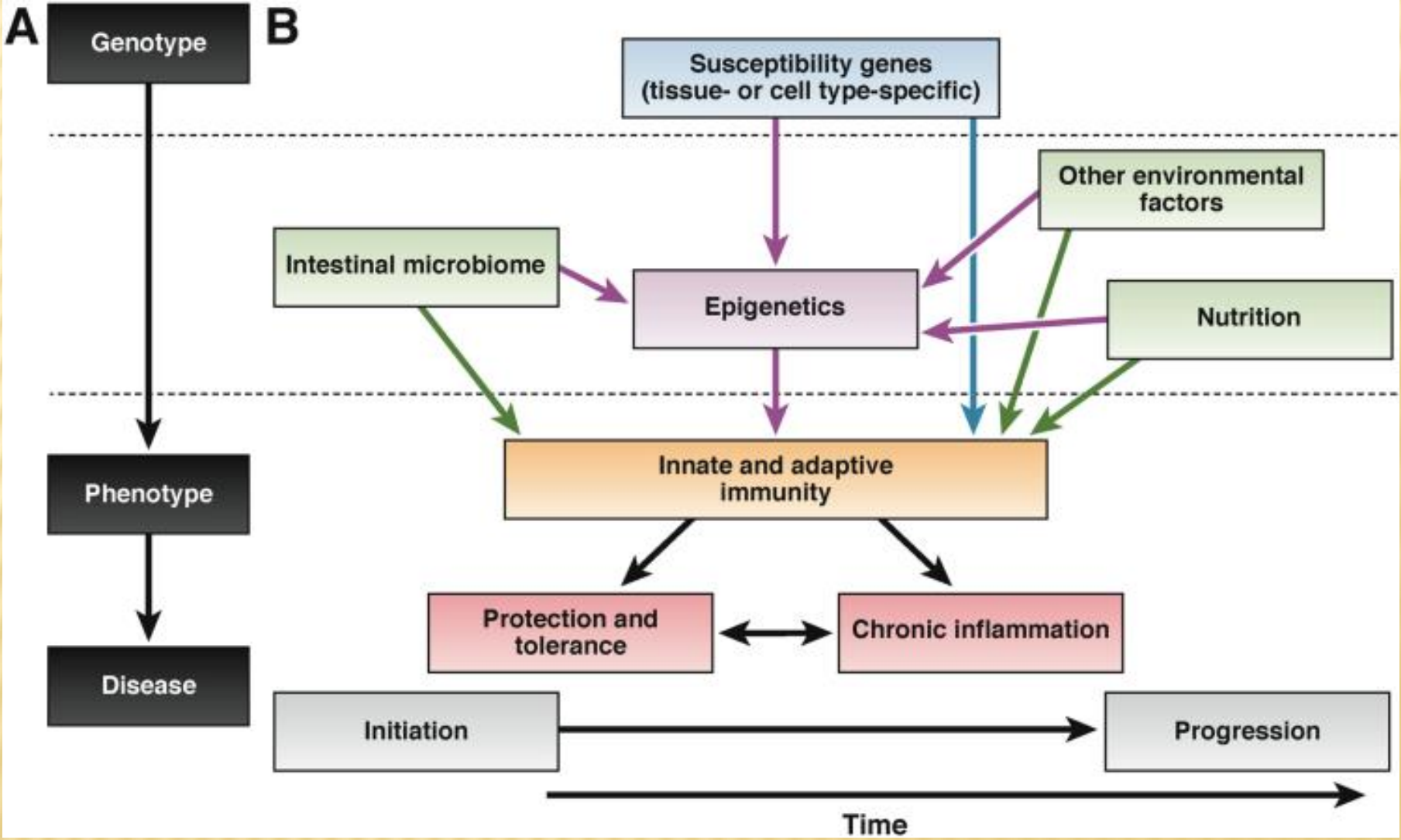
PATHOPHYSIOLOGY OF HYPERSENSITIVITY AND AUTOIMMUNE DISEASES

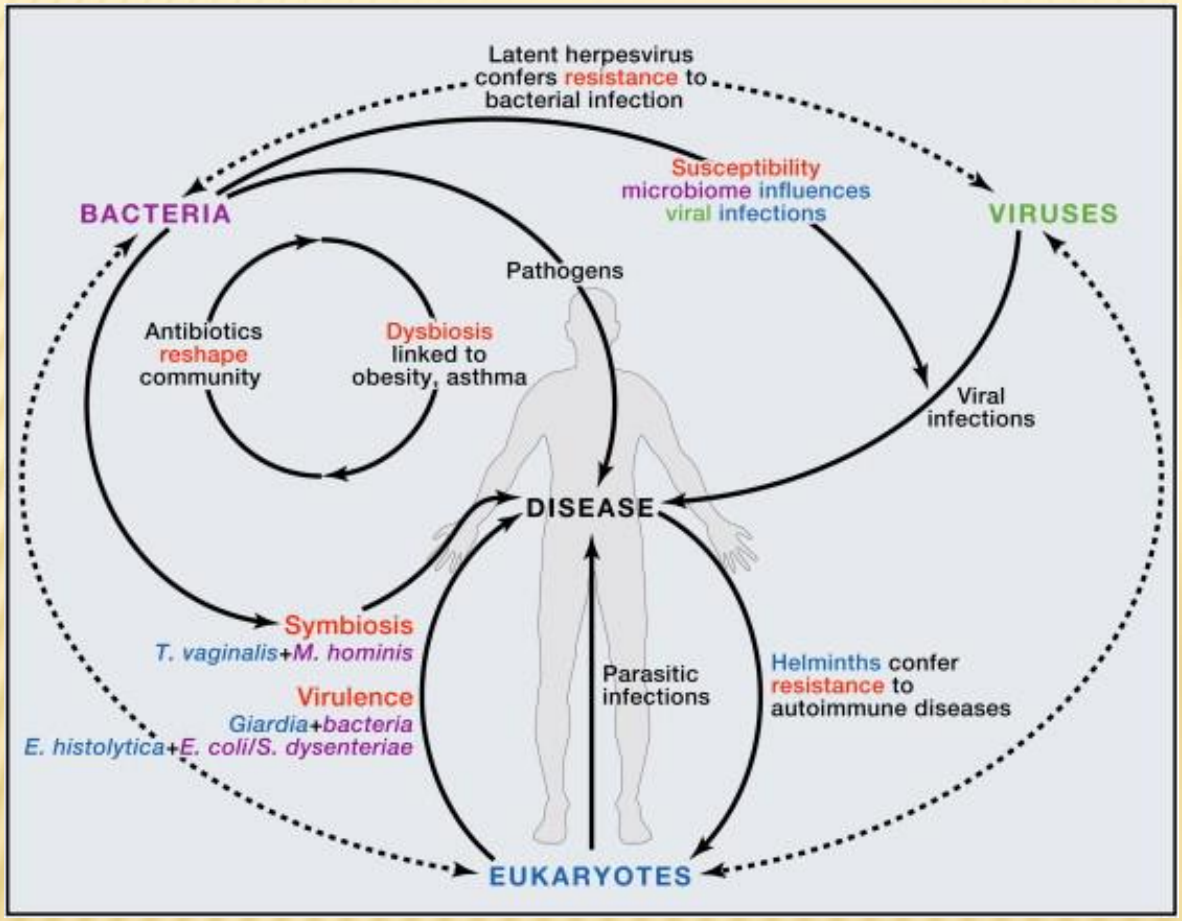
VLA- 16. 4. 2019

Contemporary view of diseases pathogenesis



Beyond Gene Discovery in Inflammatory Bowel Disease: The Emerging Role of Epigenetics
Gastroenterology. 2013 August;145(2):293-308.

EFFECT OF INTERACTIONS OF BACTERIA, VIRUSES, AND EUKARYOTES IN HEALTH AND DISEASE

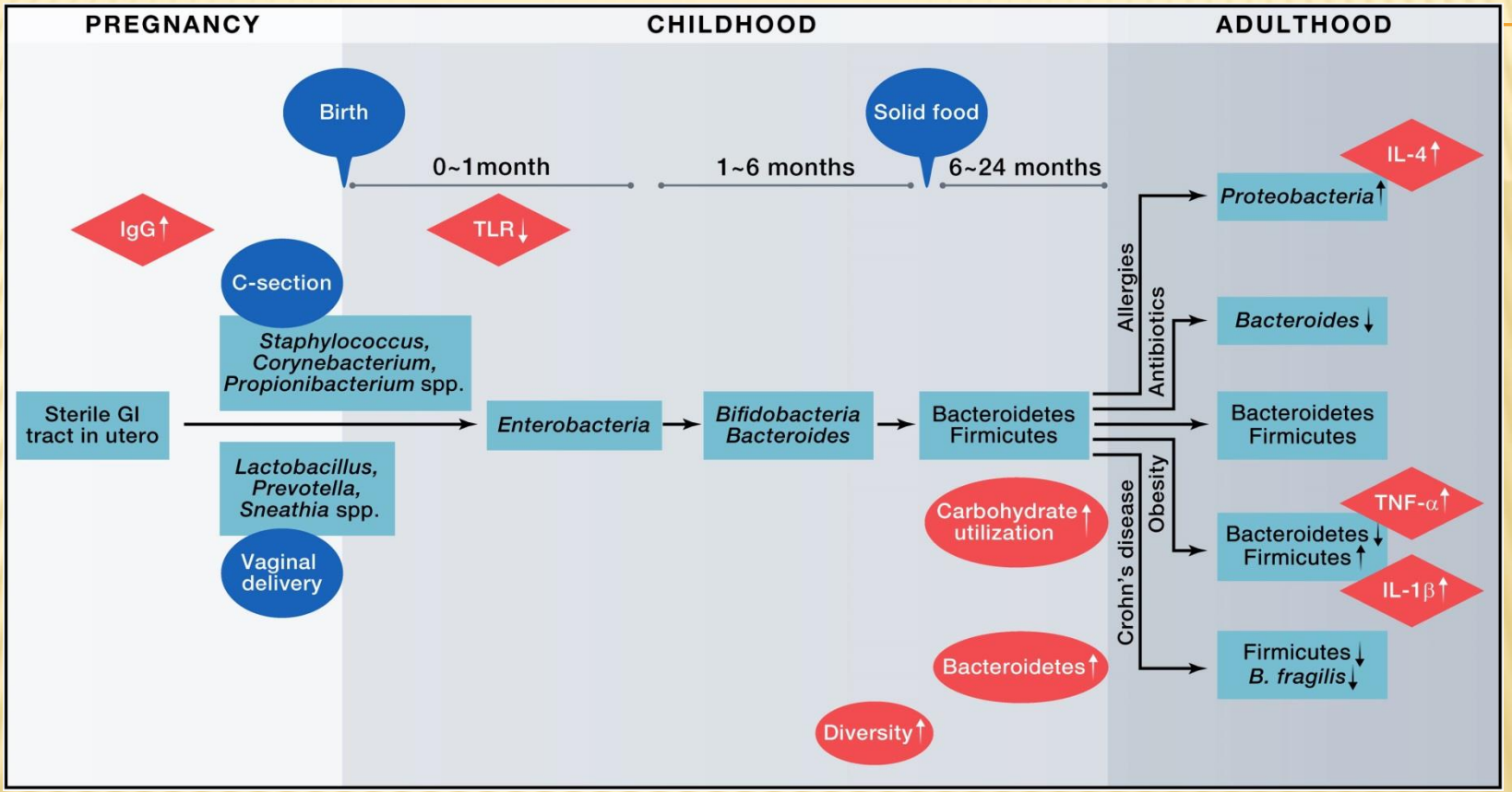


•Diseases have been traditionally studied under a paradigm of "one microbe, one disease." However, a new understanding is emerging on how disease phenotypes are actually a result of complex interactions between bacteria, viruses, and eukaryotes, as well as their interactions with the host or with certain drugs. Virulence of some eukaryotes is, for instance, linked to the presence of certain bacteria, such as in the case of *E. histolytica* and *E. coli* or *S. dysenteriae*. The susceptibility of the host to viral infections is conditioned by the particular configuration of the microbiota, whereas herpesvirus infection can confer resistance to certain bacterial infections. Antibiotics can significantly reshape the composition of the microbiota. As a clear correlation has been observed between many diseases and dysbiosis, the widespread use of antibiotics may be linked to the dramatic increase observed in autoimmune diseases over the last years. Conversely, helminthes confer resistance to autoimmune diseases.

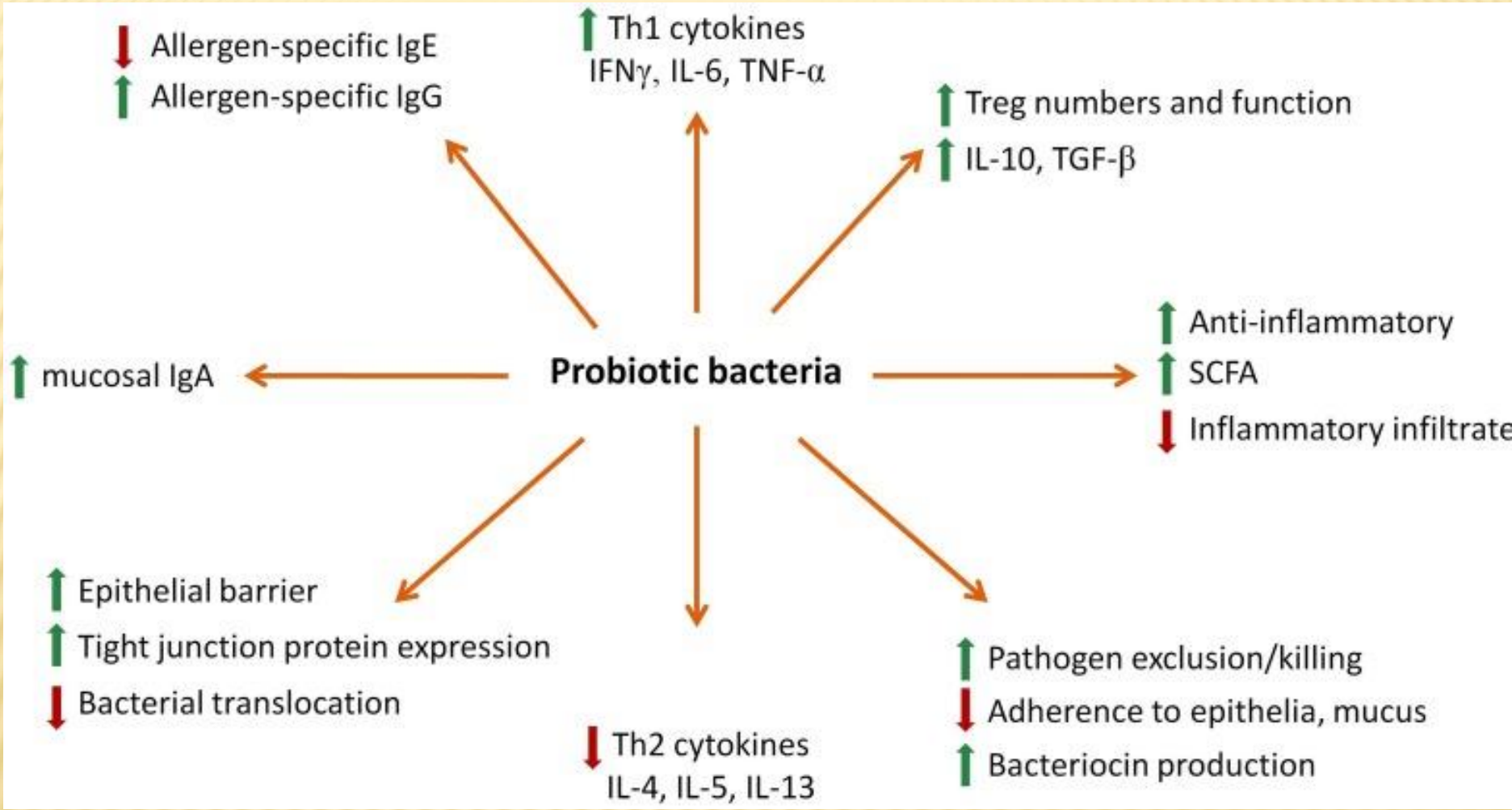
Cell 2012; 148: 1258–1270

Cell 2012; 148: 1258–12

DEVELOPMENT OF THE MICROBIOTA

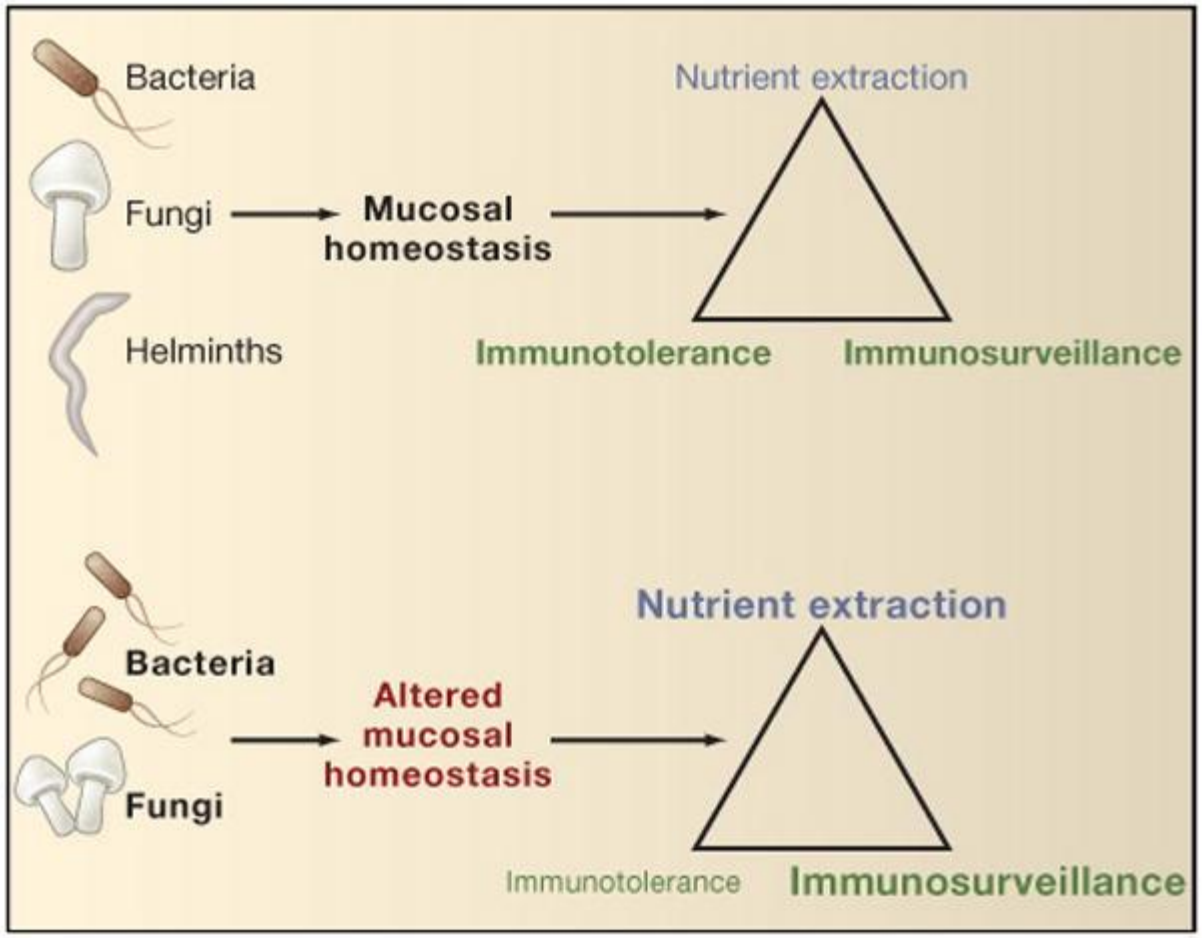


The gastrointestinal tract of the fetus is sterile until birth, after which the newborn is initially colonized. Depending on delivery mode, the initial communities tend toward a skin-like (caesarean section) or a vaginal-like (vaginal delivery) configuration. During the first weeks of life, there is a reduced activity of TLRs, potentially allowing the necessary formation of a stable bacterial community in the gut. As the infant grows, and with the introduction of solid foods, the microbiota diversity increases, and the community converges toward an adult-like state. At the same time, the immune system "learns" to differentiate between commensal and pathogenic bacteria. By adulthood, a relatively stable community composition (but varying between different individuals) is achieved, dominated mostly by Bacteroidetes and Firmicutes. Different diseases are characterized by significant changes in the microbiota and associated changes in the production of cytokines.


Allergen-specific IgE
Allergen-specific IgG
Th1 cytokines
IFNγ, IL-6, TNF-α
Treg numbers and function
IL-10, TGF-β
mucosal IgA
Probiotic bacteria
Anti-inflammatory
SCFA
Inflammatory infiltrate
Epithelial barrier
Tight junction protein expression
Bacterial translocation
Th2 cytokines
IL-4, IL-5, IL-13
Pathogen exclusion/killing
Adherence to epithelia, mucus
Bacteriocin production

Probiotics demonstrating a beneficial effect in clinical studies of eczema.

Type of clinical study	Probiotic
Treatment	*Lactobacillus rhamnosus GG*
	Lactobacillus rhamnosus HN001
	Lactobacillus sakei KCTC
	Lactobacillus acidophilus La-5
	Lactobacillus acidophilus[*]
	Lactobacillus salivarius LS01
	Lactobacillus fermentum VR1
	Bifidobacterium lactis Bb12
	Bifidobacterium lactis UABLA-12[**]
	Bifidobacterium bifidum
Prevention	*Lactobacillus rhamnosus GG*
	Lactobacillus rhamnosus LC705
	Lactobacillus paracasei F19
	Bifidobacterium breve Bb99
	Propionibacterium freudenreichii[***]

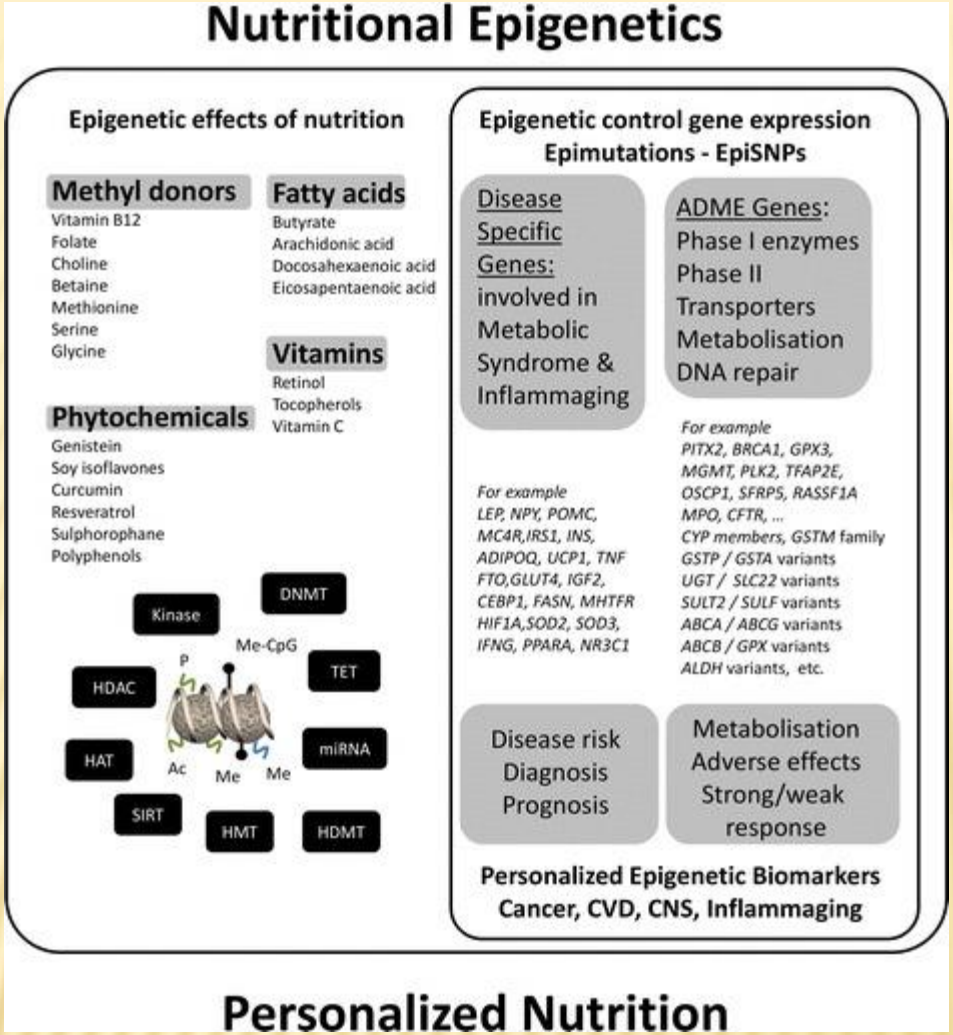


2015 Mar 25;7(1):33. doi: 10.1186/s13148-015-0068-2. eCollection 2015.

From inflammaging to healthy aging by dietary lifestyle choices: is epigenetics the key to personalized nutrition?

Vel Szic KS[1], Declerck K[1], Vidaković M[2], Vanden Berghe W[1].

The loss of universal helminth infection as occurred in earlier human evolution may alter the numbers or types of bacterial and fungal commensals and thus affect normal mucosal tissue homeostasis. In susceptible or highly exposed individuals, such alterations might alter the balance between immunotolerance, immunosurveillance and nutrient extraction. This imbalance may contribute to the appearance of inflammatory systemic dysregulation at mucosal surfaces, resulting in increases in asthma and allergic diseases, particularly in the setting of environmental changes that have increased exposure to indoor allergens and pollutants, and even to increases in obesity, which can be a risk factor for severe asthma.



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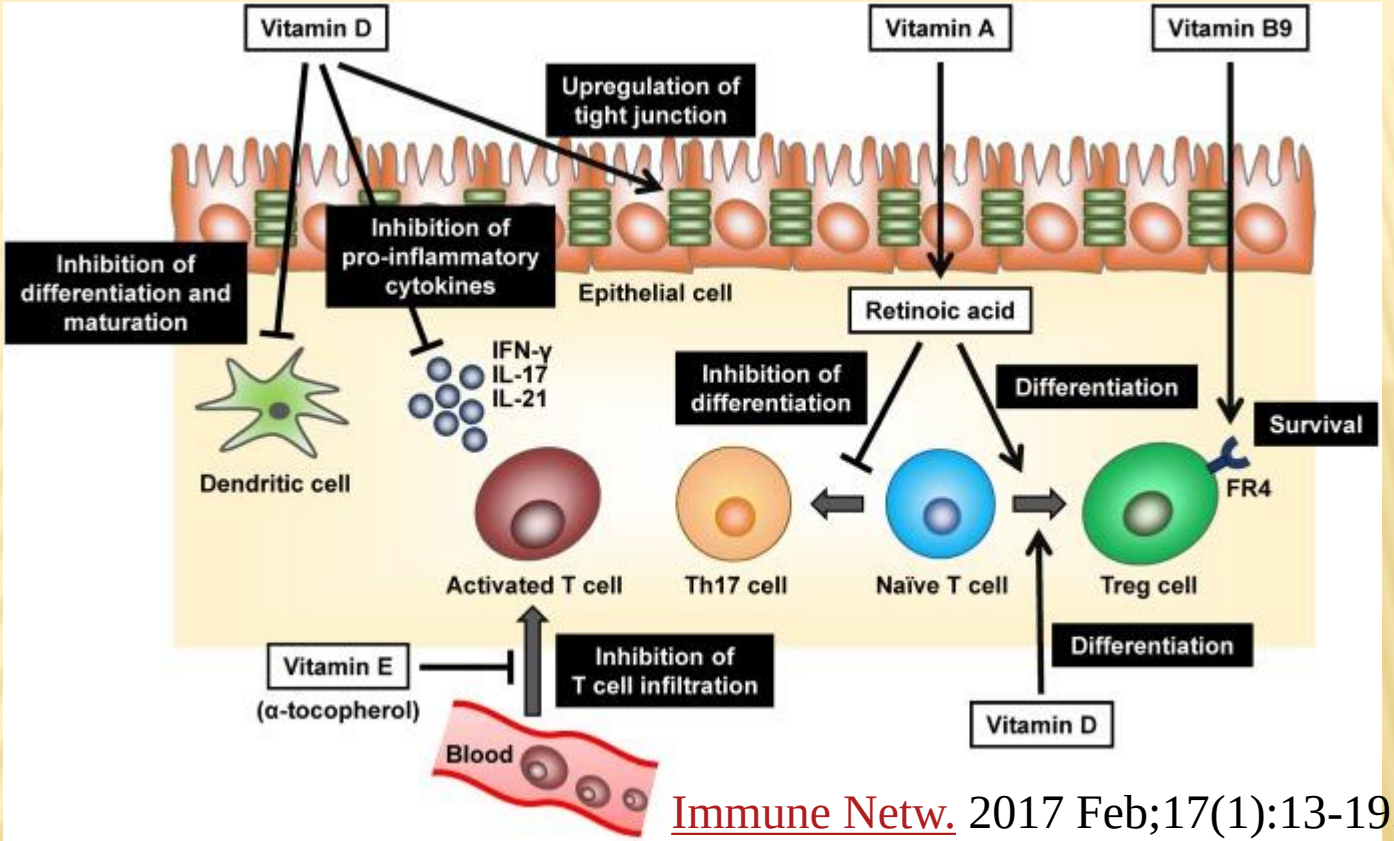
Overview of the mechanisms and consequences of epigenetic regulation by nutritional compounds. Modulation of different classes of chromatin writers-erasers by phytochemicals (left panel). Genes encoding absorption, distribution, metabolism, and excretion (ADME) proteins can be epigenetically regulated and thereby determine individual nutritional responses. Epigenetic modification of disease-related genes can contribute to diagnosis (biomarker) as well as disease prevention or progression (right panel).

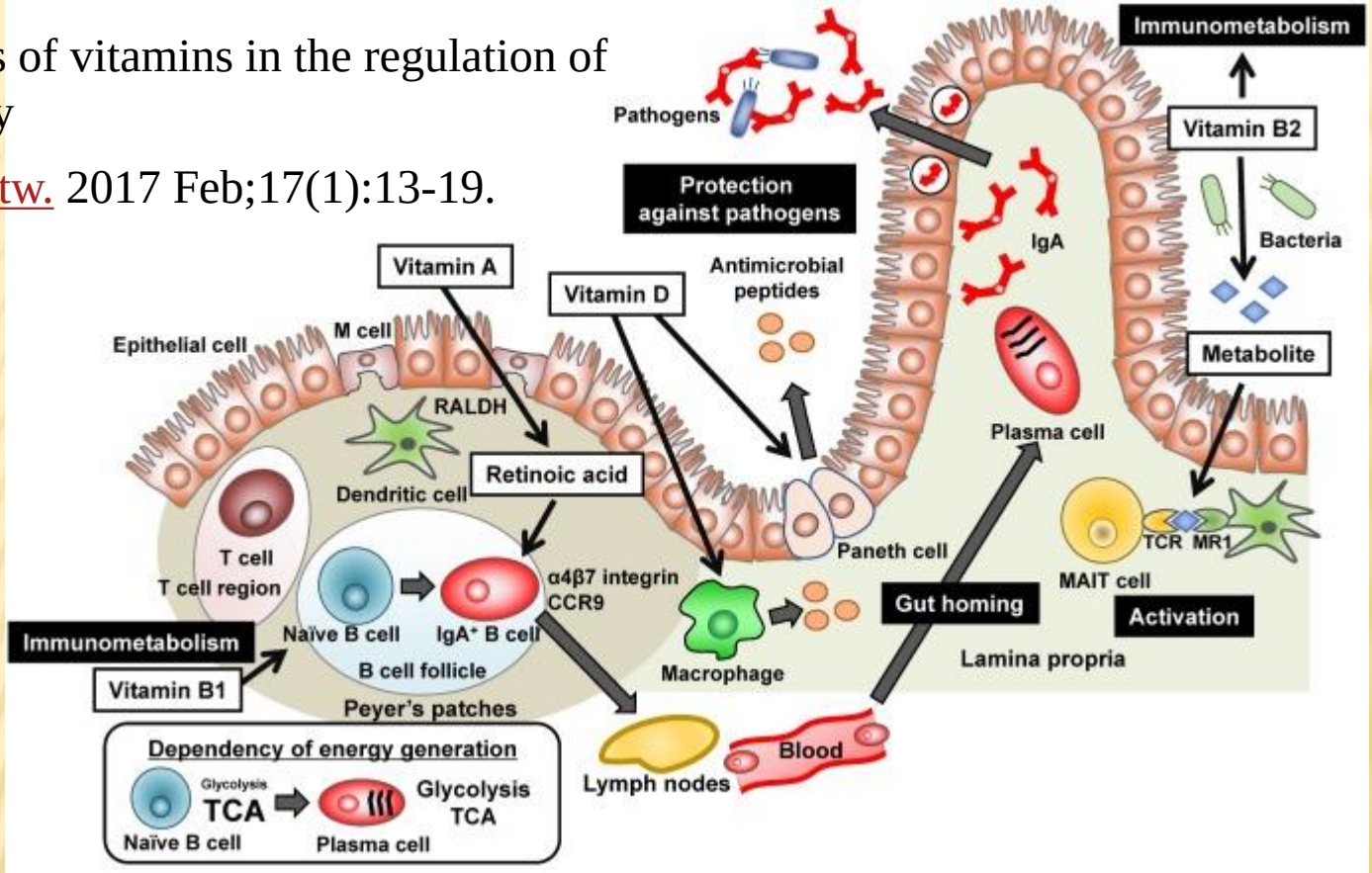


Immune Netw. 2017 Feb;17(1):13-19.

Pivotal roles of vitamins in the maintenance of immunologic homeostasis in the gut. Vitamin A-derived retinoic acid promotes the differentiation of naive T cells to Treg cells and simultaneously inhibits the induction of Th17 cells in the steady state. Like retinoic acid, Vitamin D (as an active form1α,25-dihydroxyvitamin D_3) inhibits the production of pro-inflammatory cytokines such as IFN-γ, IL-17 and IL-21 from T cells together with the promoted differentiation of Treg cells. It also prevents differentiation and maturation of DCs and increases the expression of tight junction protein such as claudins in the epithelial cells. Upon the differentiation of Treg cells, they express high levels of vitamin B9 receptor (folate receptor 4, FR4), which essential for their survival. α-tocopherol, an isoform of vitamin E, can inhibit T cell infiltration into intestine through the negative regulation of signal transduction from VCAM-1 and ICAM-1 by antagonizing protein kinase C.

Various roles of vitamins in the regulation of gut immunity

Immune Netw. 2017 Feb;17(1):13-19.

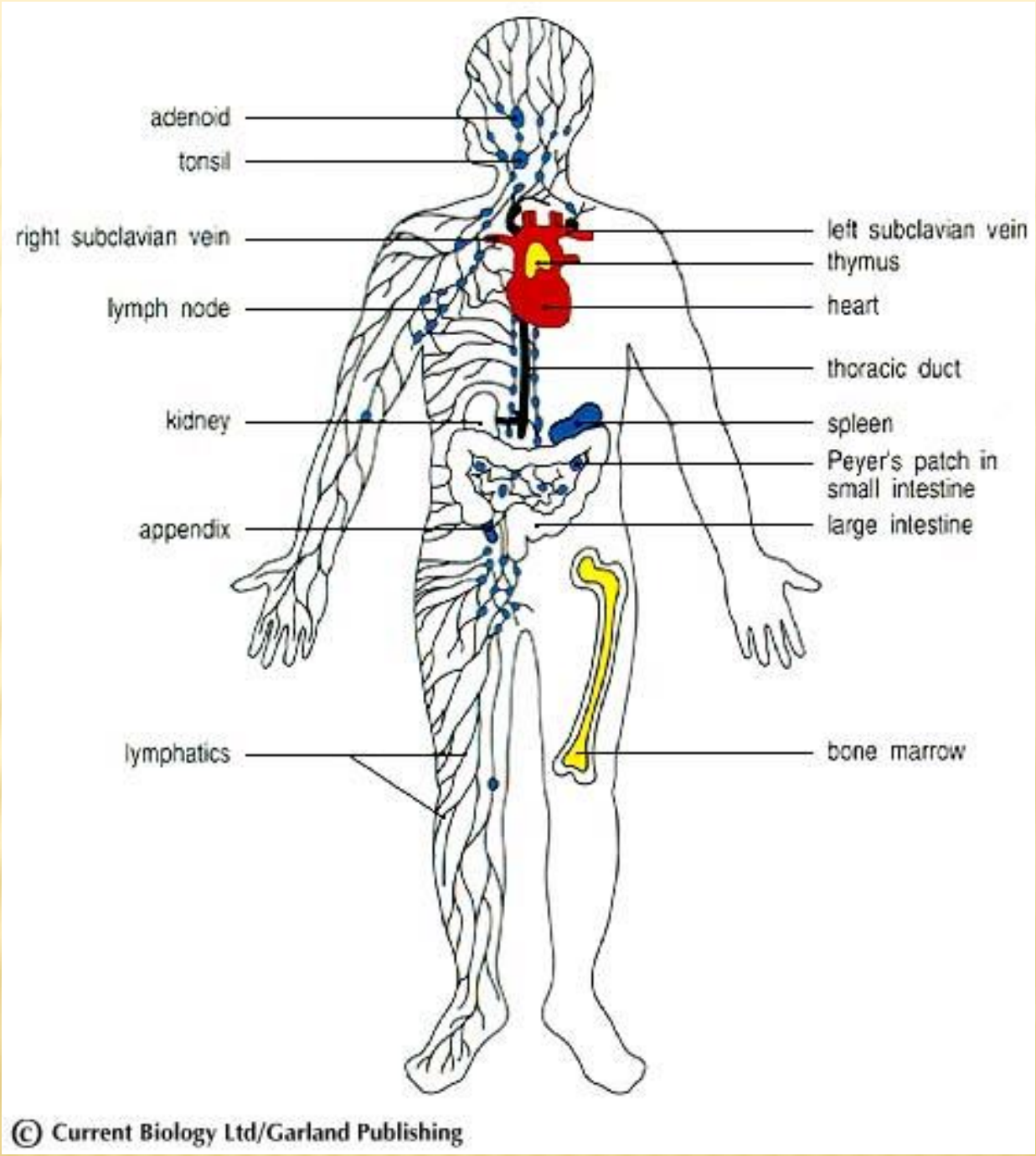


Vitamin A is converted to retinoic acid by retinal dehydrogenases (RALDH) expressing dendritic cells in the Peyer's patches, which induces the expression of gut homing molecules (α4β7 integrin and CCR9) on antigenprimed cells (e.g., IgA^+ B cells) and allows them to traffic into the intestinal lamina propria. In the lamina propria, IgA^+ B cells differentiate into IgA-producing plasma cells. IgA is then transported into the intestinal lumen, where it binds to pathogens to inhibit their invasion and function. Vitamin B1 is essential for energy metabolism, especially maintenance of TCA cycle, and therefore associates with maintenance of naive B cells which utilize predominantly TCA cycle for energy generation. Vitamin B2 also involves in the energy metabolism of immune cells. In addition, bacterial metabolite of vitamin B2 activates mucosal associated invariant T (MAIT) cells via the presentation by major histocompatibility complex (MHC) related protein MR1. Vitamin D enhances production of antimicrobial peptides from Paneth cells and macrophages via vitamin D receptor, which provides an additional immunosurveillance system.

IMMUNE SYSTEM AND ITS FUNCTION

distinguishes „good and bad“
guarantees protection of the organism
guarantees immunosurveillance
guarantees immunotolerance

Decresed resistance to infection	immunodeficiency
Pathological reaction to extrinsic antigens	allergy
Pathological reaction to intrinsic antigens	autoimmunity
Decrease of immunosurveillance	oncologic diseases


adenoid
tonsil
right subclavian vein
lymph node
kidney
appendix
lymphatics
left subclavian vein
thymus
heart
thoracic duct
spleen
Peyer's patch in small intestine
large intestine
bone marrow
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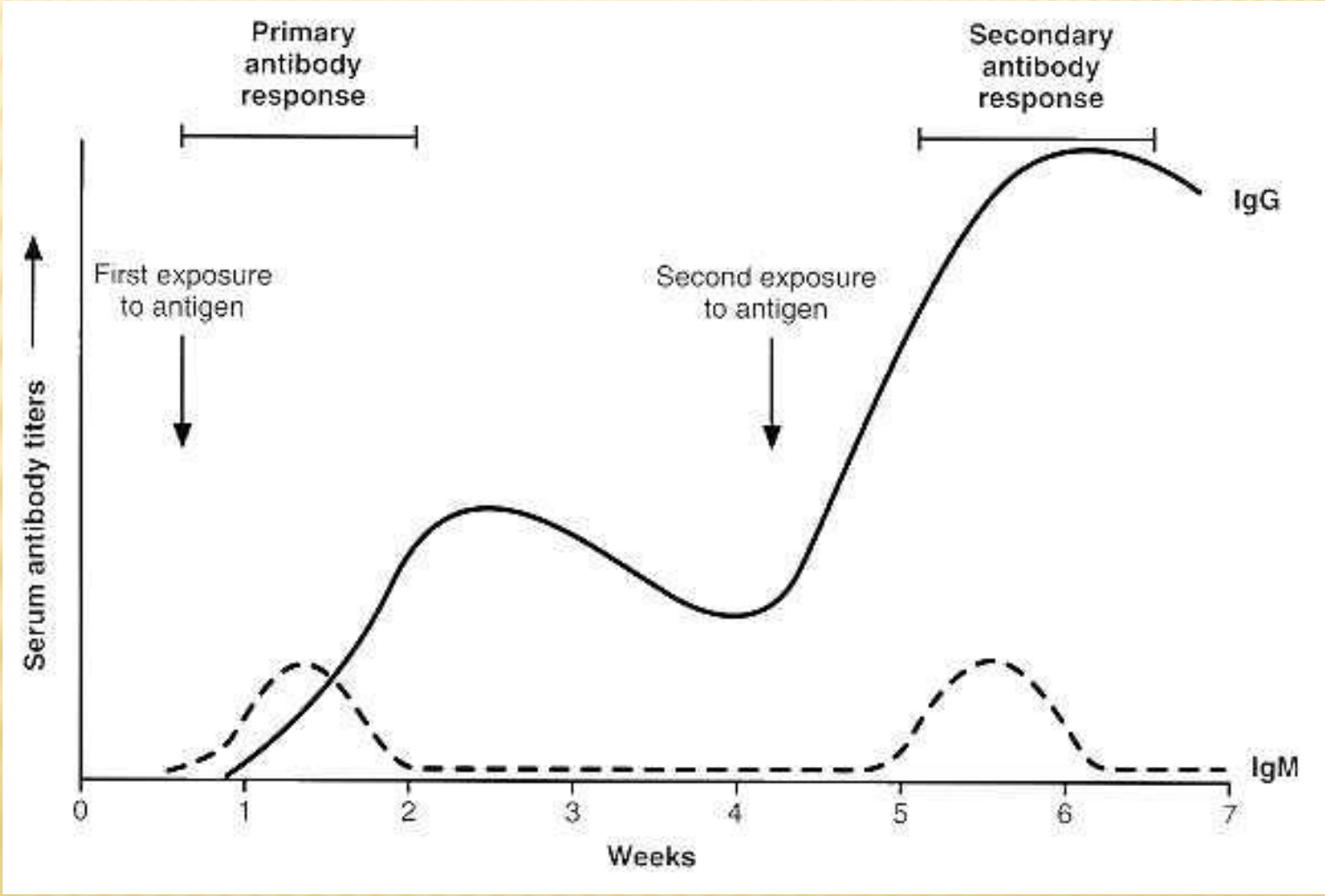
ANTIBODY RESPONSE - TIMING



HLA – MHC-6p21.3

- Responsibility for histocompatibility
- Immunotolerance
- HLA molecule combination is unique for every human being
- The only total HLA compatibility – monozygotic twins
- Graft rejection

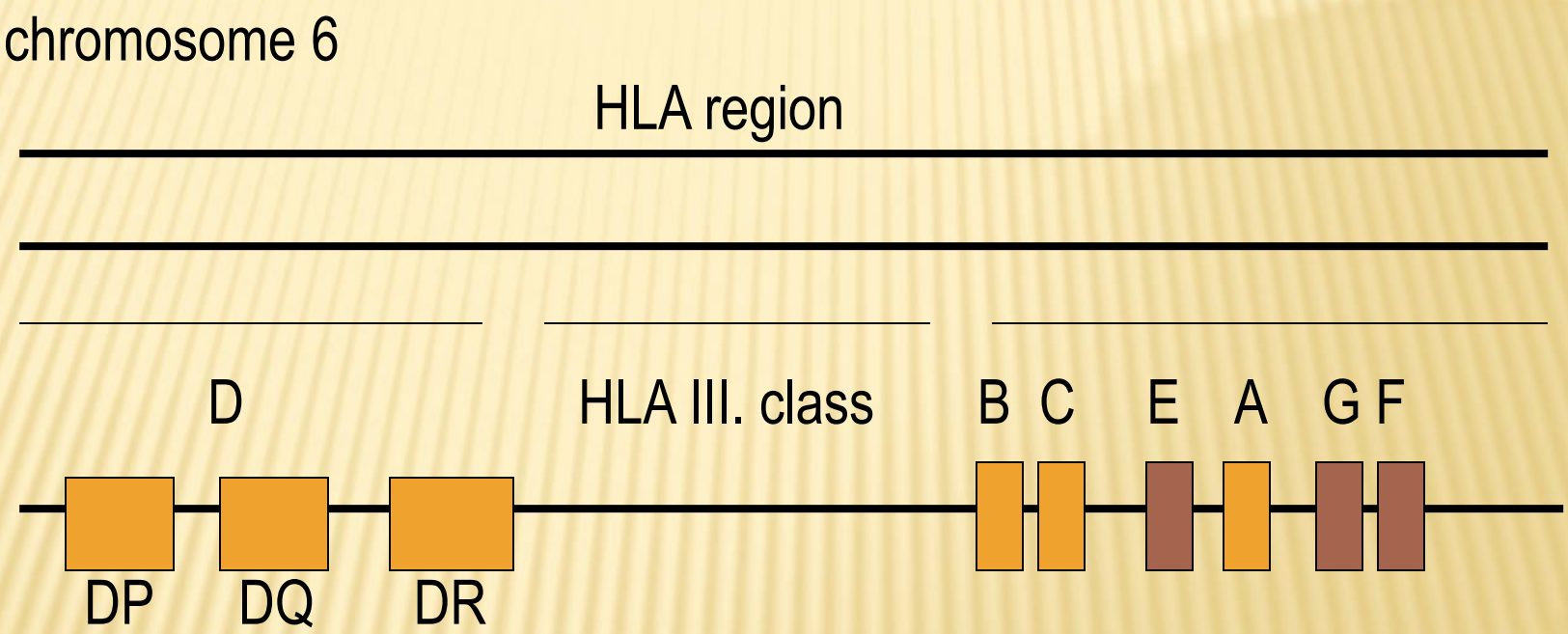
MHC

- MHC class I and II classical molecules are cell surface glycoproteins which mediate presentation of peptides to T-cell receptors, and play a key role in triggering adaptive immune responses when the bound peptide is recognized as foreign.
- In humans, they are coded by **HLA class I (*HLA-A*, *-B*, and *-C*), and II (*HLA-DR*, *-DQ*, and *-DP*)** classical genes. The class I and class II HLA classical genes are the most polymorphic in the human genome, and knowledge about their function in the immune response supports a role for balancing selection in driving the diversity patterns at these loci.

MHC

- A number of findings suggest MHC genes have experienced balancing selection: unusually high level of heterozygosity with respect to neutral expectations; existence of trans-species polymorphisms ; high levels of linkage disequilibrium ; site frequency spectra with excess of common variants; high levels of identity-by-descent compared to genomic averages ; positive correlation between HLA polymorphism and pathogen diversity, and significant associations of HLA alleles with the course of infectious diseases.
- Information on the crystal structure of MHC molecules allowed the identification of a specific set of amino acids that make up the antigen recognition site (ARS), which determines the peptides that the molecule is able to bind. The codons of the ARS were shown to have increased nonsynonymous substitution rates consistent with the hypothesis that adaptive evolution at HLA loci is driven by peptide binding properties.

HLA GENES



- HLA III.class: complement compounds, TNF, HSP…

HLA AND ANTIGENS

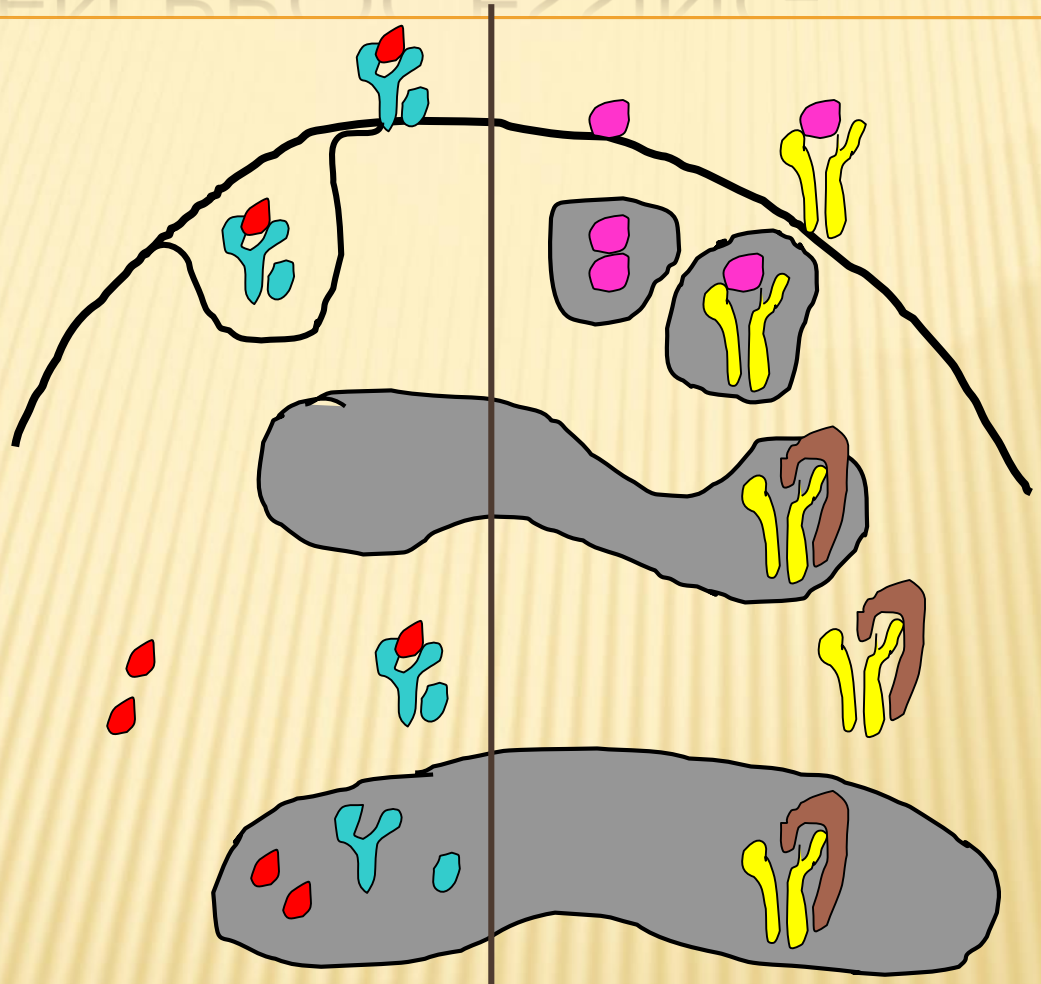
- Antigenes originate either from extracellular compartment (extrinsic antigens), or from intracellular compartment (intrinsic antigenes).

- There are great differences betwwen these two antigen types. They induce different type of immune reaction.
- Intrinsic antigenes are presented using HLA class I;
- extrinsic antigenes use HLA class II.

ANTIGENE PRESENTATION

- Antigens are able to stimulate immune response
- They are proteins, glycoproteins and/or polysaccharides.
- Outer antigens get to body by GIT tract, respiratory tract, skin and or artificially (injection…)
- Inner antigens found in cells (proteins coded by viral genes, proteins coded by mutated genes in tumor cells)
-

ANTIGEN PROCESSING



endogenic antigens, HLA class I

exogenic antigens, HLA class II

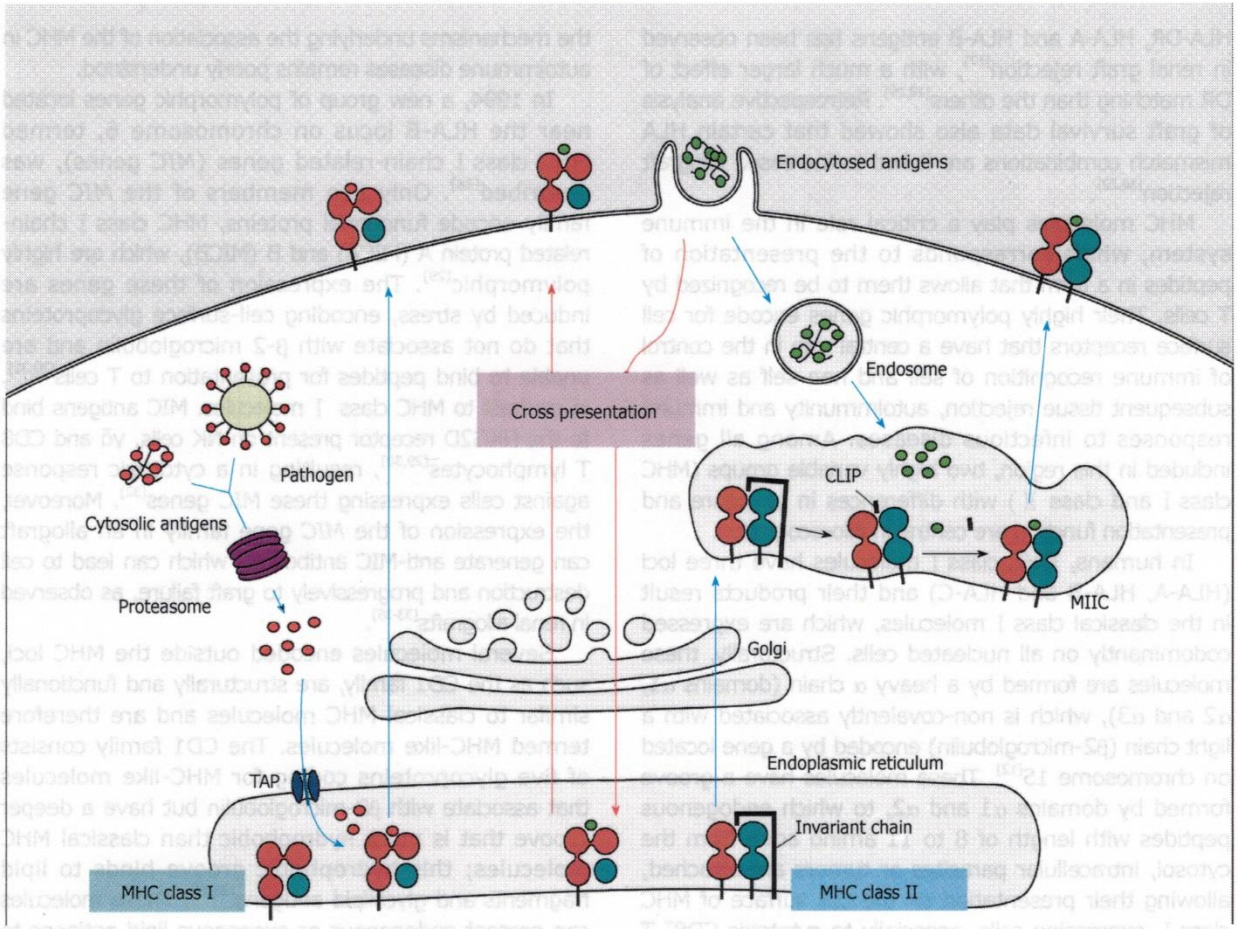


Figure 1 Major histocompatibility complex class Ⅰ and Ⅱ pathways. (1) MHC class Ⅰ molecules present peptides derived from proteins presented in the cytosol of endogenous or pathogen origin. The proteasome breaks down these proteins into peptides, which are then translocated to ER by the transporter associated with antigen processing (TAP) to access the MHC class Ⅰ molecules. In absence of peptides, MHC class Ⅰ molecule is stabilized by ER chaperones (calreticulin, PDIA3, PDI and tapasin), but when peptides with sufficient affinity bind to class Ⅰ molecules, these chaperones are released and the peptide: MHC complex leaves the ER for presentation on cell surface of $CD8^+$ T cells; (2) MHC class Ⅱ molecules present peptides derived from proteins that enter the cell through endocytosis. The chains α and β are assembled in the endoplasmatic reticulum associated with the invariant-chain (Ii) to prevent binding of endogenous proteins. This complex (MHC:Ii) is translocated to MHC class Ⅱ compartment (MIIC) where Ii is degraded to class Ⅱ-associated invariant chain (CLIP). In the MIIC the MHC class Ⅱ molecules acquire HLA-DM to facilitate the exchange of CLIP to specific antigen derived from degraded protein on the endosomal pathway, thus the complexes are transported to the plasma membrane to present the peptide to $CD4^+$ T cells; (3) Cross presentation involves dendritic cells with the unique ability to present exogenous antigens *via* MHC class Ⅰ (by a mechanism not completely understood). MHC: Major histocompatibility complex.

CD NOMENCLATURE

CD	Alternative Name	HLDA Section	Ligand/ receptor/ substrate/ associated molecule	Description and Function	MW (kDa)
CD1a	R4	T		Non-peptide antigen presenting molecules; involved in lymphocyte activation; related to thymic T-cell development.	49/-
CD1b	R1	T		Non-peptide antigen presenting molecules; involved in lymphocyte activation; related to thymic T-cell development.	45/-
CD1c	M241, R7	T		Non-peptide antigen presenting molecules; involved in lymphocyte activation; related	43/-
CD8p	Lyt3	T		Co-receptor molecule, binds to MHC class I.	
CD9	p24, DRAP-1, MRP-1	Platelet	CD63, CD81,CD82	Modulates cell adhesion and migration; triggers platelet activation; expressed on eosinophils and basophils.	-/24,26
CD10	CALLA, NEP, gp100	B		Zinc Metalloprotease; neutral endopeptidase; regulator of B-cell growth and proliferation by hydrolysis of peptides with proliferative/anti-proliferative effects.	100/-
CD11a	LFA-1a	Adhesion	ICAM-1,2,3	Intracellular adhesion and co-stimulation; binds to ICAM-1, ICAM-2, ICAM-3;	170/

CD3 = T cells

CD4 = T (helpers)*

CD8 = cytotoxic T*

CD19 = B cells

CD10 = inmature lymphoid cells *

CD34 = progenitors*

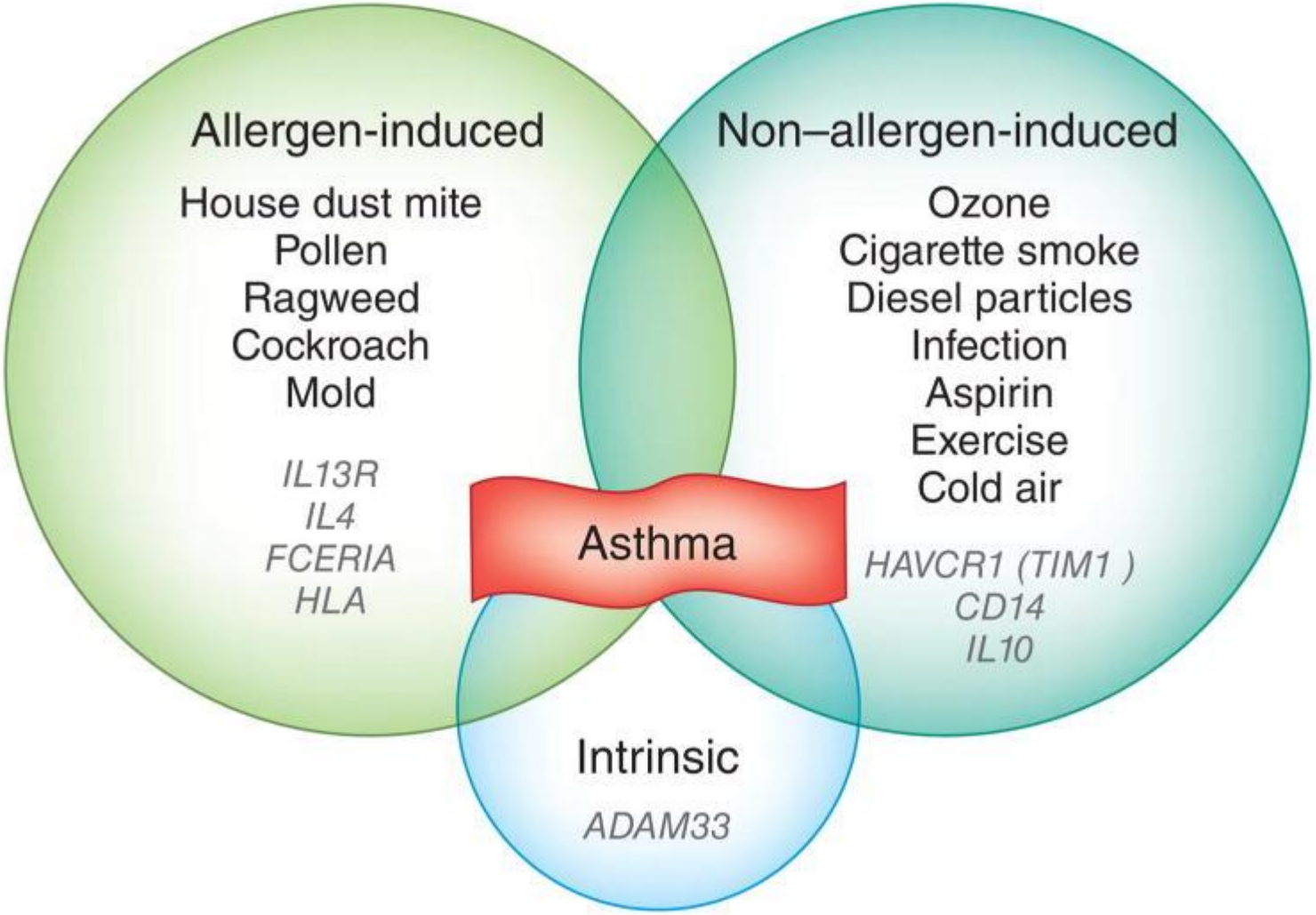
*and other cells

CD40/CD40L

ALLERGY AND ATOPY

Atopy:

- Family history
- Characteristic reaction on extrinsic allergens
- Circulating antibodies
- IgE antibodies (30-40% of population)
- Correlation between IgE blood levels and hyperreactivity of airways.
- Genetic and epigenetic factors which modify IgE levels.
- Candidate genes for IL-3, IL-4, IL-5, IL-9, IL-13 and GM-CSF –cluster on 5q31-33.
- Hygienic theory of asthma development

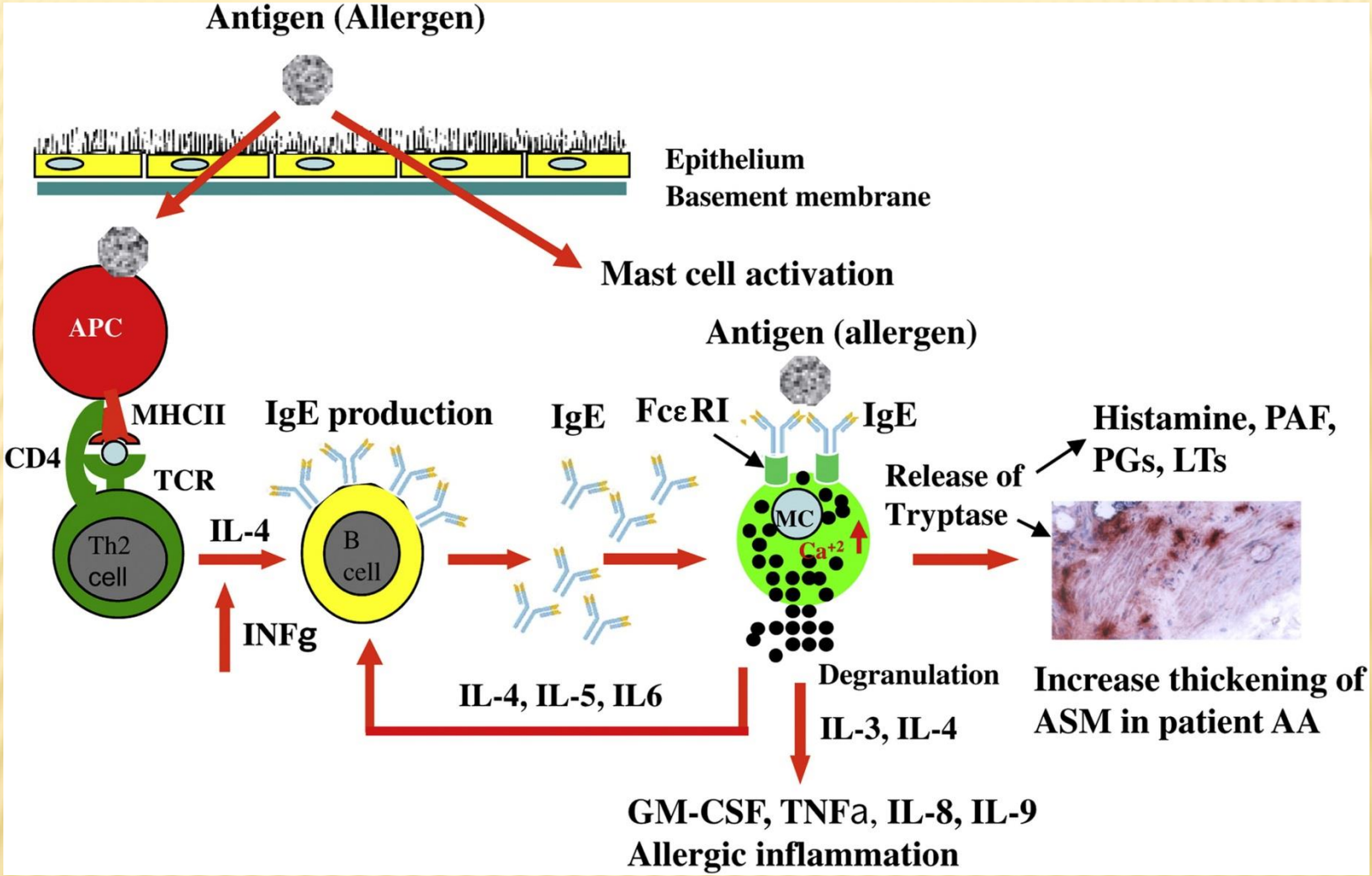


The heterogeneity of asthma. Asthma is a complex disease caused by multiple factors. There are several different forms of asthma (allergic, non-allergic and intrinsic), and in some patients these forms can coexist. Allergic asthma can be induced by allergens and is mediated by T_H2 immune responses. Non-allergic asthma can also be caused by several factors, such as air pollution and infection. Non-T_H2 cells and various cells of the immune system other than T_H2 cells contribute to non-allergic asthma. Some of the many genes involved in development of spontaneous asthma are presented here.

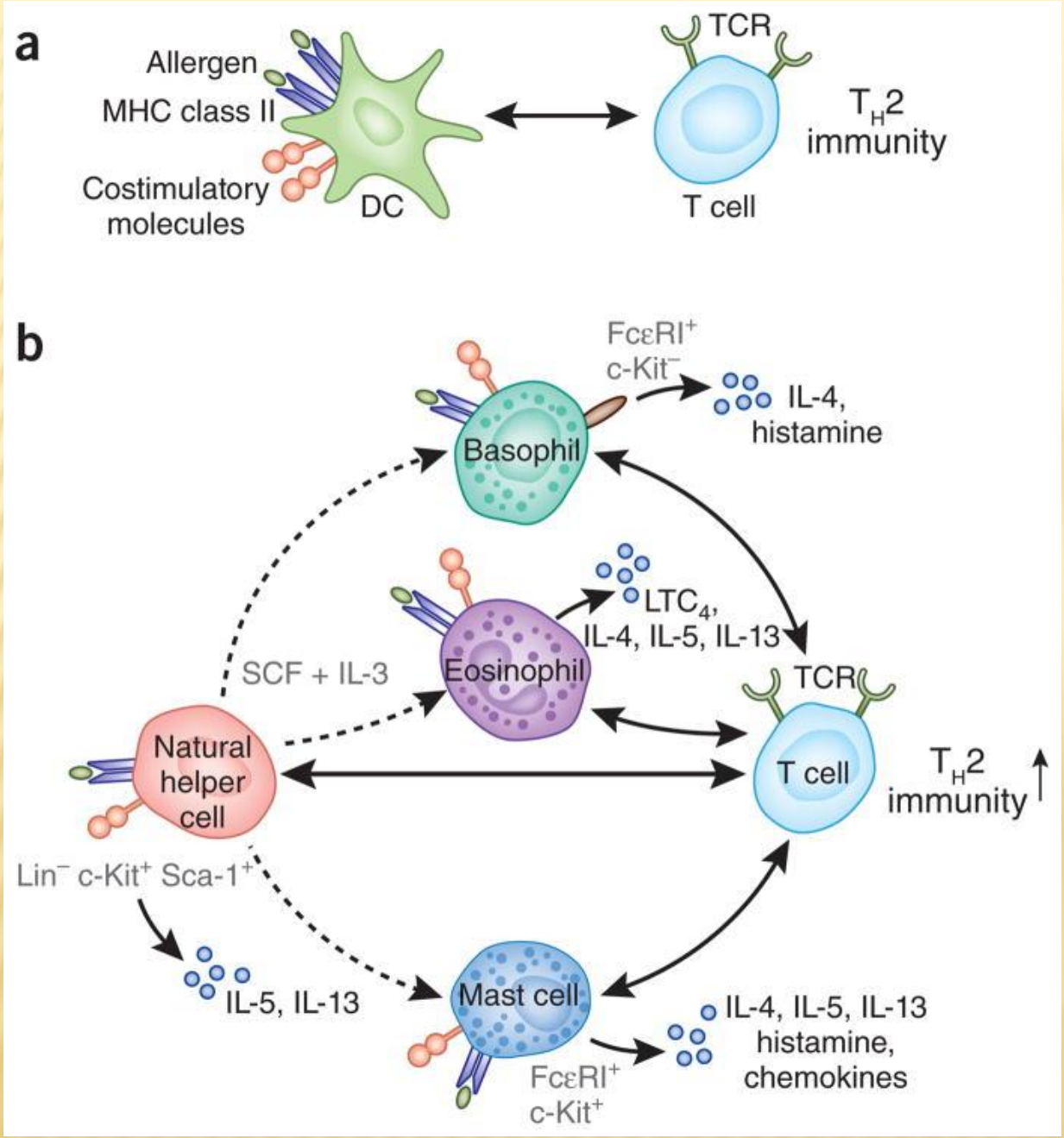
ASTHMA TYPES

- Extrinsic – clear external cause.
- Intrinsic – there is no clear cause.
- Extrinsic asthma in atopic patients with positive prick tests for inhalation antigens (90% of children with persistent asthma, only 50% adult patients). Child asthma often combined with atopic dermatitis
- Intrinsic asthma - delayed onset

Clinical asthma phenotype	Requirement for T_H2 cell	Mechanisms or effector cells
Allergen	Yes	IL-4, IL-5, IL-9, IL-13, TSLP, IL-25, IL-33, IL-17? $CD4^+$ cells, DCs, eosinophils, mast cells, basophils, NKT cells
Viral infection	No	IL-13? (T_H2 cytokines?) alveolar macrophages, NKT cells (innate immune cells)
Air pollution, cigarette smoke, diesel particles, smoke	No	IL-17, oxidative stress, small particles, neutrophils, NKT cells
Aspirin	No	Leukotrienes, loss of prostaglandin E_2
Obesity	No	Oxidative stress?
Severe, steroid resistant	No	IL-17, neutrophils, NKT cells?
Exercise, cold air	No	Heat transfer, change in mucosal osmolality, cytokines?
Intrinsic	?	Smooth muscle irritability?



Induction and effector mechanisms in type I hypersensitivity



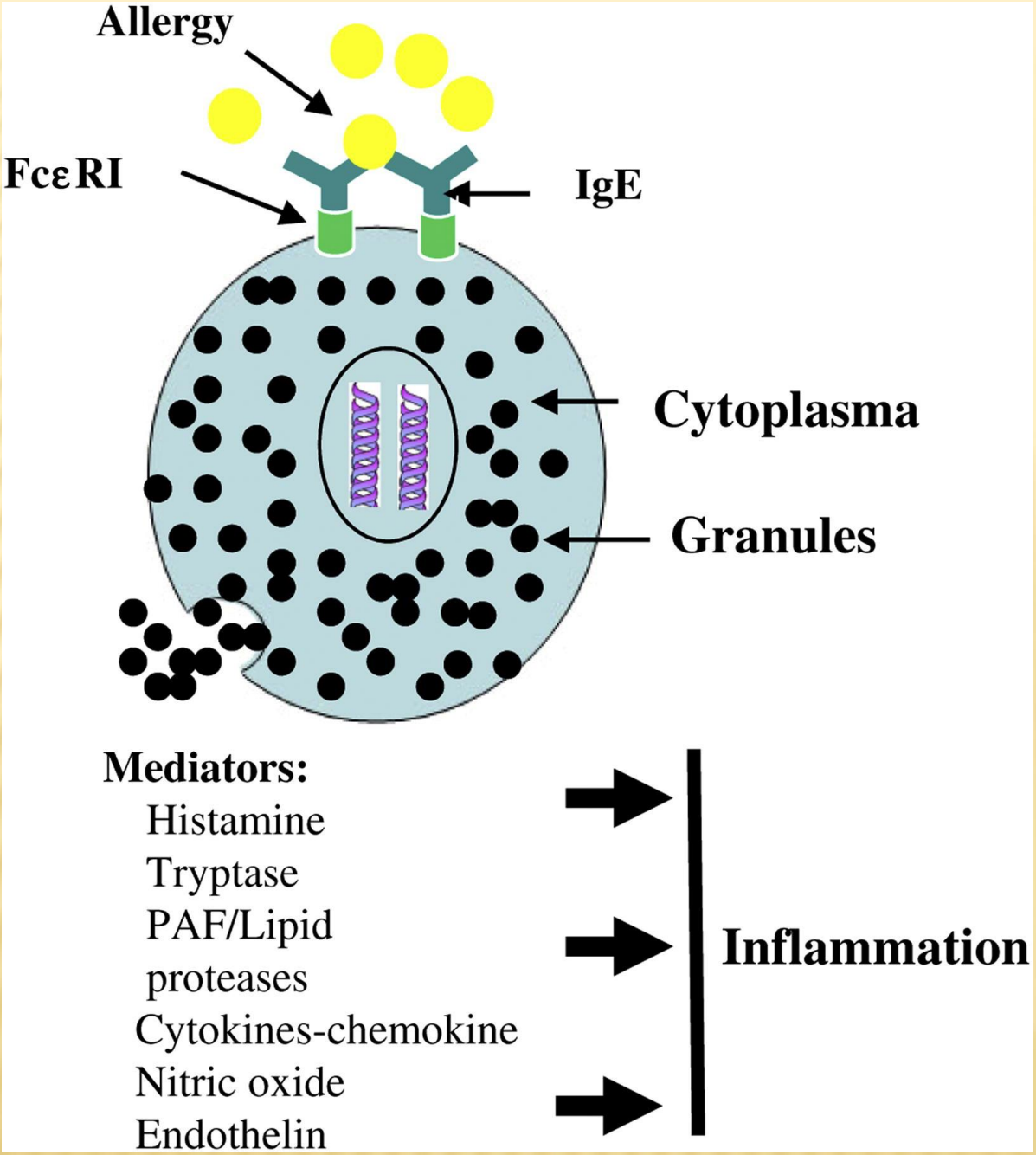
APCs in the lung.

(a) DCs are key APCs in the lung. After antigen challenge, lung DCs process antigen and induce antigen-specific T_H2 cell responses. TCr, T cell antigen receptor.

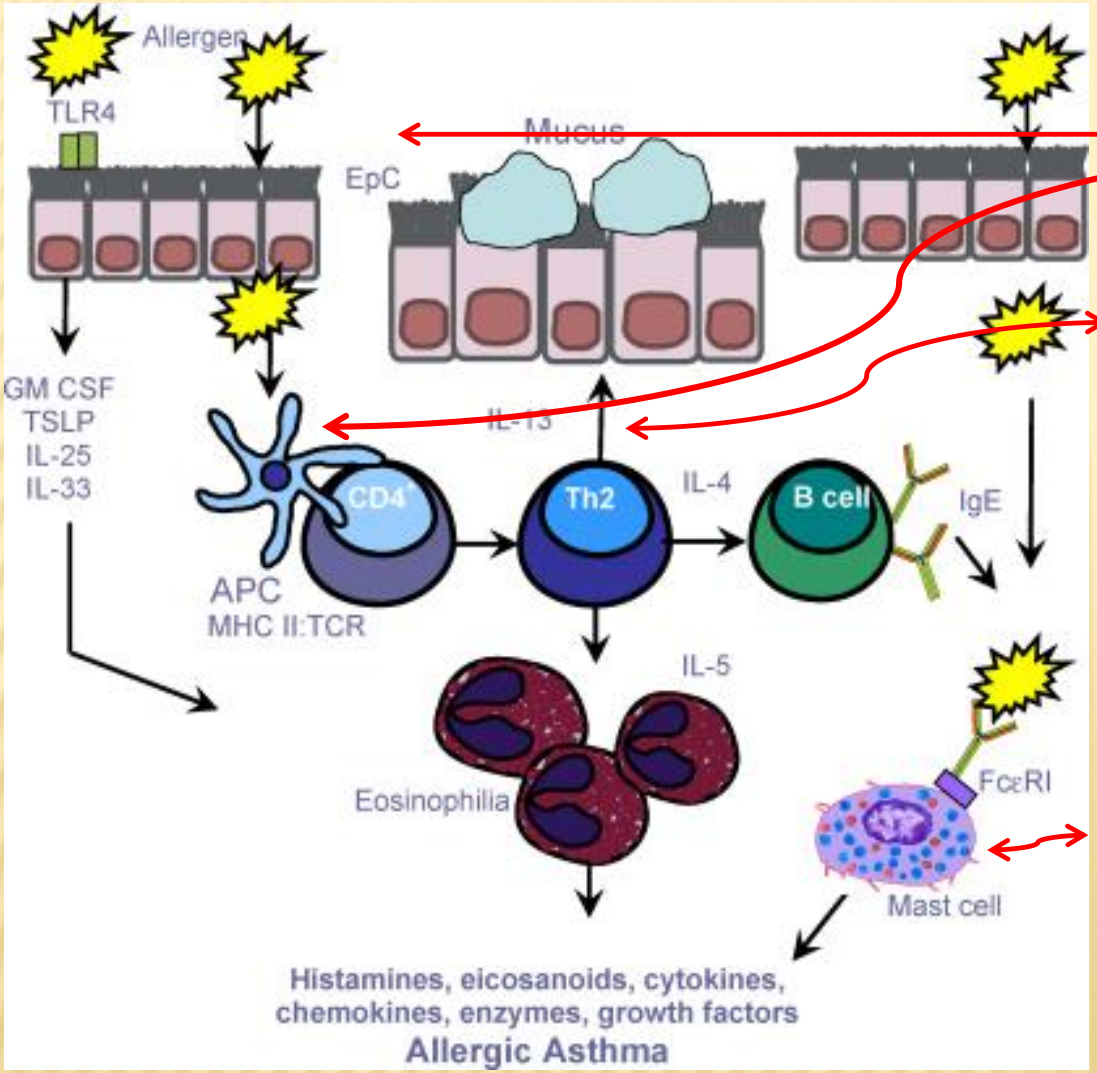
(b) (**b**) Other cells can also function as APCs to initiate T_H2 responses. Basophils, eosinophils, mast cells and natural helper cells express MHC class II and costimulatory molecules. Therefore, these cells of the innate immune system can be the initial sources of T_H2 cytokines as well as potential APCs in the lung. SCF, stem cell factor; LTC_4, leukotriene C_4; Lin, lineage.

ACQUIRED IMMUNITY IN PATHOGENESIS OF ASTHMA

- The induction of adaptive immunity requires antigen-presenting cells (APCs), and dendritic cells (DCs) are the main type of APC involved in the induction of T_H2 responses to allergens in asthma. In the lung,
- DCs can be found throughout the conducting airways, interstitium, vasculature and pleura and in bronchial lymph nodes. Lung DCs express many receptors, including Toll-like receptors, Nod-like receptors and C-type lectin receptors and upregulate the expression of several costimulatory molecules (such as CD80 and CD86) and chemokines (such as CCL17 and CCL22) that attract T cells, eosinophils and basophils into the lungs.
- In humans, monocyte-derived conventional DCs promote T_H2 responses by secreting proinflammatory cytokines and upregulating the expression of costimulatory molecules after antigen stimulation. Together these findings indicate that lung DCs are the main APCs and are necessary for T_H2 cell stimulation during airway inflammation.



The IgE-primed mast cell releases granules and powerful chemical mediators, such as histamine, cytokines, granulocyte macrophage colony-stimulating factor (GM-CSF), leukotrienes, heparin, and many proteases into the environment. These chemical mediators cause the characteristic symptoms of allergy.



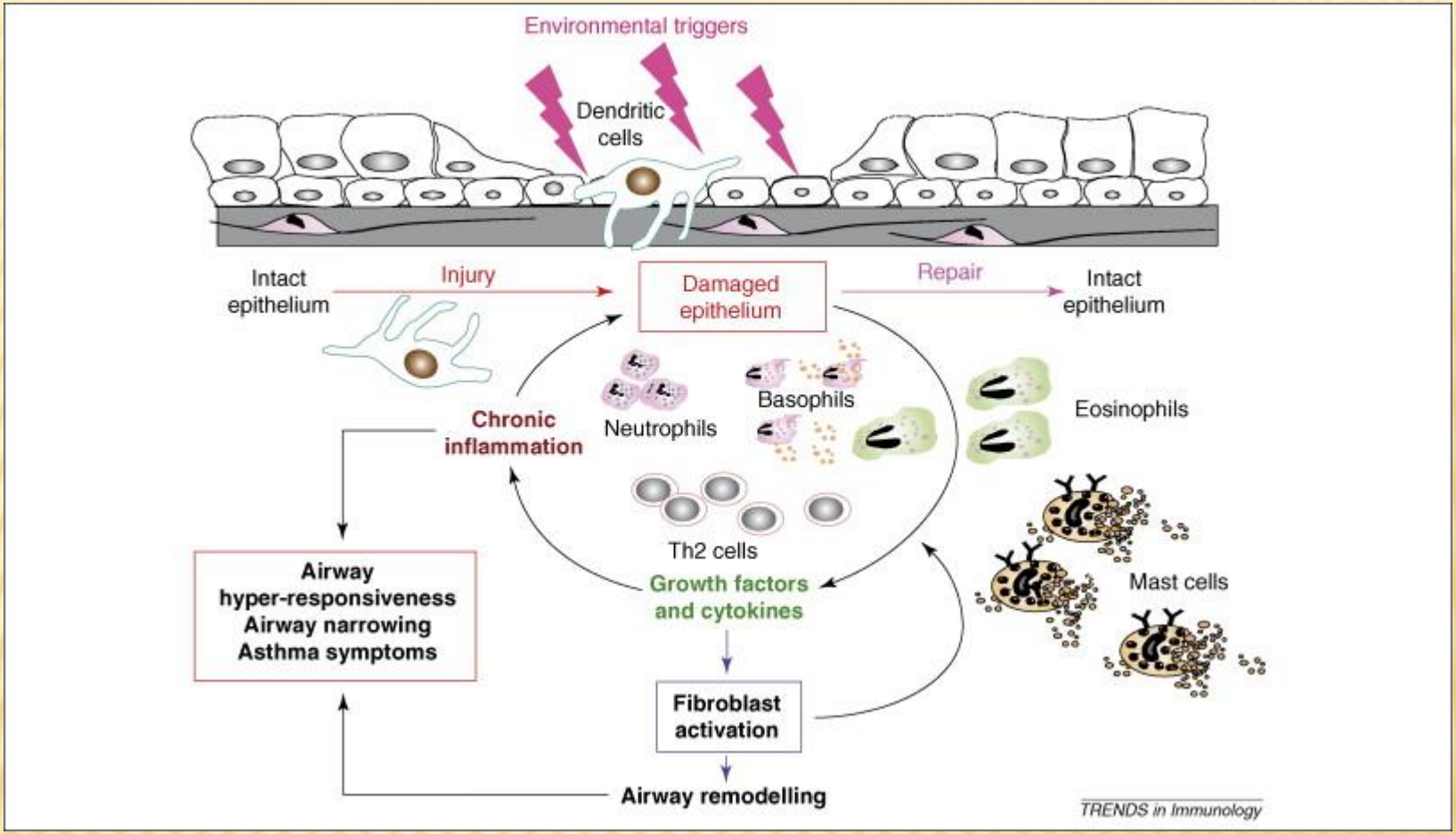
APC, antigen-presenting cell; EpC, epithelial cell; GM-CSF, granulocyte monocyte colony stimulating factor; MHC, major histocompatibility; TCR, T cell receptor; TSLP, thymic stromal lymphopoietin

Immune cells and the inflammatory cascade in asthma. Initial exposure(s) to allergen leads to the activation of allergen-specific Th2 cells and IgE synthesis (sensitization). Subsequent allergen exposures cause inflammatory-cell recruitment, activation and mediator release. IgE-sensitised mast cells expressing the high affinity IgE receptor (FcεRI) degranulate, releasing both pre-formed and newly synthesized mediators including histamine, leukotrienes and cytokines, which promote vascular permeability, smooth muscle contraction and mucus production. Chemokines released by inflammatory and resident cells direct recruitment of inflammatory cells characterized eosinophils and Th2 cells. Eosinophils release an array of pro-inflammatory mediators, including leukotrienes and basic proteins and mediators such as, IL-5.

Atopic bronchial asthma

Mutat Res. 2010 August 7; 690(1-2): 24–39.
doi: 10.1016/j.mrfmmm.2009.09.005

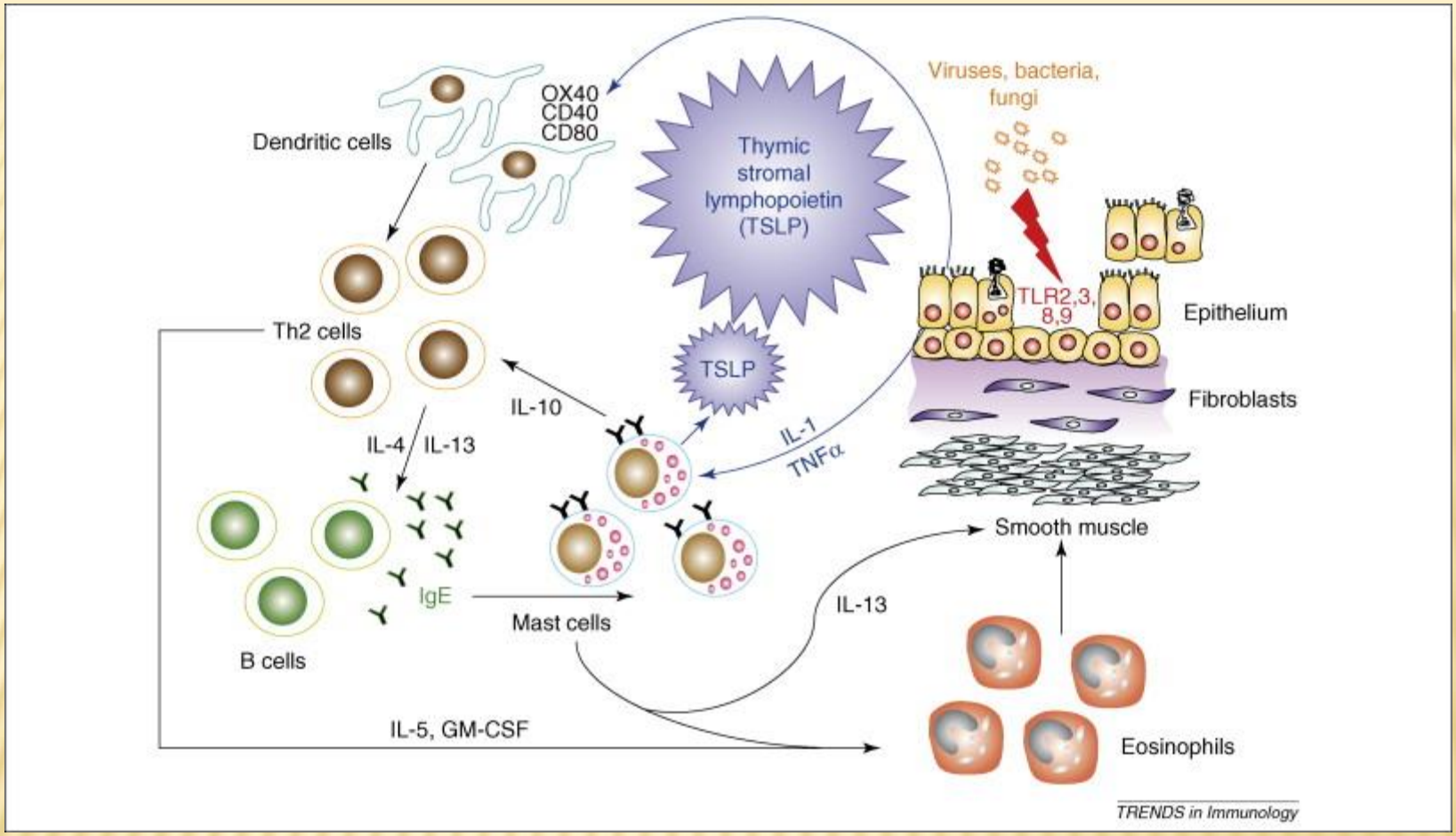
Trends Immunol. 2007 Jun;28(6):248-51. Epub 2007 Apr 27



Schematic representation of asthma pathophysiology. A range of environmental factors interact with the epithelium and dendritic cells to direct a Th2 inflammatory response, comprising mast cell activation, and eosinophil, basophil and neutrophil recruitment. Growth factors and cytokines from these cells also activate fibroblasts for new matrix deposition to remodel the airways and contribute to increased airway narrowing and asthma symptoms. Damage to the epithelium and the release of a range of cytokines and growth factors sustains the inflammation and drives remodelling of the airways in an aberrant 'wound response' to injury. Together, these two processes generate the hyper-responsive airway characteristic of asthma

CLINICAL SIGNS OF BRONCHIAL ASTHMA

- Bronchioles are narrowing (as a result of remodeling – higher content of smooth muscle cells).
- Atelectasis develops (microscopic, segmental or lobar) as a result of complete obstruction by mucus or by edema of airways.
- Decrease ventilation/ perfusion proportion with decreased hemoglobin saturation by oxygen.
- Hyperinflation and hyperexpansion of thorax decrease function and ability of breathing muscles.



TSLP provides a link between epithelial injury and the generation of an allergic-type inflammatory response. TSLP interacts with dendritic cells to upregulate the co-stimulatory molecules OX40, CD40 and CD80 that facilitate polarization of helper T lymphocytes to a Th2 phenotype. Th2 cells generate the allergic inflammatory response through induction of IgE, activation of mast cells and recruitment of eosinophils.

Trends Immunol. 2007 Jun;28(6):248-51. Epub 2007 Apr 27

TSLP (= THYMIC STROMAL LYMPHOPOIETIN)

- TSLP is expressed by structural and immune cells at the site of allergen entry in the airways.
- Stimuli for release of TSLP include common triggers of asthma symptoms.
- TSLP levels correlate with disease severity.
- TSLP regulates helper T cell 2 (Th2) humoral immunity through upregulating OX40L on dendritic cells (DCs), which drives Th2 lymphocytes; however, activation of several other cells by TSLP also supports the development of Th2 inflammation.

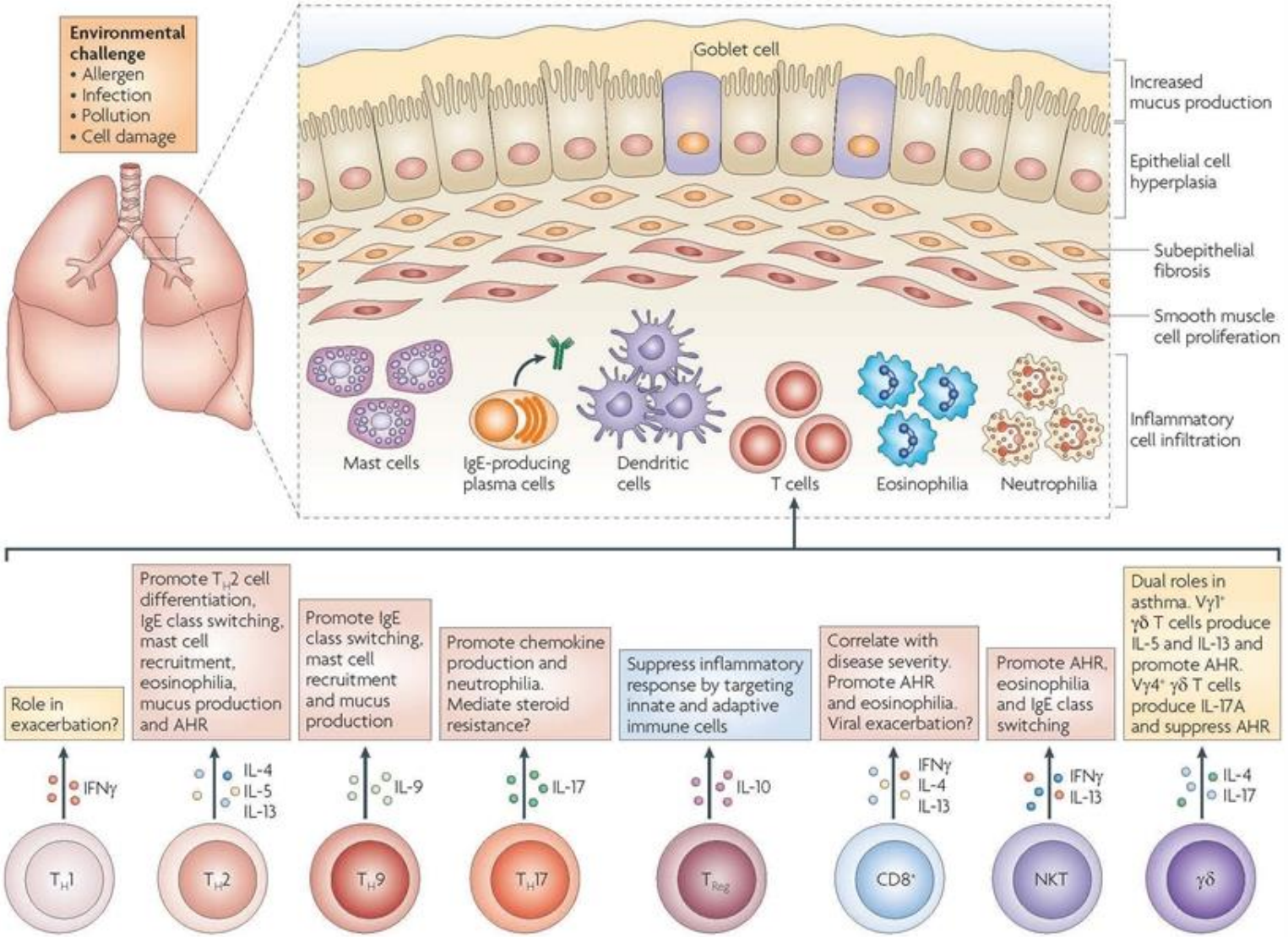
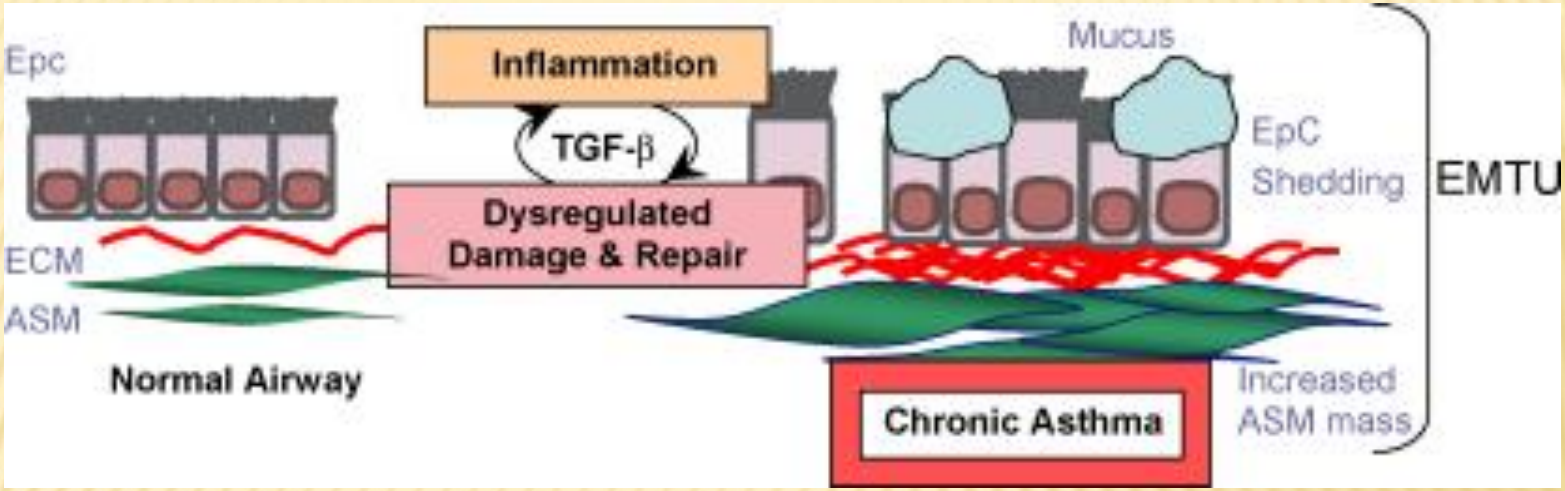
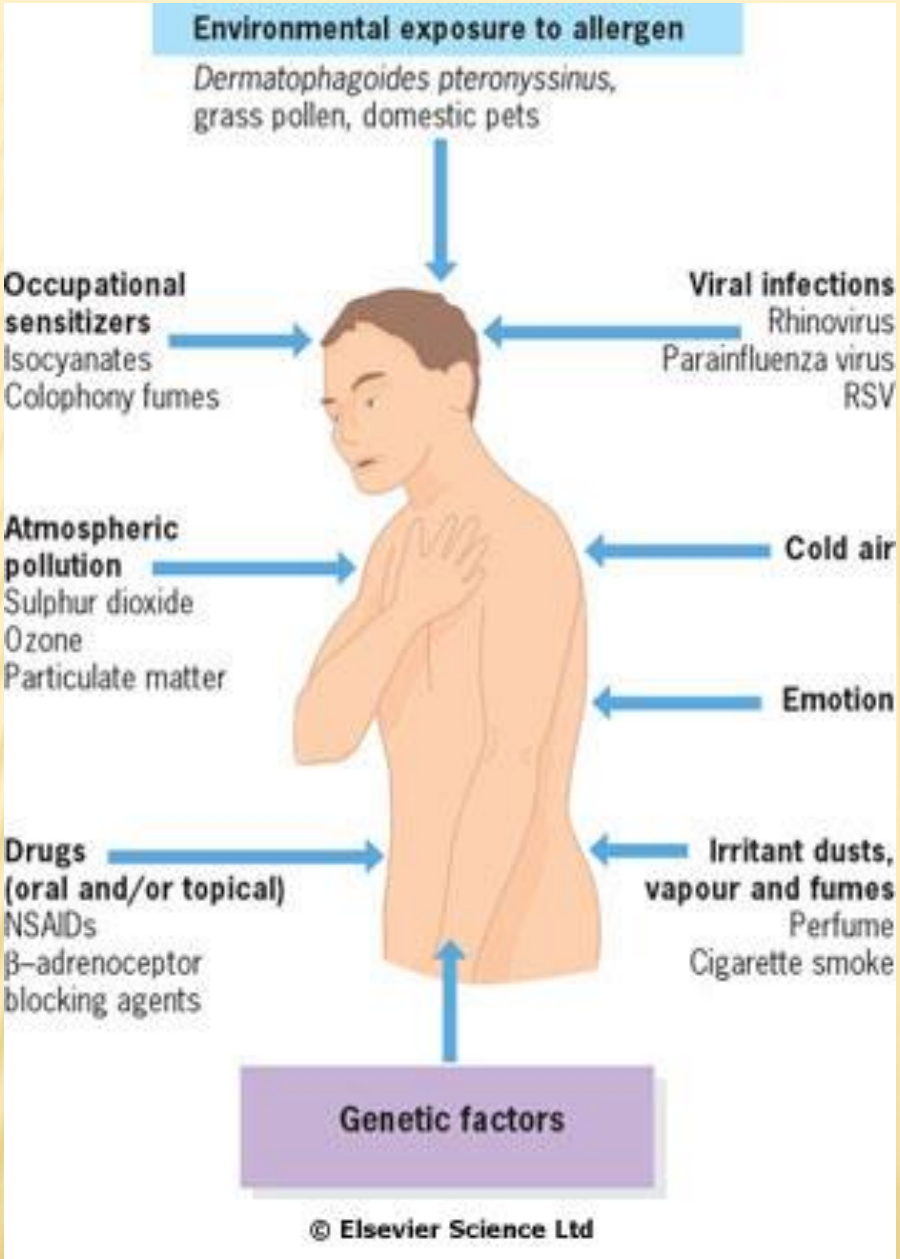


Figure 1 | **T cells involved in the induction of the allergic phenotype.** Asthma is a heterogeneous disease that is characterized by airway hyperresponsiveness (AHR), recruitment of inflammatory leukocytes to the lung and tissue remodelling, including mucus production and airway smooth muscle changes. A number of different T cell subsets are thought to influence the nature and magnitude of the allergic immune response by the cytokines that they secrete. T helper 2 (T_H2) cells are thought to promote eosinophil recruitment, in conjunction with nature killer T (NKT) cells and $CD8^+$ T cells. By contrast, T_H1 cells and T_H17 cells are thought to be associated with severe, steroid-resistant asthma, which is often marked by neutrophilic infiltrates. Regulatory T (T_{Reg}) cells and subtypes of γδ T cells are able to downregulate pulmonary immune responses and are thought to be important for maintenance of immune homeostasis in the lungs. The nature and magnitude of allergic inflammation in the lung is influenced by external environmental stimuli, such as exposure to allergens and pollution as well as infection with pathogens. IFNγ, interferon-γ; IL, interleukin.



Remodelling of airways in asthma
Key: ASM, airway smooth muscle; ECM, extracellular matrix; EMTU, epithelial to mesenchymal trophic unit; Epc, EpC, epithelial cell; TGF-β, transforming growth factor-β.

Mutat Res. 2010 August 7; 690(1-2): 24–39.
doi: 10.1016/j.mrfmmm.2009.09.005


Environmental exposure to allergen
Dermatophagoides pteronyssinus, grass pollen, domestic pets
Occupational sensitizers
Isocyanates
Colophony fumes
Viral infections
Rhinovirus
Parainfluenza virus
RSV
Atmospheric pollution
Sulphur dioxide
Ozone
Particulate matter
Cold air
Emotion
Drugs (oral and/or topical)
NSAIDs
β–adrenoceptor blocking agents
Irritant dusts, vapour and fumes
Perfume
Cigarette smoke
Genetic factors
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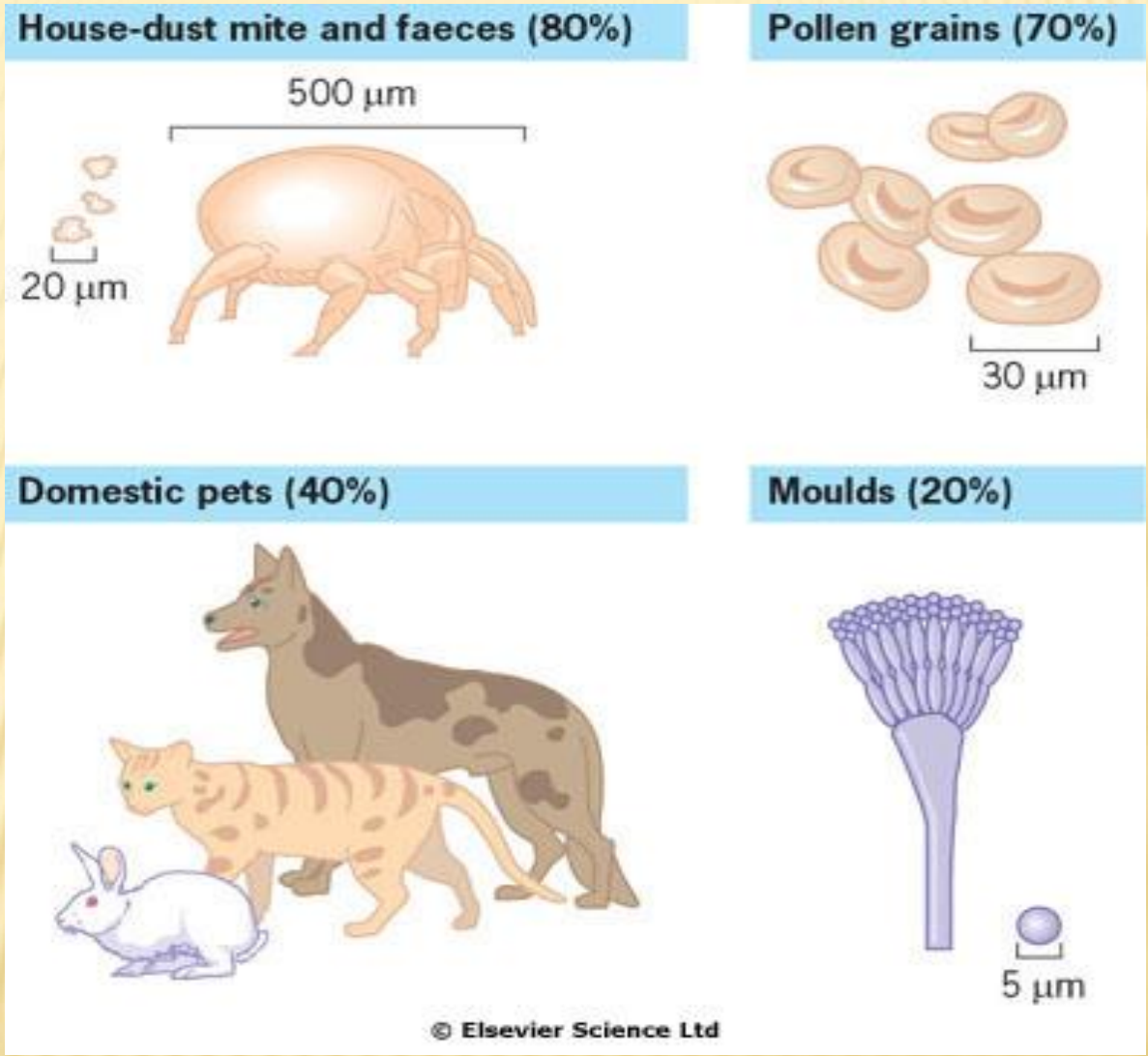
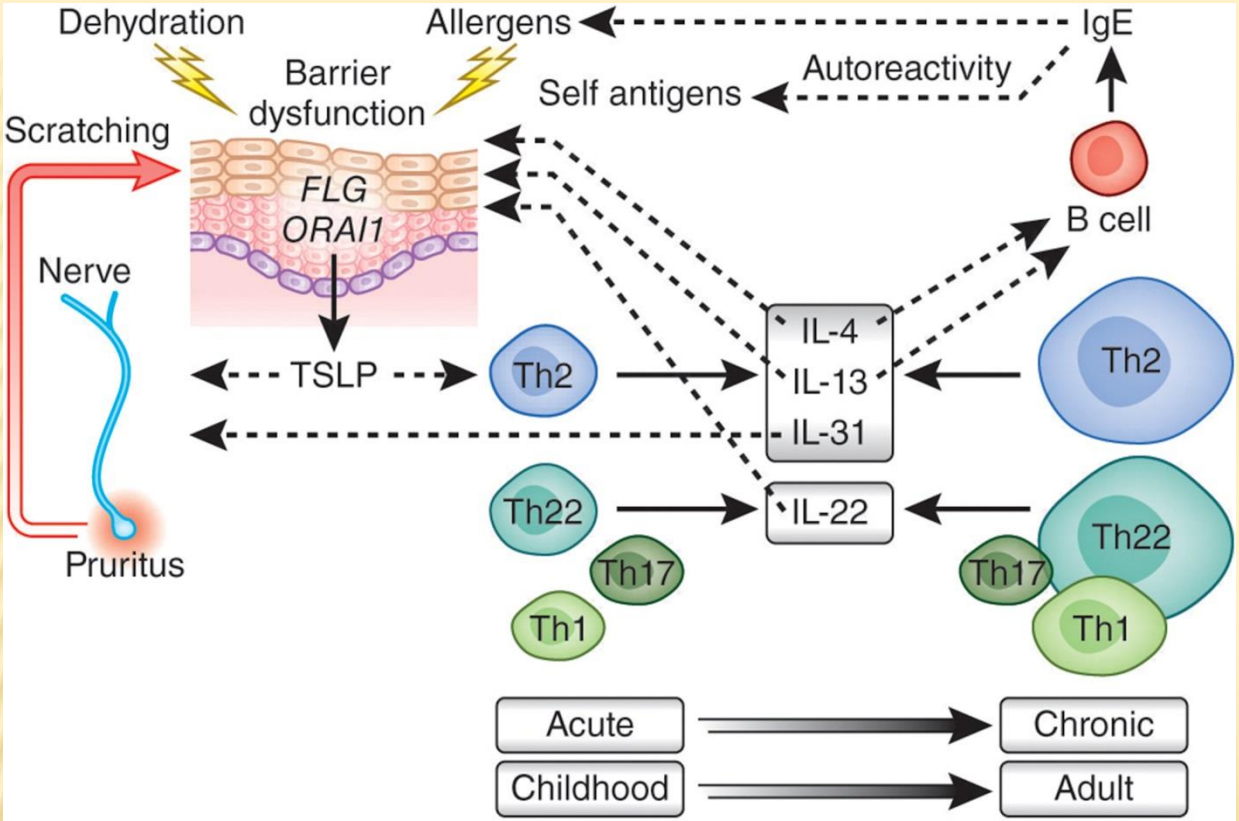


Antigens causing allergic rhinitis and bronchial asthma

ATOPIC DERMATITIS (AD)

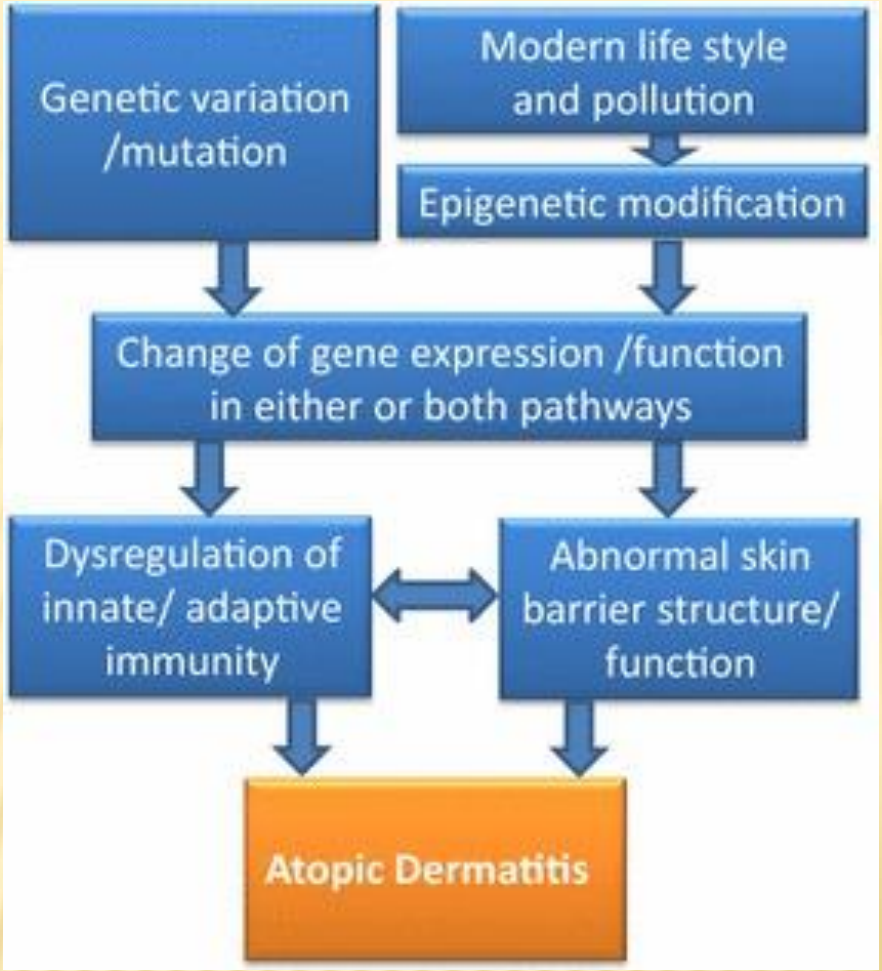
- is a chronic or chronically relapsing, eczematous, severely pruritic skin disorder mostly associated with IgE elevation and skin barrier dysfunction due to decreased filaggrin expression. The lesional skin of AD exhibits Th2- and Th22-deviated immune reactions that are progressive during disease chronicity. Th2 and Th22 cytokines further deteriorate the skin barrier by inhibiting filaggrin expression. Some IgEs are reactive to self-antigens. The IgE autoreactivity may precipitate the chronicity of AD. Upon activation of the ORAI1 calcium channel, atopic epidermis releases large amounts of thymic stromal lymphopoietin (TSLP), which initiates the Th2 and Th22 immune response. Th2-derived interleukin-31 and TSLP induce an itch sensation. Taken together, TSLP/Th2/Th22 pathway is a promising target for developing new therapeutics for AD. Enhancing filaggrin expression using ligands for the aryl hydrocarbon receptor may also be an adjunctive measure to restore the disrupted barrier function specifically for AD.



Pathogenesis of atopic dermatitis (AD)

Allergol Int. 2017 Jan 2.

Skin barrier dysfunction and Th2/Th22-deviated immune reactions are the fundamental abnormality in AD. Genetic mutations in filaggrin (*FLG*) cause barrier disruption and dehydration, which make the external allergens permeable. The barrier-disrupted epidermis abundantly releases thymic stromal lymphopoietin (TSLP), which triggers the Th2/Th22 immune response. The Th2/Th22 deviation is further accelerated during disease progression, for example, from acute to chronic or childhood to adult AD. In addition, Th1 but not Th17 cells tend to participate in the chronic phase of AD. Th2 cytokines (IL-4 and IL-13) stimulate B cells to produce IgE antibodies to allergens. Some IgEs react to self-antigens. IgE autoreactivity also contributes to disease activity. In addition, IL-4, IL-13 and IL-22 are strong suppressors of *FLG* expression. Pruritus is evoked by TSLP and Th2-derived IL-31, and the subsequent scratching further worsens skin barrier dysfunction. The release of TSLP from keratinocytes is dependent on calcium influx regulated by the ORAI1 channel. Targeting TSLP/Th2/Th22 as well as ORAI1 pathways is a promising strategy to overcome atopic inflammation.



Allergy Asthma Clin Immunol. 2016; 12: 52.

The schematic illustration of AD etiology. Genetic and epigenetic reasons lead to the alteration of gene expression and function of AD associated genes. AD associated genes majorly belong to two pathways: skin barrier and innate/adaptive immunity. Dysregulation of innate/adaptive immune responses and impaired skin barrier reciprocally affect each other to drive AD development.

AUTOIMMUNE DISEASES

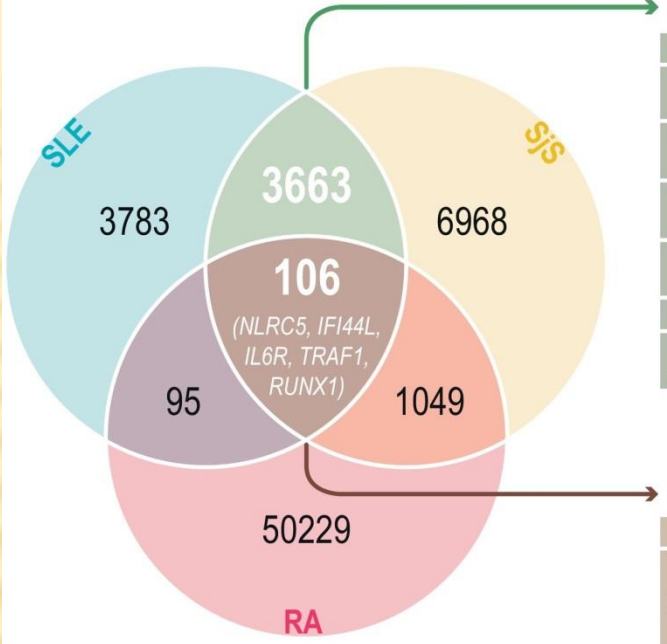
- Autoimmune disorders (AIDs), which as a group affect approximately 8.5% of individuals worldwide, are responsible for a substantial amount of disability and morbidity.
- Some AIDs are organ specific (for example, type 1 diabetes (T1D) targets the pancreas, autoimmune thyroid disease (AITD) attacks the thyroid gland), whereas others can affect multiple organs and/or be associated with systemic manifestations.
- Systemic lupus erythematosus (SLE) is the prototypic systemic AID that can affect multiple organs and can also be associated with significant systemic manifestations, morbidity and early mortality.

AUTOIMMUNE DISEASES

- Most AIDs, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD) and multiple sclerosis (MS) have a predilection for specific organs (for example, the synovial joints in RA and the gastrointestinal tract in IBD) but are also associated with manifestations outside the primary target organ. Reasons for the diverse manifestations exhibited by different AIDs remain unclear, but recent progress in elucidating genetic susceptibility loci for this group of disorders promises to shed light on this important issue.

AUTOIMMUNE DISEASES

- several features suggest that they share common etiologic factors.
- Most AIDs are characterized by female predominance, and
- many are associated with the production of autoantibodies (for example, anti-citrullinated-peptide antibodies are observed among 70 to 80% of RA patients).
- These shared disease features, in conjunction with epidemiologic evidence that demonstrates the clustering of multiple AIDs within individuals and families, strongly implicate shared etiologic factors, including shared genetic loci.



SjS-SLE shared DMCs

Reactome pathway	q-value	Genes
Innate Immune System	$3x10^{-10}$	*PIK3AP1,MANBA,ACPP,TMEM173,MEFV,ADCY9,AGL,MAP3K11,ALDH3B1,ALOX5,RASAL1,MPO,CUL3,CUL1, ADCY4,AMPD3,ANXA2,ATP6V1E2,BIRC2,BIRC3,etc*
Neutrophil degranulation	$1x10^{-8}$	*MANBA,ACPP,TMEM173,AGL,ALDH3B1,ALOX5,MPO,AMPD3,ANXA2,ARG1,PYCARD,AZU1,CEACAM6,UNC13D, BST2,OLR1,P2RX1,MS4A3,CD44,CD59,etc*
Cytokine Signaling in Immune system	$2x10^{-6}$	*MCL1,MAP3K3,MAP3K11,ALOX5,RASAL1,CUL3,CUL1,ANXA1,IFITM1,BIRC2,BIRC3,FASLG,SOCS1,EIF4G3,MX1, TNFRSF25,TNFSF13,BCL2,NEDD4,SOCS2,etc*
Hemostasis	$2x10^{-6}$	*ACTN4,ACTN1,ANXA2,DGKZ,APP,ATP2A2,MYB,CEACAM6,TNFRSF10D,NFE2,CAV1,SLC7A7,SLC7A6,OLR1,P2RX1, CD9,SLC16A3,SERPINB2,CD44,TREM1,etc*
Nephrin interactions	$8x10^{-3}$	*ACTN4,ACTN1,NCK2,NCK1,WASL,PIK3R1,PIK3R2,MAGI2,KIRREL1,FYN,SPTBN1*
Interferon alpha/beta signaling	$8x10^{-3}$	*IFITM1,SOCS1,MX1,BST2,OAS1,OAS2,OAS3,SAMHD1,RSAD2,ISG15,PSMB8,IFITM3,GBP2,USP18,HLA-A, HLA-E,IFI27,IFIT1,IRF1,IRF5,IRF7*

cross-SADs shared DMCs

Reactome pathway	q-value	Genes
TCR signaling, Second messenger molecules, Translocation of ZAP-70 to Immunological synapse PD1-signaling; CD3 and TCR phosporylation	$<1x10^{-4}$	*CD3G,CD247,LCK,PSMA4*
Signaling by Interleukins	$6x10^{-4}$	*IL12RB2,PSMA4,SMARCA4,LCK,S1PR1,IL6R,PTK2,STAT5B,SYNGAP1*
DCC mediated attractive signaling	$2x10^{-3}$	*ABLIM1,PTK2*

Degree of epigenetic sharing across systemic autoimmune diseases.
Venn diagram showing the number of differentially methylated CpG sites in whole blood comparing those obtained from EWAS results for SLE (blue), SjS (yellow) and RA (red). Data was obtained from supplementary materials of Yeung et al., Imgerberg-Kreuz et al. and Liu et al. Reactome pathway enrichment analyses were performed in the set of genes showing overlapped DMCs using the ToppGene Suite database https://toppgene.cchmc.org. q-value refers to adjusted *P*-values corrected for Benjamini & Hochberg False Discovery Rate. DMCs: Differentially methylated CpG sites. SAD: Systemic autoimmune diseases

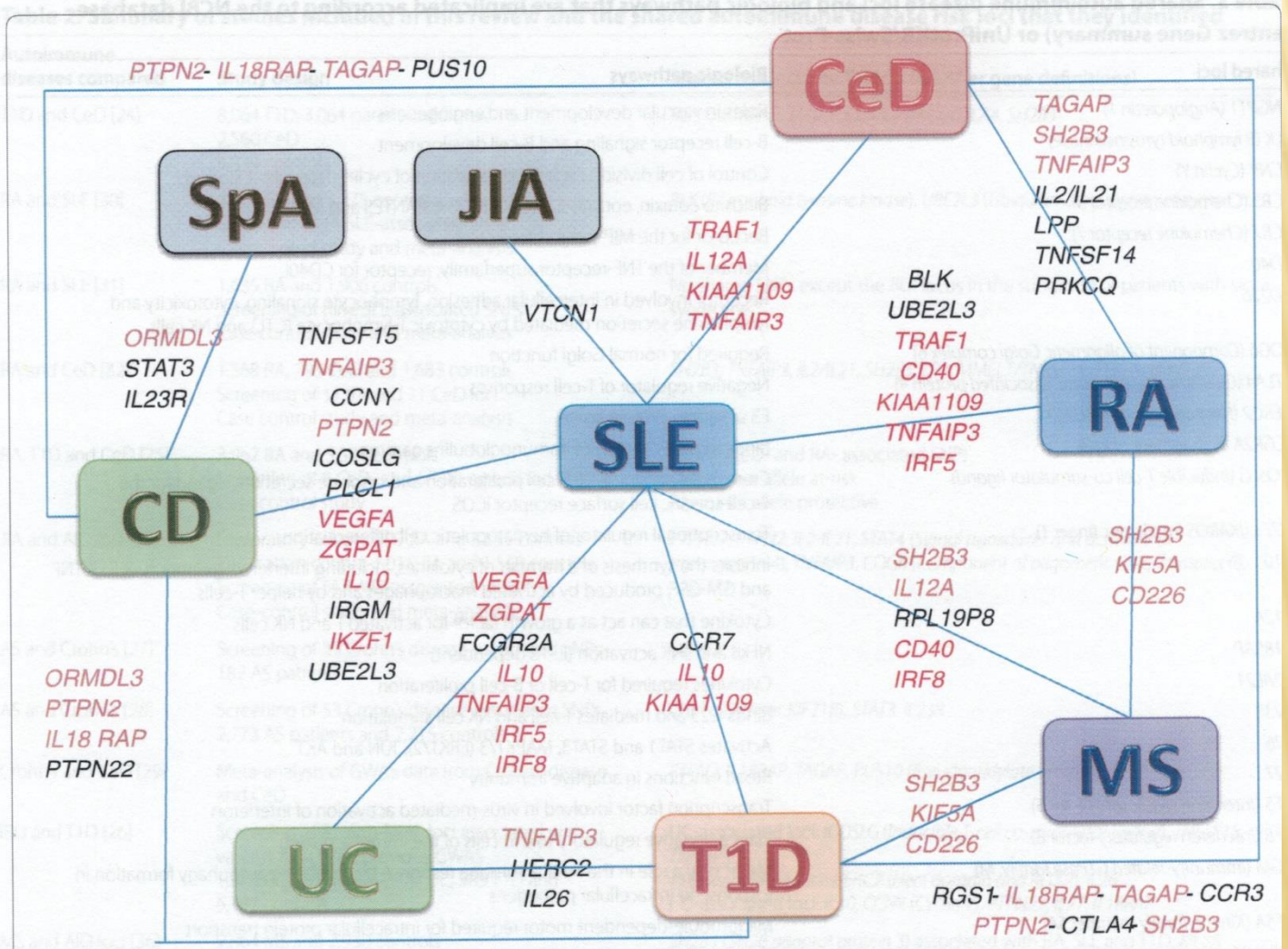


Figure 1. Overlap of associated loci among autoimmune diseases highlighted in this review. Loci depicted in red are those shared by more than two autoimmune diseases. Loci depicted in black are those shared only by two autoimmune diseases. CD, Crohn's disease; CeD, celiac disease; JIA, juvenile idiopathic arthritis; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthropathy; T1D, type 1 diabetes; UC, ulcerative colitis.

Děkuji vám za pozornost