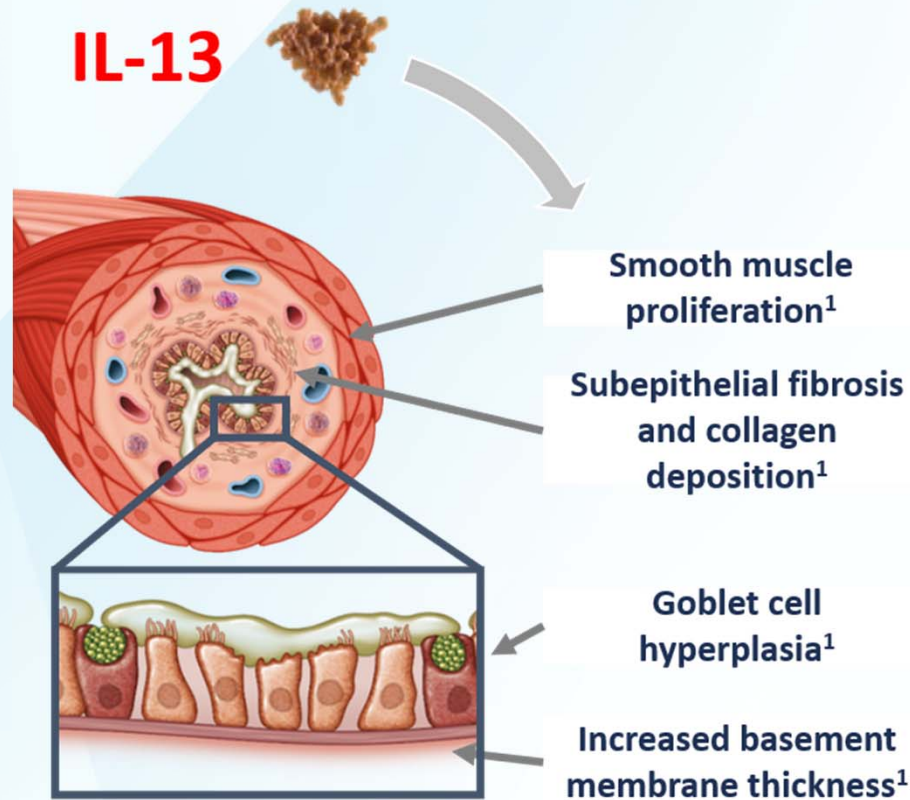
Doucet C, et al. Int Immunol. 1998;10:1421–1433; 2.
 Doucet C, et al. J Clin Invest. 1998;101:2129–2139

RUOLO DELL'INFIAMMAZIONE DI TIPO 2 NEL RIMODELLAMENTO BRONCHIALE



L'alterata architettura delle vie aeree è anche conseguenza dell'attivazione dei fibroblasti da parte dell'IL-13 e, in misura minore, dell'IL-4

IL-13 Contributes to Airway Remodeling



l'IL-13 è responsabile della secrezione di muco, dell'iper-reattività delle vie aeree e del rimodellamento tessutale

IL-13 Contributes to Excess Mucus Production, Which Contributes to Airflow Obstruction



Journal of
Clinical Medicine



Review

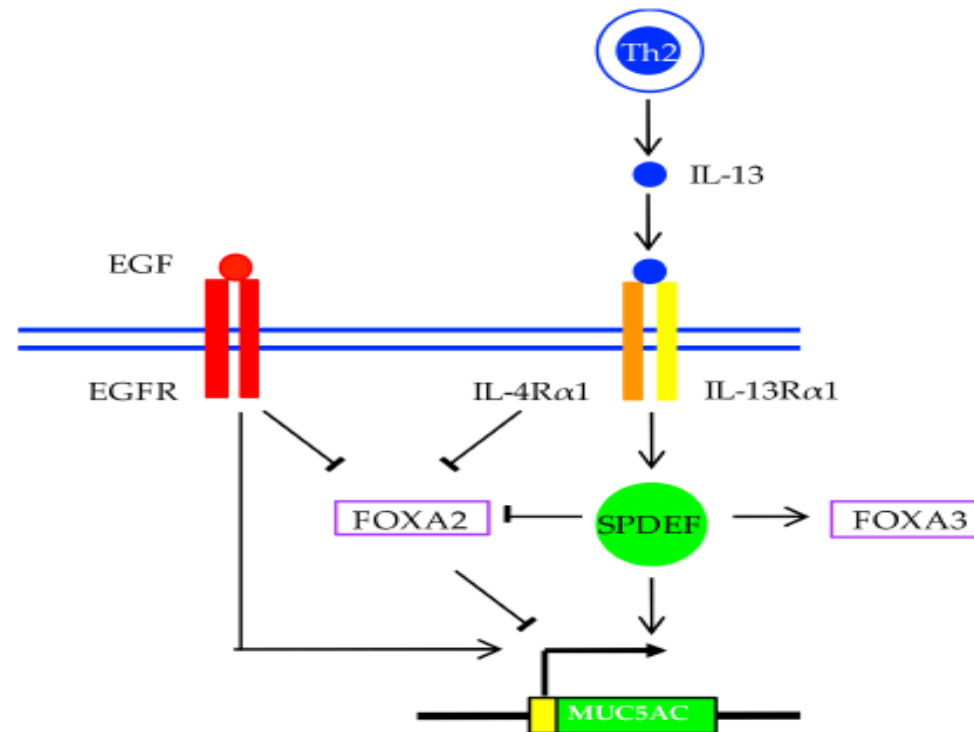
Airway Mucus and Asthma: The Role of MUC5AC and MUC5B

Luke R. Bonser and David

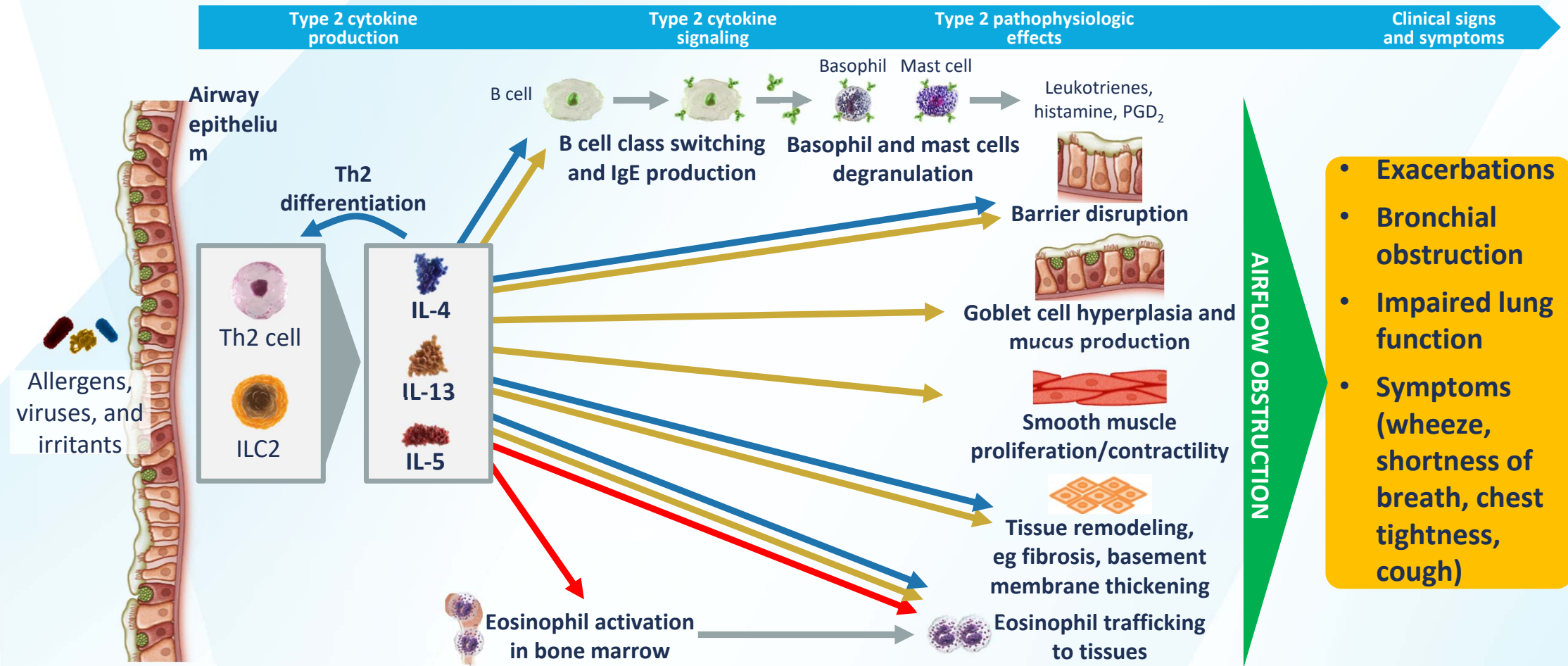
MUC5AC induction and goblet cell differentiation in asthma.

Goblet cell metaplasia and hyperplasia are induced by various inflammatory mediators, including type 2 cytokines (e.g., interleukin-13 (IL-13))

MUC5AC e MUC5B sono i principali componenti del muco delle vie aeree e la loro sintesi risulta alterata in pazienti affetti da asma. L'esposizione di cellule epiteliali respiratorie all'IL-13 comporta un significativo aumento dell'espressione di MUC5AC



MECCANISMI MOLECOLARI DELL'INFIAMMAZIONE DI TIPO 2 NELL'ASMA GRAVE



1. Gandhi NA, et al. *Nat Rev Drug Discov.* 2016;15:35–50; 2. Fahy JV. *Nat Rev Immunol.* 2015;15:57–65; 3. GINA. Diagnosis and management of difficult-to-treat and severe asthma in adolescent and adult patients. 2019