L'Immunologia nello Sviluppo della Specie Umana: Perché le Patologie Autoimmuni?

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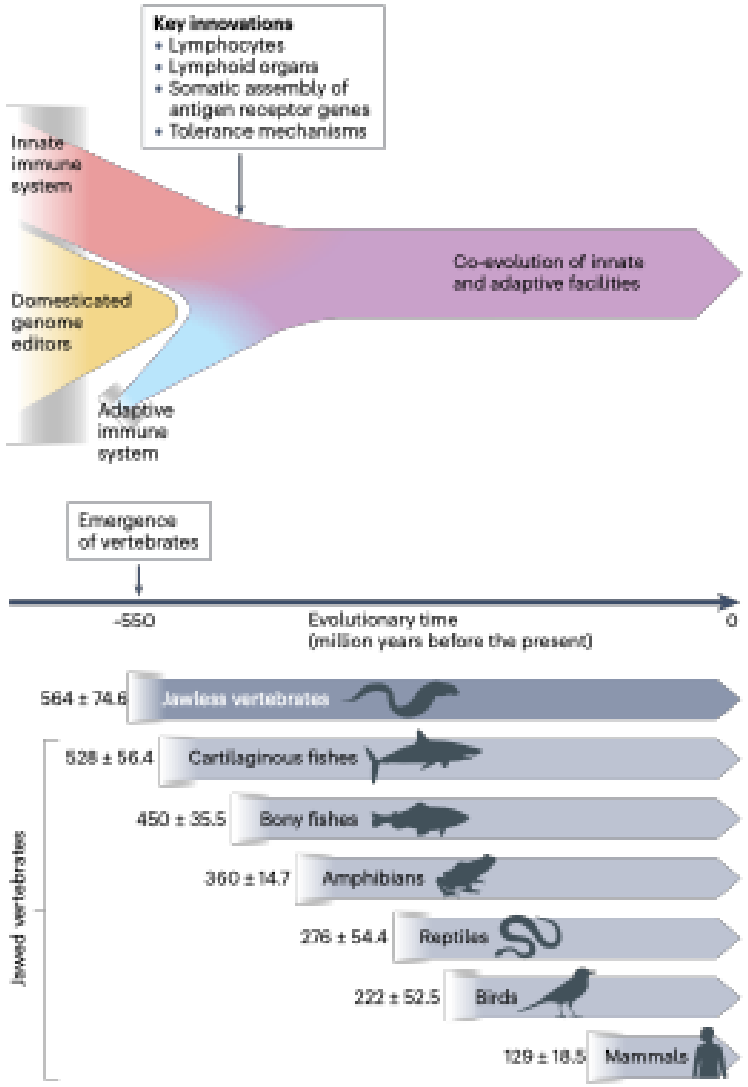
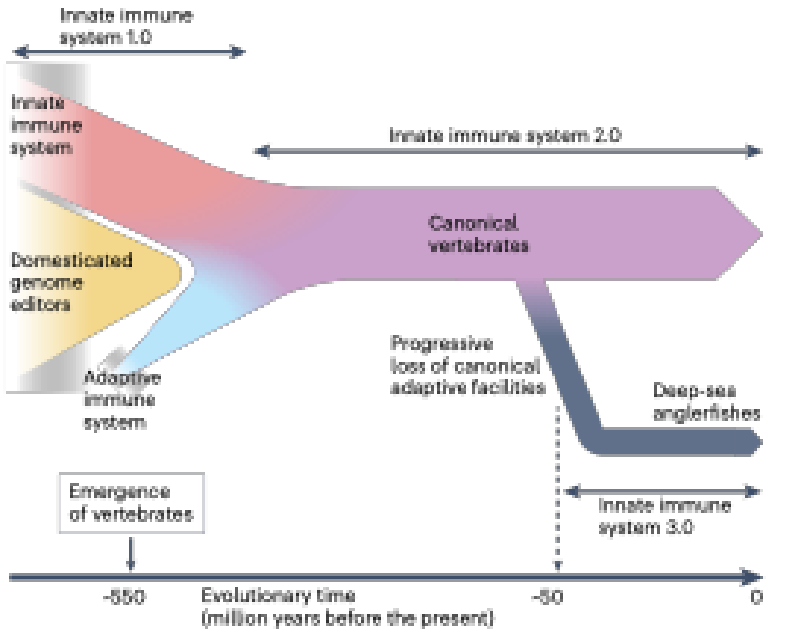
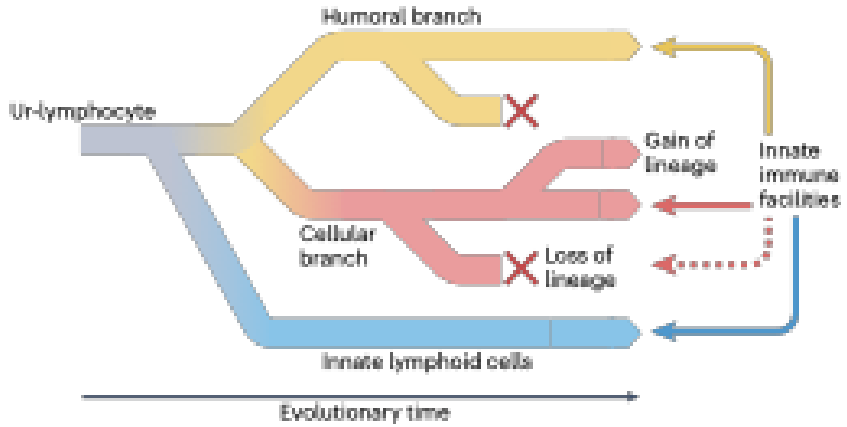
- No Disclosure

Evoluzione del Sistema Immunitario







T Boehm, Nat. Rev. Immunol. 2025; 25:141-152

1882

Elie Metchnikoff

While studying starfish larvae, Metchnikoff saw wandering cells engulfing foreign material and named them phagocytes. He demonstrated that these cells were a crucial part of the immune system, protecting against infection and aiding in tissue repair.

1890

Emil von Behring and Shibasaburo Kitasato

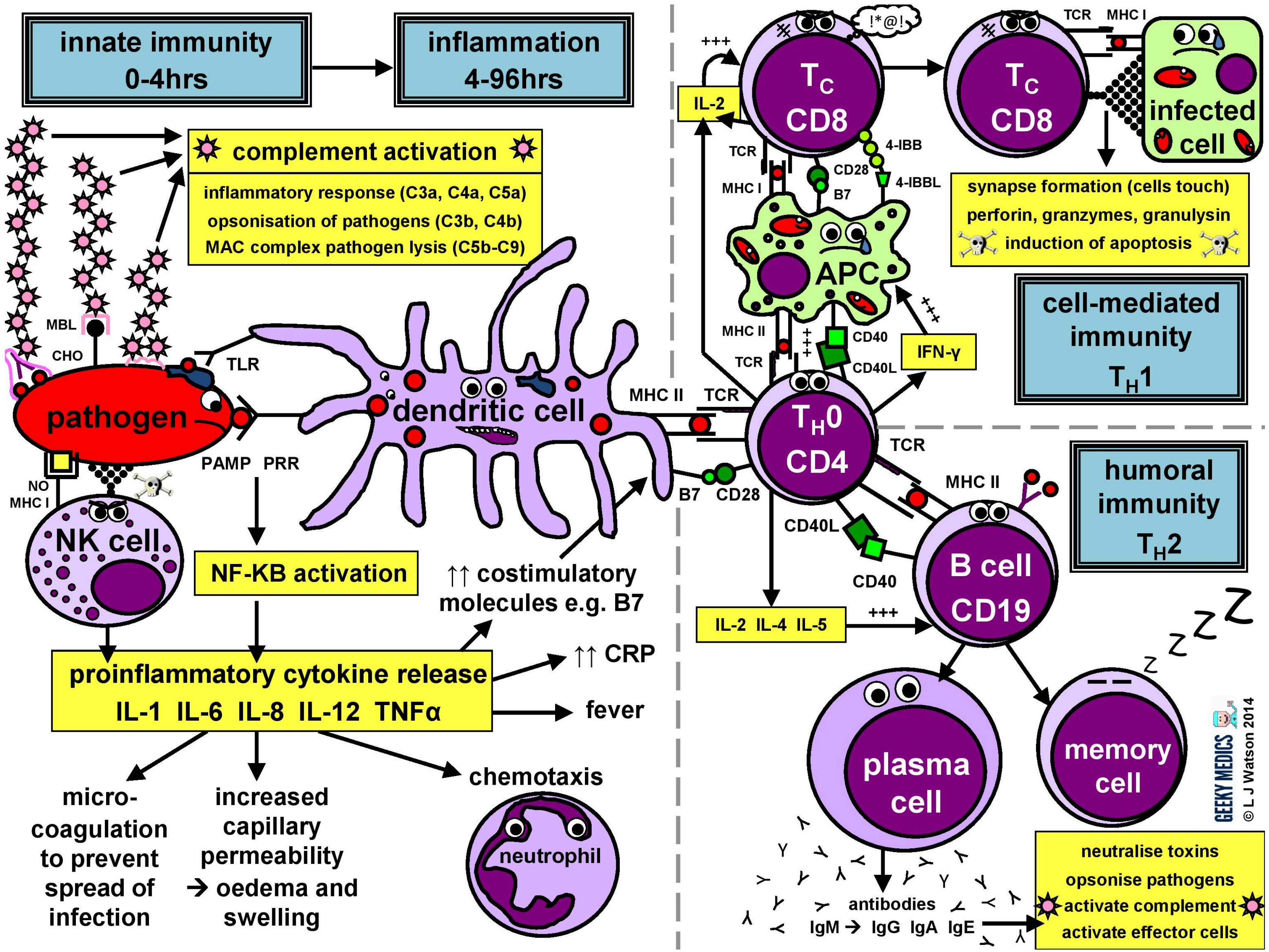
By transferring serum from animals immunized against diphtheria to sick animals, they were able to cure the disease.

Dagli inizi alla fine degli anni '60

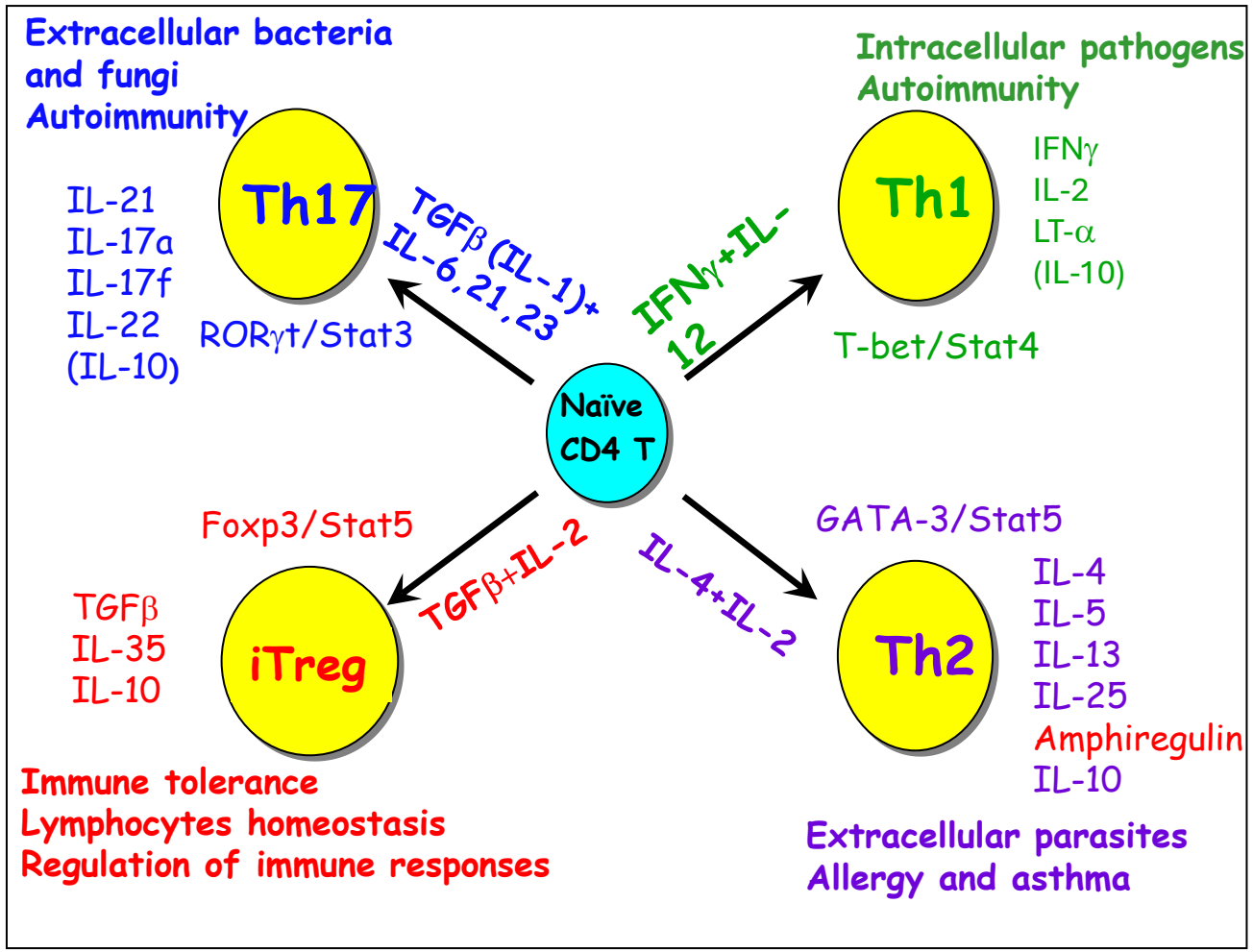
Jacques Miller; Max Cooper; Robert Good

T and B cells, T-B cooperation; PID

1985-2005


innate immunity 0-4hrs
inflammation 4-96hrs
complement activation
inflammatory response (C3a, C4a, C5a)
opsonisation of pathogens (C3b, C4b)
MAC complex pathogen lysis (C5b-C9)
MBL
CHO
TLR
pathogen
dendritic cell
PAMP PRR
NO MHC I
NK cell
NF-KB activation
↑↑ costimulatory molecules e.g. B7
proinflammatory cytokine release
IL-1 IL-6 IL-8 IL-12 TNFα
↑↑ CRP
fever
micro-coagulation to prevent spread of infection
increased capillary permeability → oedema and swelling
chemotaxis
neutrophil
!*@!
+++
IL-2
TC CD8
TCR
MHC I
4-IBB
CD28
4-IBBL
B7
APC
infected cell
synapse formation (cells touch)
perforin, granzymes, granulysin
induction of apoptosis
cell-mediated immunity TH1
MHC II
CD40
TCR
CD40L
IFN-γ
MHC II TCR
TH0 CD4
B7 CD28
TCR
MHC II
CD40L
CD40
humoral immunity TH2
B cell CD19
IL-2 IL-4 IL-5
+++
plasma cell
memory cell
antibodies
IgM → IgG IgA IgE
neutralise toxins
opsonise pathogens
activate complement
activate effector cells
GEEKY MEDICS
© L J Watson 2014

Fates and Functions of CD4 Th Cells



Courtesy of
Dr.WE Paul

Cytokine
Biology
Unit,
LI, NIAID

Era of Fixed Th subset disease

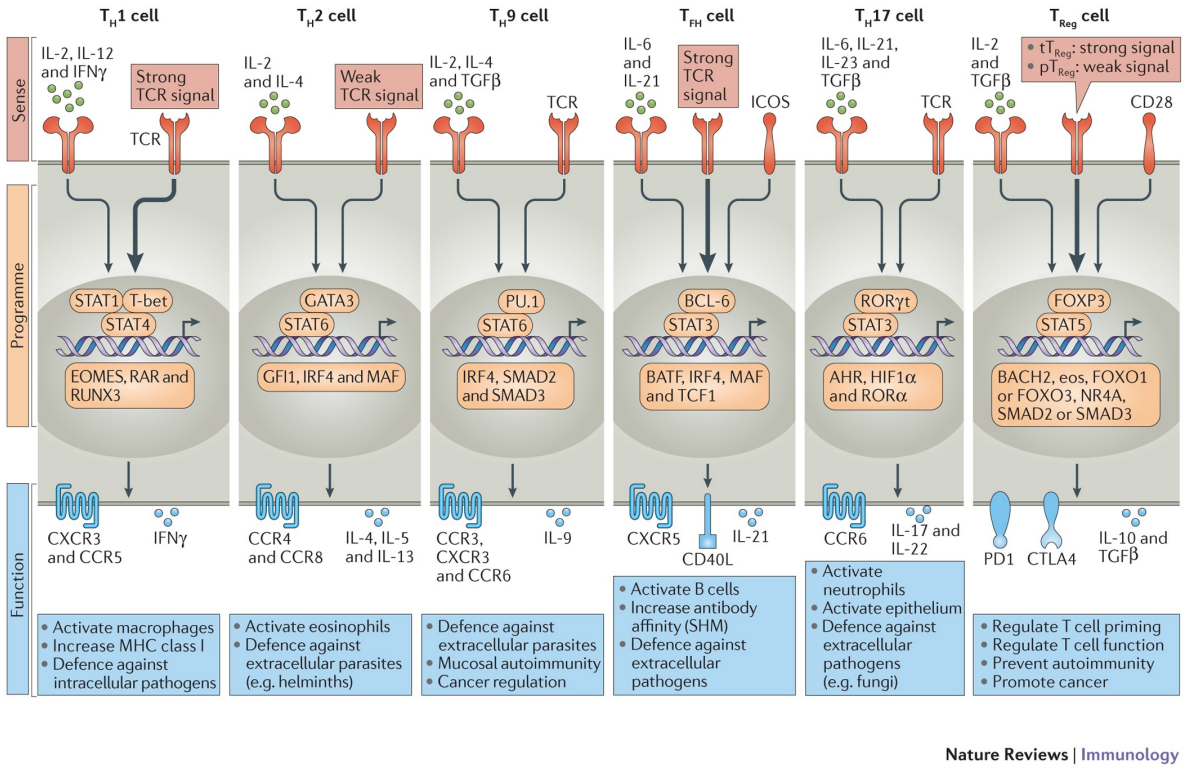
Th1 Diseases

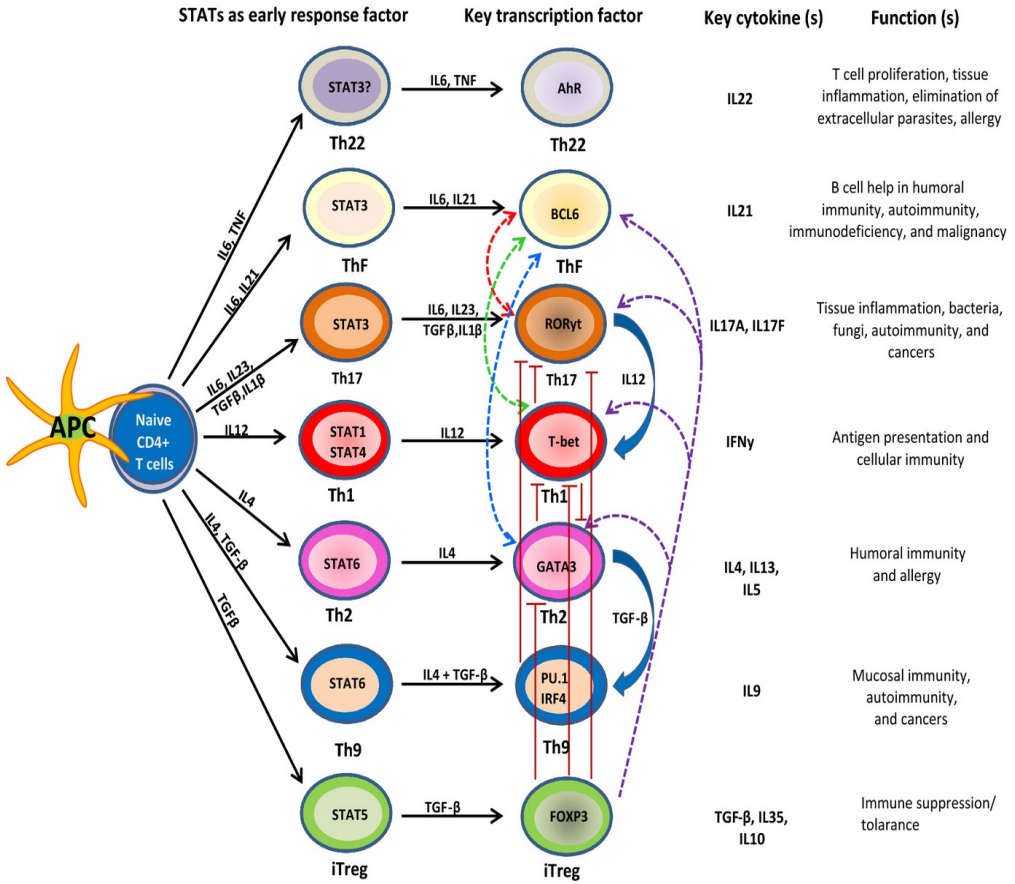
Th2 Diseases

Th17 Diseases

Th22 Diseases

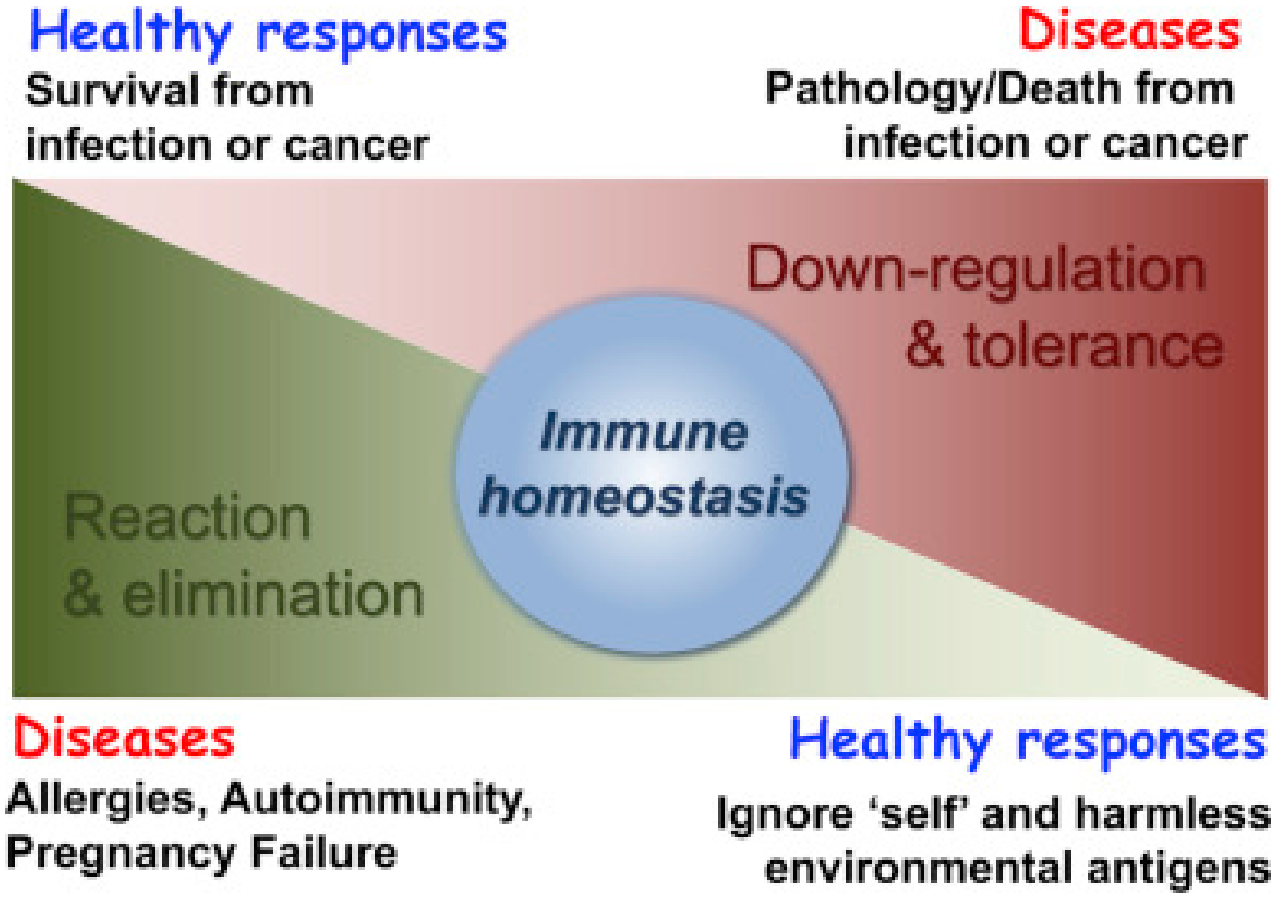
Nel «Real World» i linfociti T sono estremamente «plastici»





Courtesy of William Paul

Funzioni del Sistema Immunitario



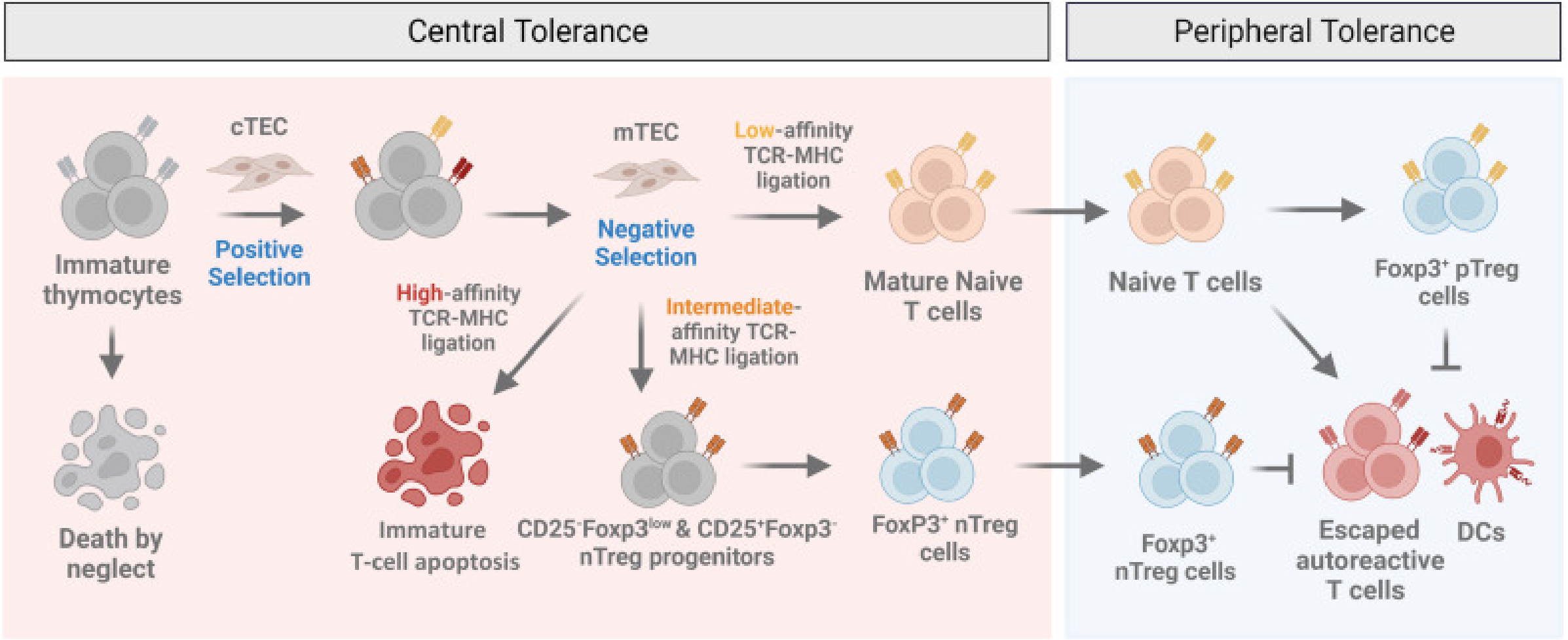
Courtesy of Abul Abbas

»To serve and Protect«

Imparare quando «attaccare», come, chi-riconoscendo i discriminando «i pericoli», per quanto tempo rispondere, quando fermarsi, come farlo nei differenti tessuti

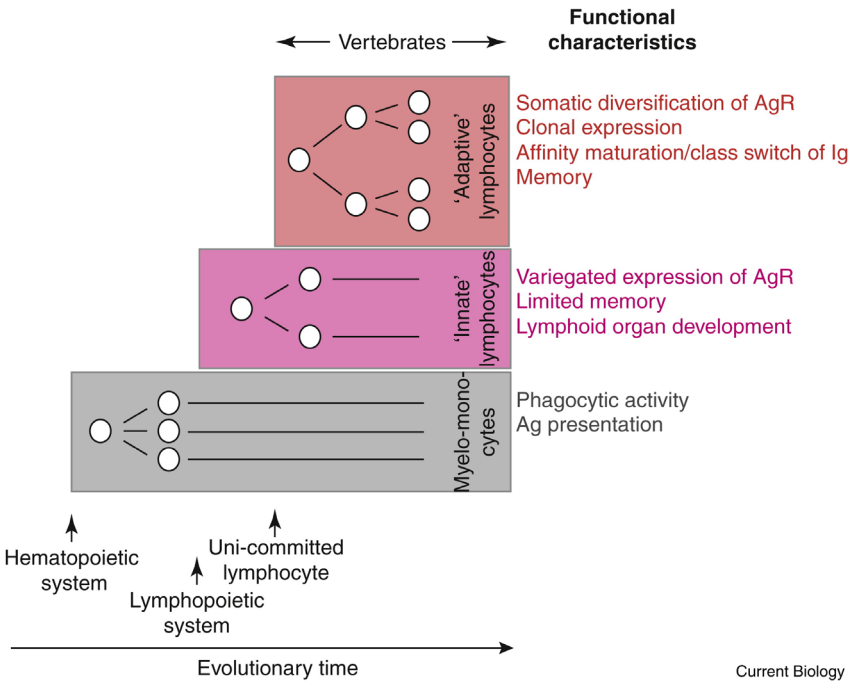
Le risposte immunitarie avvengono con modalità differenti in tessuti differenti.

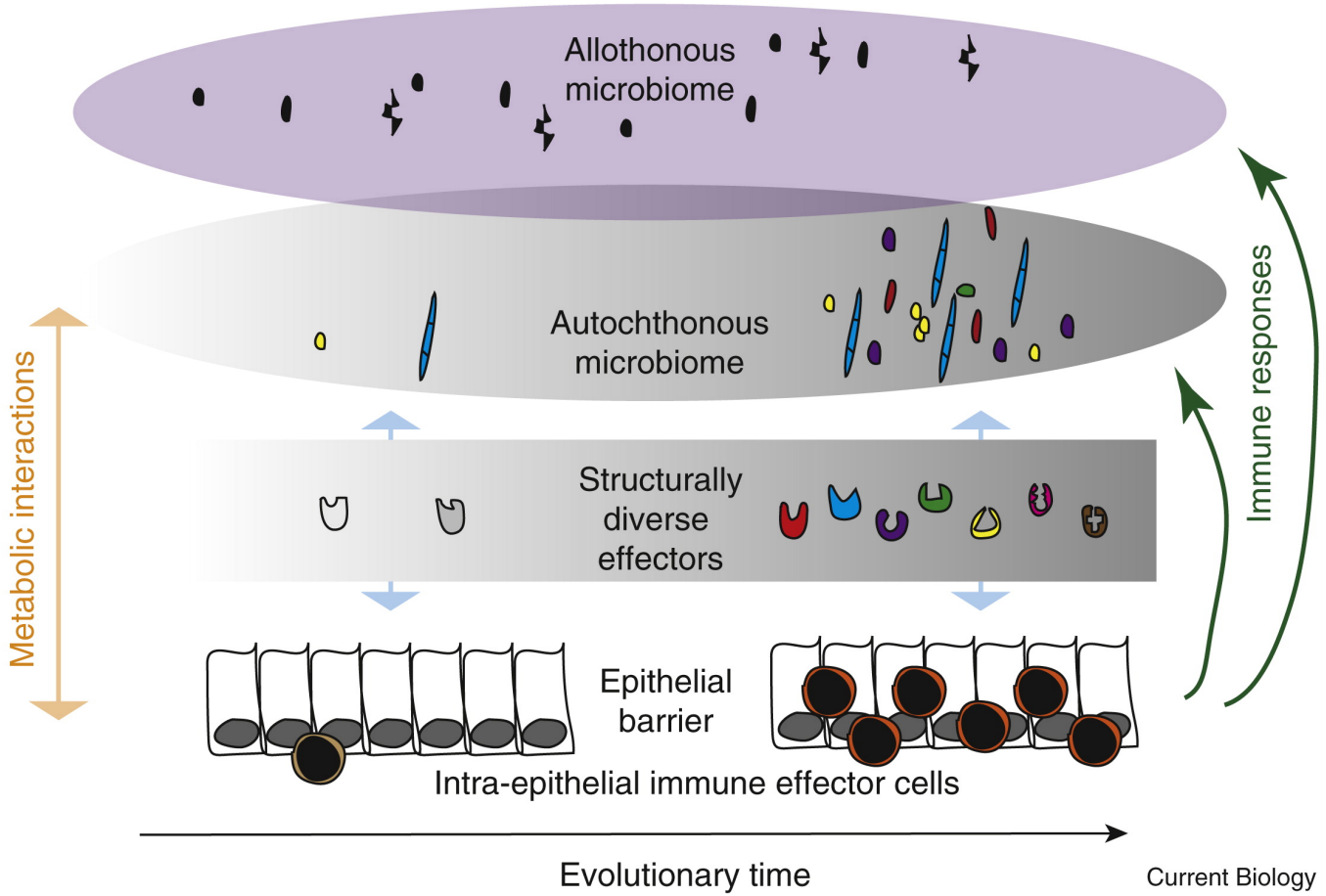
Come si Stabilisce la Tolleranza-Cellule T



I geni che codificano per il TCR non riarrangiano più nei linfociti T quando queste escono dal timo per andare in periferia.

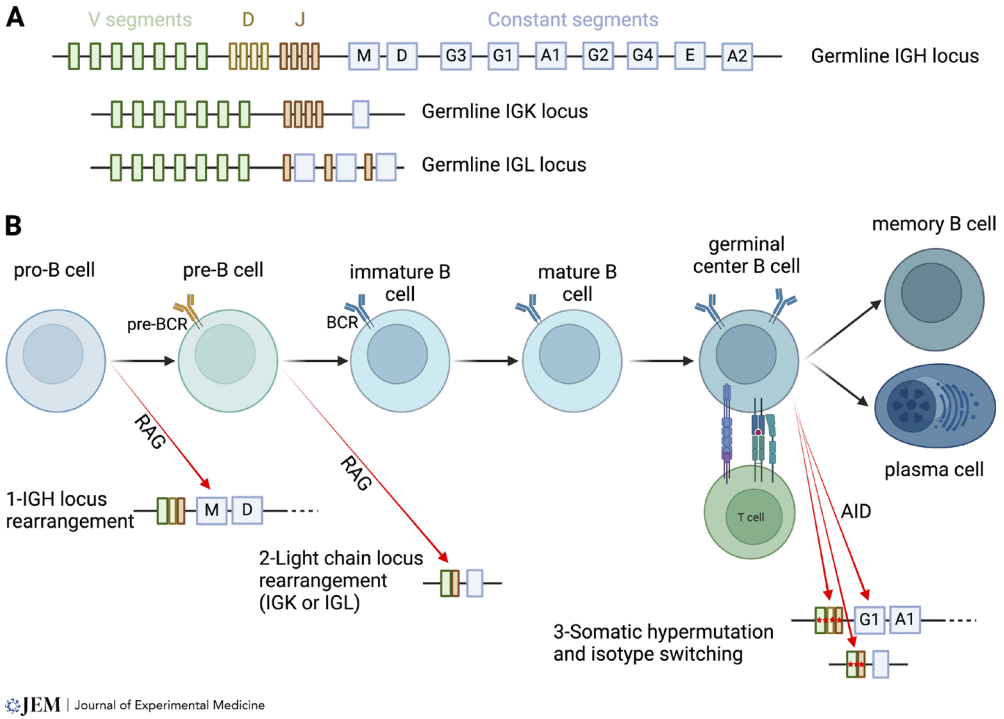
Evoluzione del Sistema Immunitario: come





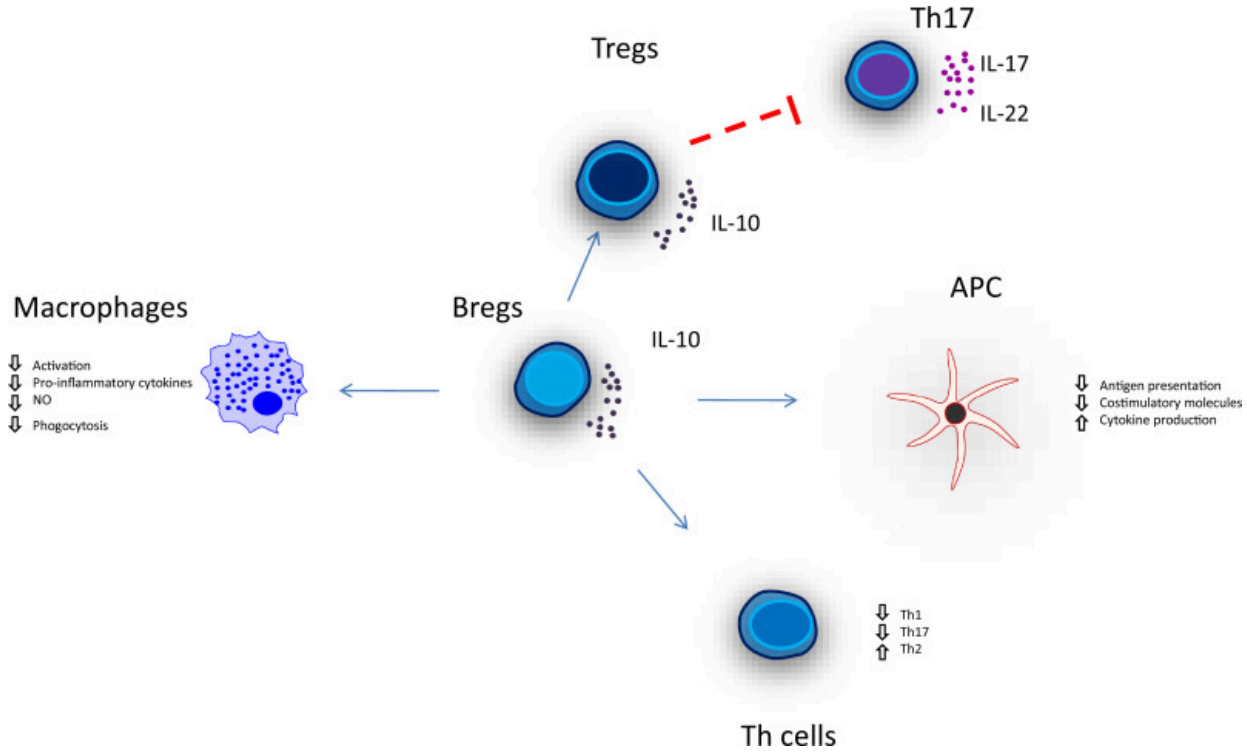
T Boehm, Current Biology 2012; 22:722-732

Come si Stabilisce la Tolleranza-Cellule B



JEM | Journal of Experimental Medicine
J Exp Med. 2024;221(9). doi:10.1084/jem.20231314

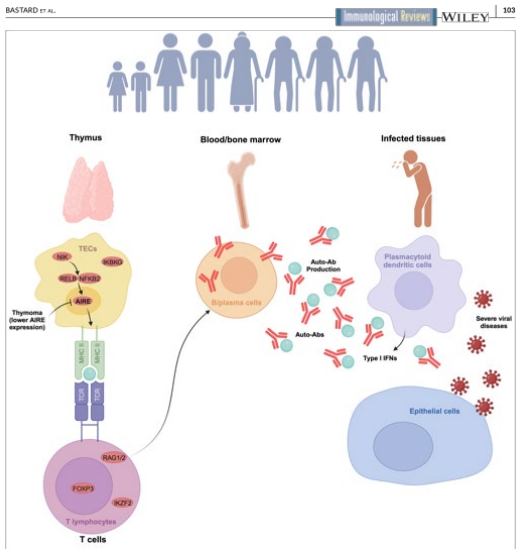
I geni per le Ig (BCR) continuano a riarrangiare nelle cellule B in periferia



Bregs come le Tregs?

While autoantibodies alone are not diagnostic for disease, they do define the presence of autoimmunity. Some cases can develop transiently after infections, immunizations, drug use, or injuries. However, in many situations, autoantibodies are persistent, pathogenic, and some of the best predictors of the development of autoimmune disease.

Grazie al lavoro di Milstein e Kohler, ispirati e guidati da Jerne che oggi usiamo MoAb per modulare la risposta immune anti-TNF, –IL4R, -IL-17, -CTLA4, -PD1.....



I linfociti B modulano le risposte Immunitarie principalmente producendo……. Anticorpi

«Network Disorders» concept può esitare in una rispota immunitaria non appropriata

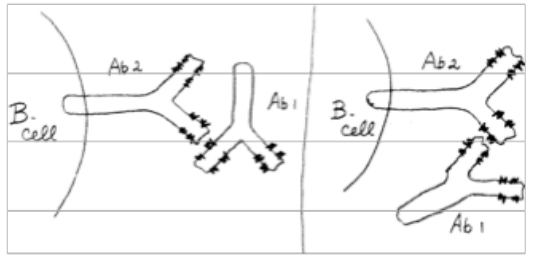
THE GENERATIVE GRAMMAR OF THE IMMUNE SYSTEM

Nobel lecture, 8 December 1984

by

NIELS K. JERNE

I should therefore like to conclude that in its dynamic state our immune system is mainly self-centered, generating anti-idiotypic antibodies to its own antibodies, which constitute the overwhelming majority of antigens present in the body. The system also somehow maintains a precarious equilibrium with the other normal selfconstituents of our body, while reacting vigorously to invasions into our body of foreign particles, proteins, viruses, or bacteria, which incidentally disturb the dynamic harmony of the system.



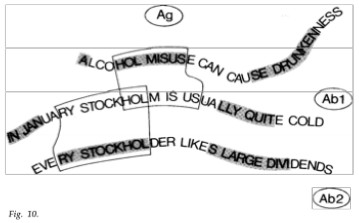


Fig. 10.

Fig. 10 shows an antigenic "sentence", part of which is mirrored by Abl. The anti-idiotopic Ab2 mirrors part of Abl, but bears no relation to the original antigen. Fig. 11 is a little more complex. Here, the original antigen is insulin, and the letter-sequence "OF INSULIN DE" represents its active site, which is mirrored by Abl. Of the two anti-idiotopic antibodies shown, Ab2α and Ab2β, the latter mirrors this mirror image, and thus displays the active site of insulin

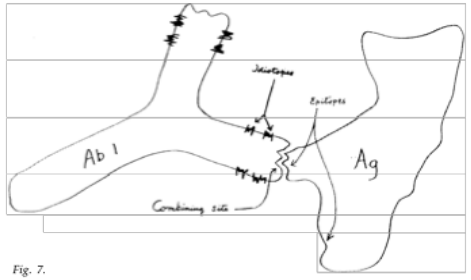
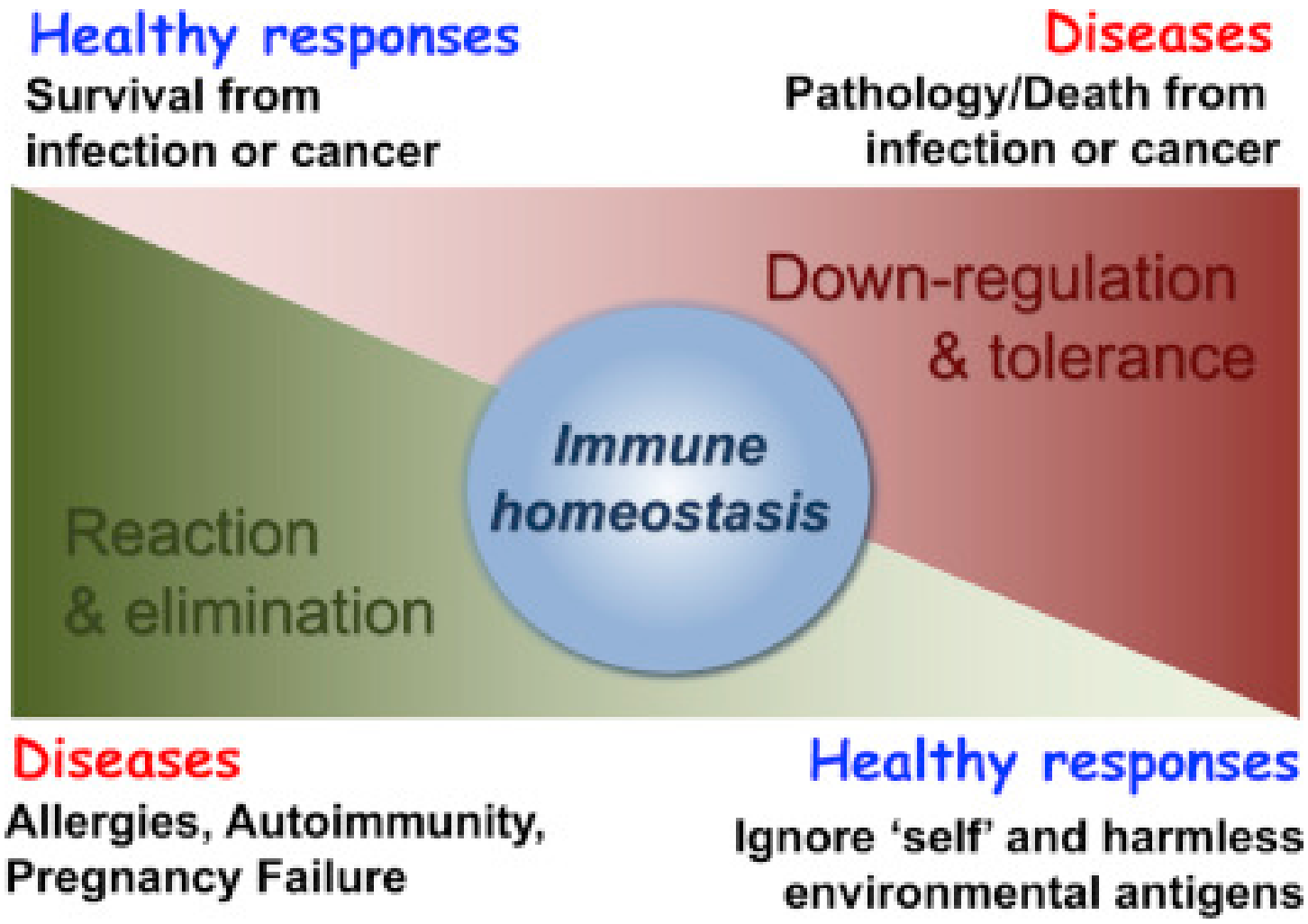
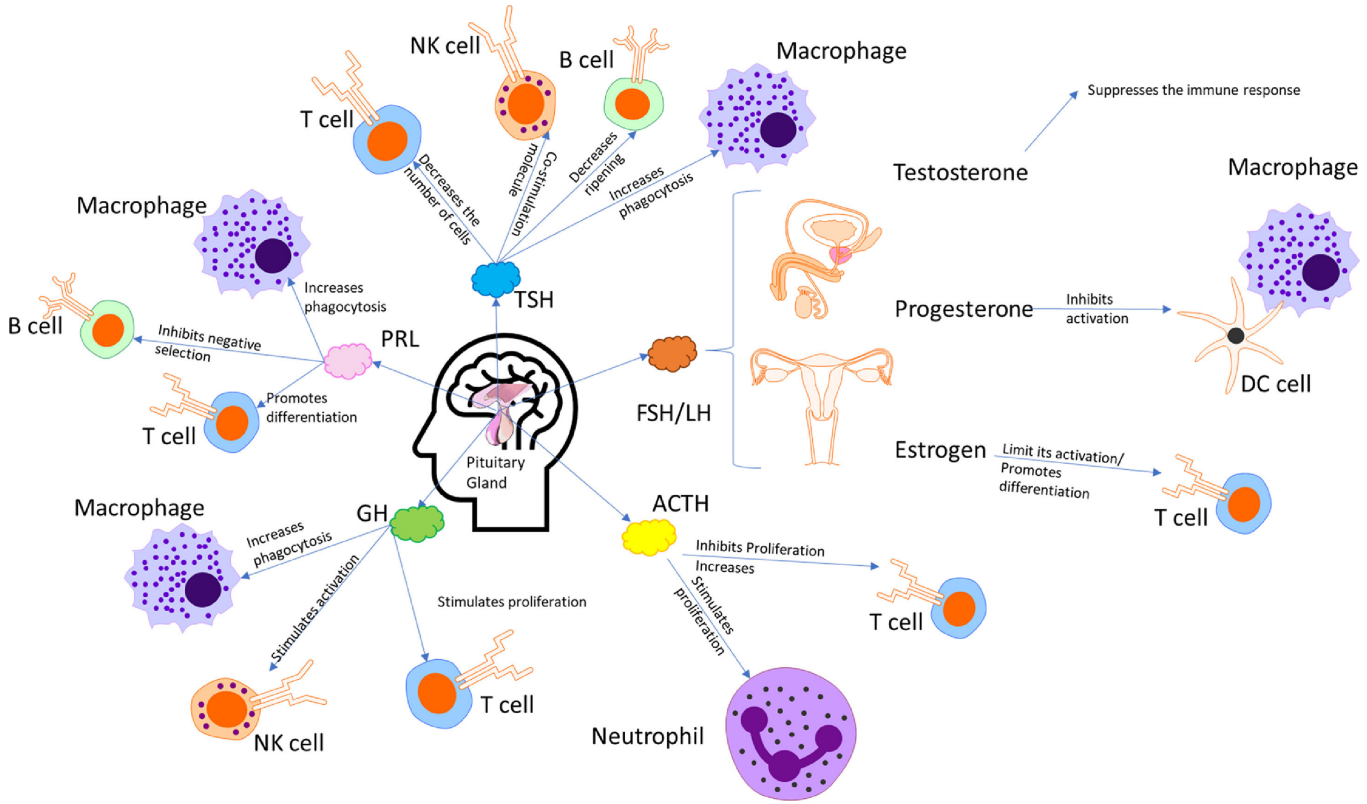


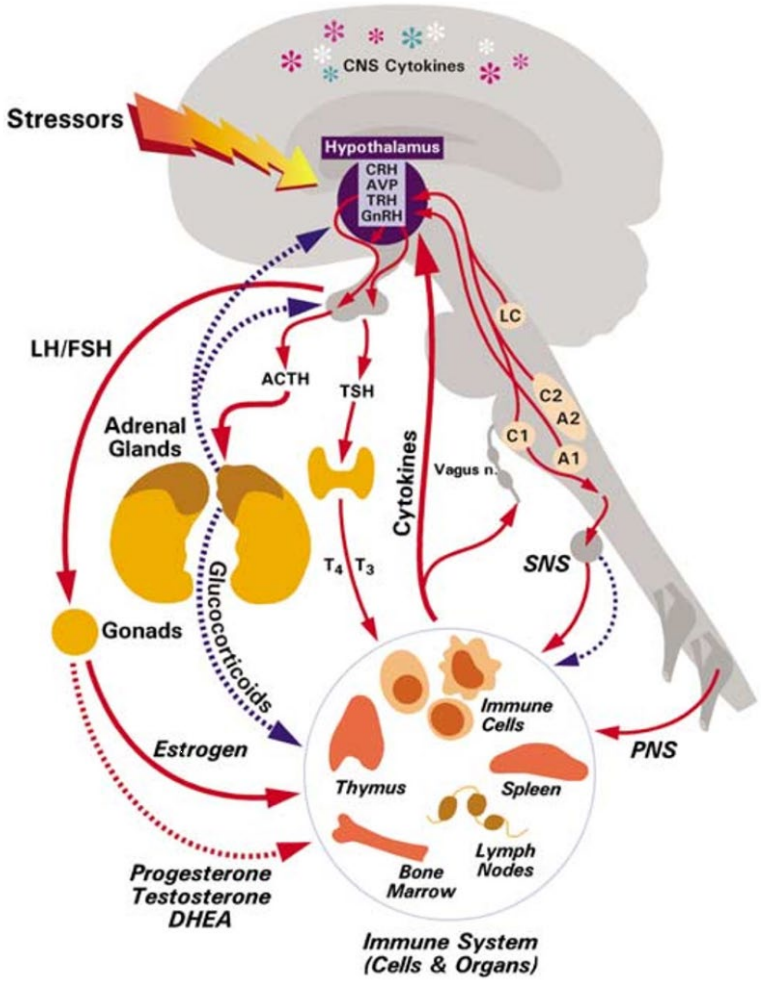
Fig. 7.

Eccesso di reazione o Perdita di Tolleranza?



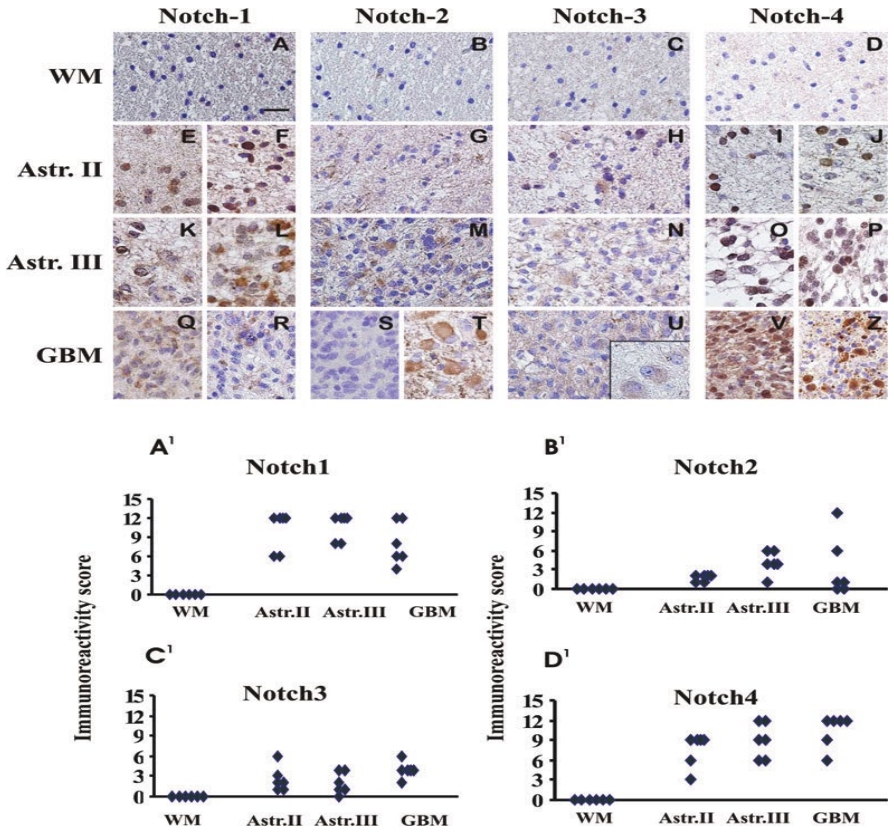
Immune System is tightly connected to Endocrine System and Nervous System



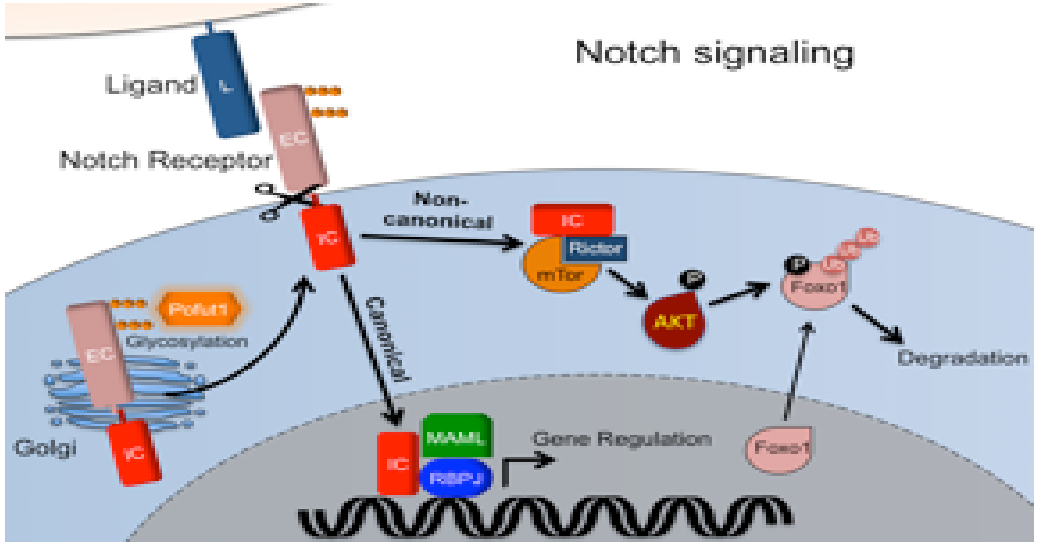


Generally, NOTCH is considered an ancient and highly conserved signaling pathway. NOTCH signaling participates in various biological processes across species, such as organ formation, tissue function, and tissue repair; thus, aberrant NOTCH signaling may cause pathological consequences.

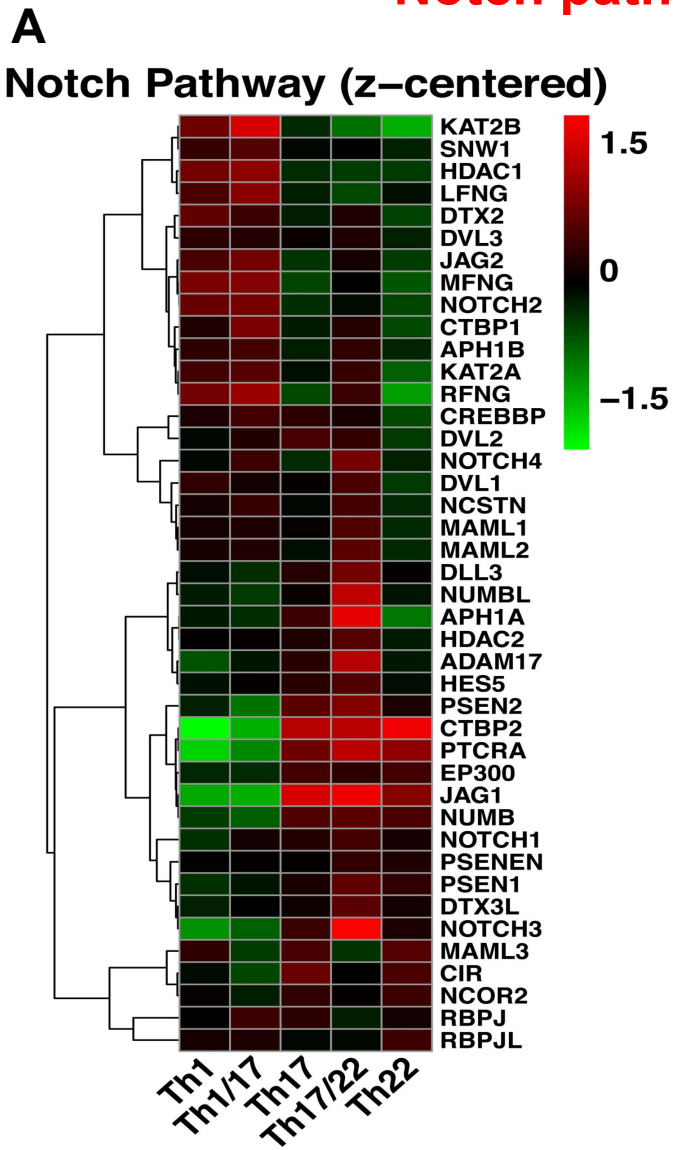
The Notchs family and signaling



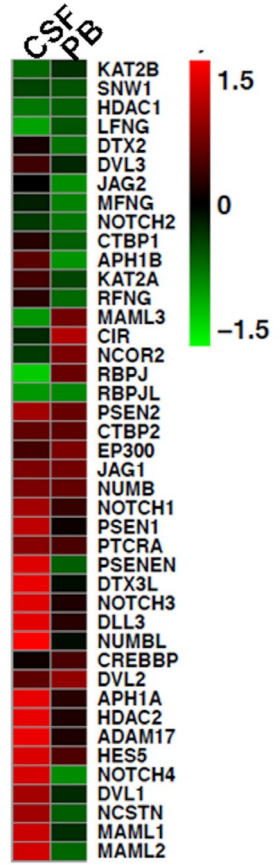
Role in Th cell polarization



Notch pathway is involved in polarization of T helper cells and in sensing tissue signals

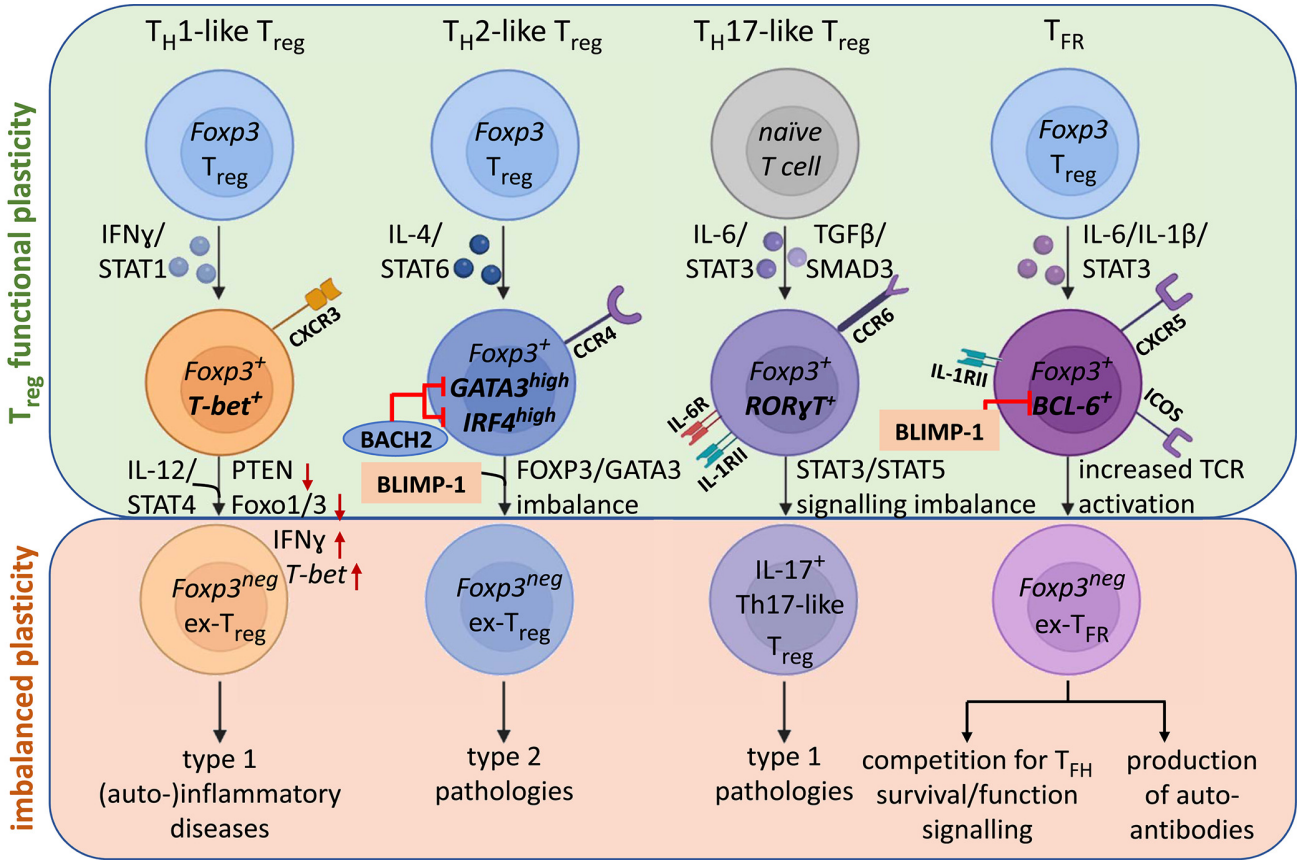


Genes of NOTCH pathway were differently regulated among T helper subsets (A). (B) shows analysis of gene belonging to Notch pathway in Th17/22 cells in CerebroSpinal Fluid versus peripheral blood.

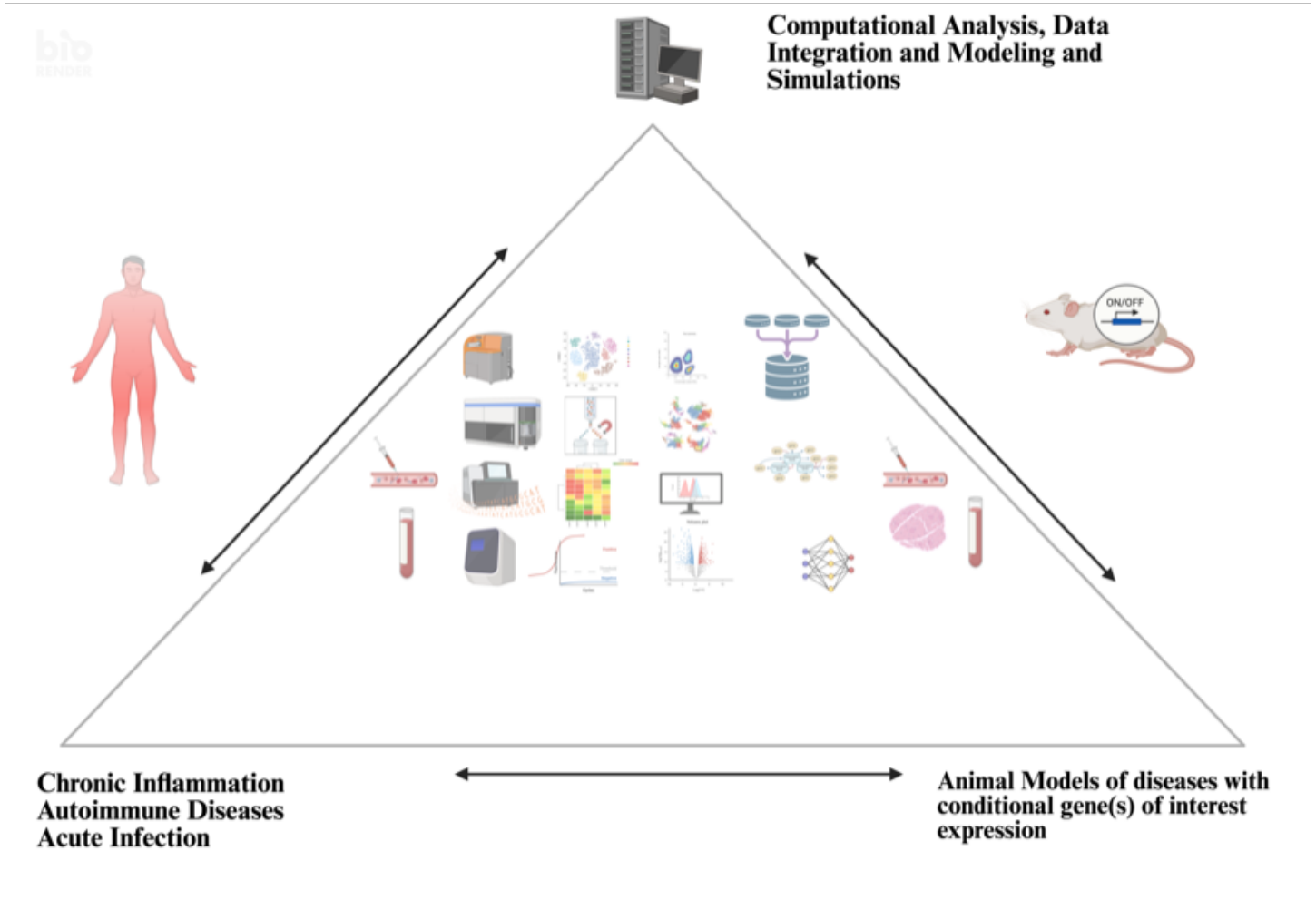


R. De Palma & C. Angelini, 2015

…che cambiò bandiera/per indagare su un fantasma/e scoprì che anche il fantasma/non era una persona soltanto (Bob Dylan-Trantula, 1968)



Foxp3, il Fattore di trascrizione che caratterizza le Treg, è estremamente promiscuo. Interagendo con una miriade di fattori, può facilmente «destabilizzarsi», permettendo la trascrizione di molti altri geni che codificano, ad esempio, per citochine proinfiammatorie enon regolatorie. Questo fa sì che queste cellule possano avere una funzione perfino opposta rispetto a quella di regolazione


Computational Analysis, Data Integration and Modeling and Simulations
ON/OFF
Chronic Inflammation
Autoimmune Diseases
Acute Infection
Animal Models of diseases with conditional gene(s) of interest expression

Tre esempi di rottura della tolleranza

Asma
Polmonite Interstiziale Virale

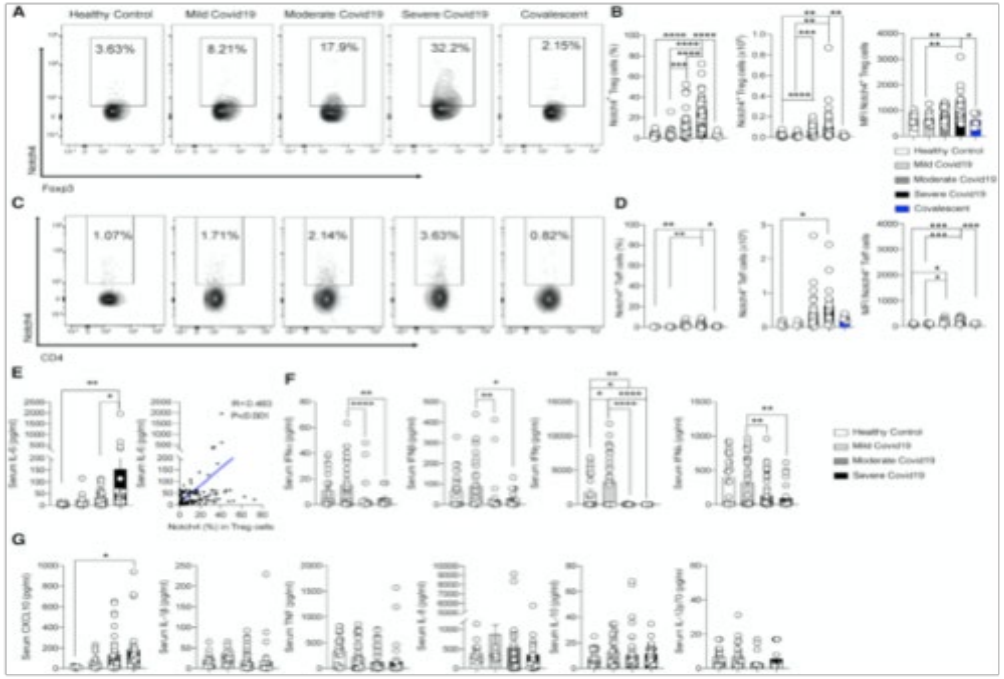
MIS-C
Kawasaki Disease

Sclerosi Multipla

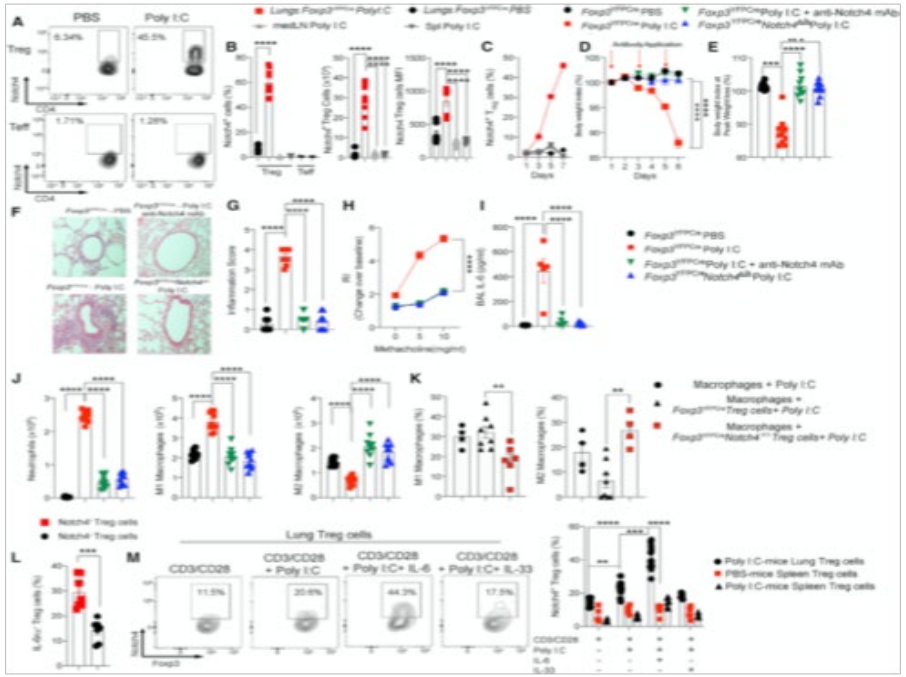
Impegno Polmonare nella Polmonite «SARS-COVID19». La Severità dei sintomi correla con la presenza di cellule Treg che esprimono Notch4, fanno IL-6, non fanno AREG

L'espressione di Notch4 sulle Treg identifica cellule T che non hanno più funzione regolatoria ma proinfiammatoria. Simile risultato nell'asma bronchiale.

Stessi risultati in modello animale di Influenza.



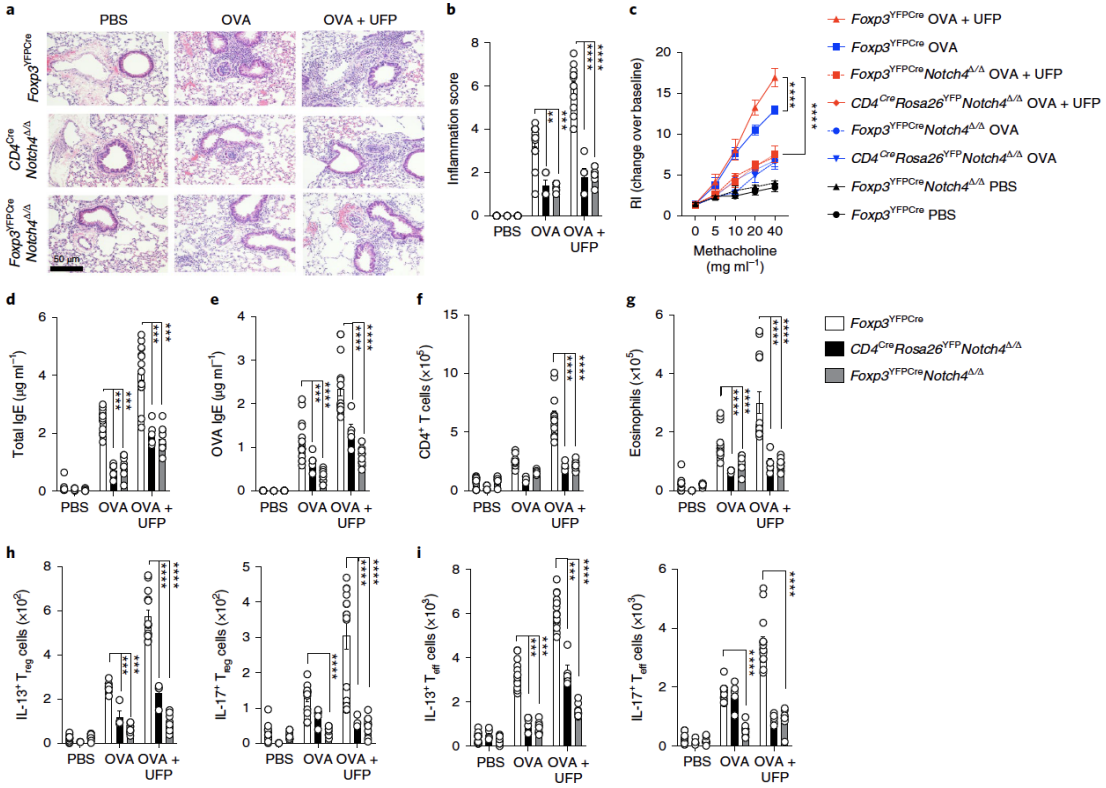
Immunity. 2021;54(6):1186-1199



L'espressione di Notch1,2 e 3 non variava e non era influente sulle cellule Teff

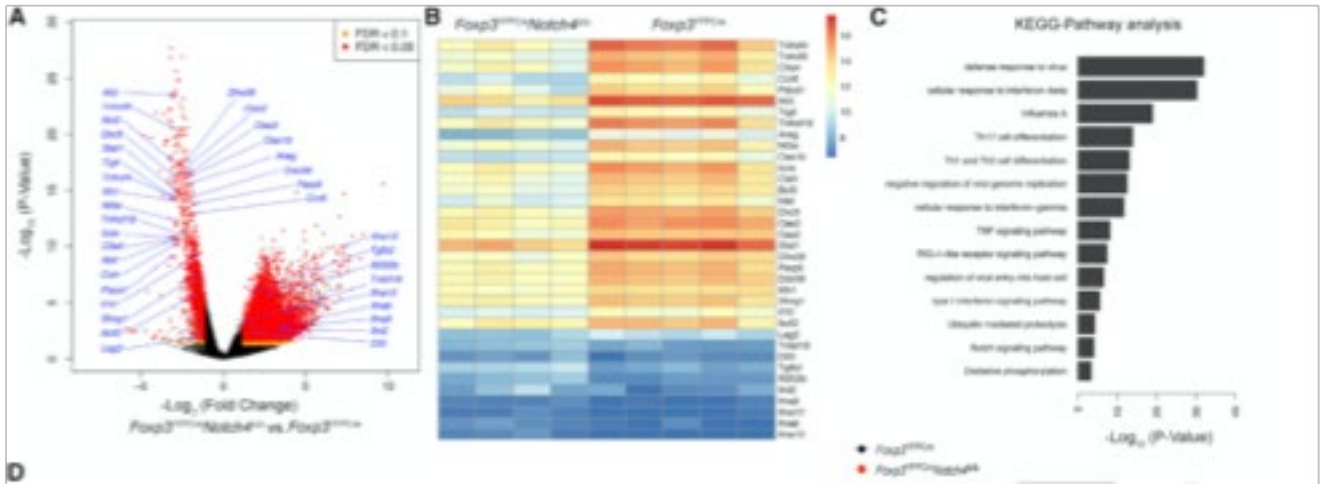
Sintomi bloccati inibendo Notch3 con MoAb, o mediante Treg specific conditional KO in modello umanizzato di Flu. Gli esperimenti con Poly I:C indicano che il meccanismo cvale per le infezioni virali dsRNA-»TLR3 mediated»

Asma bronchiale.

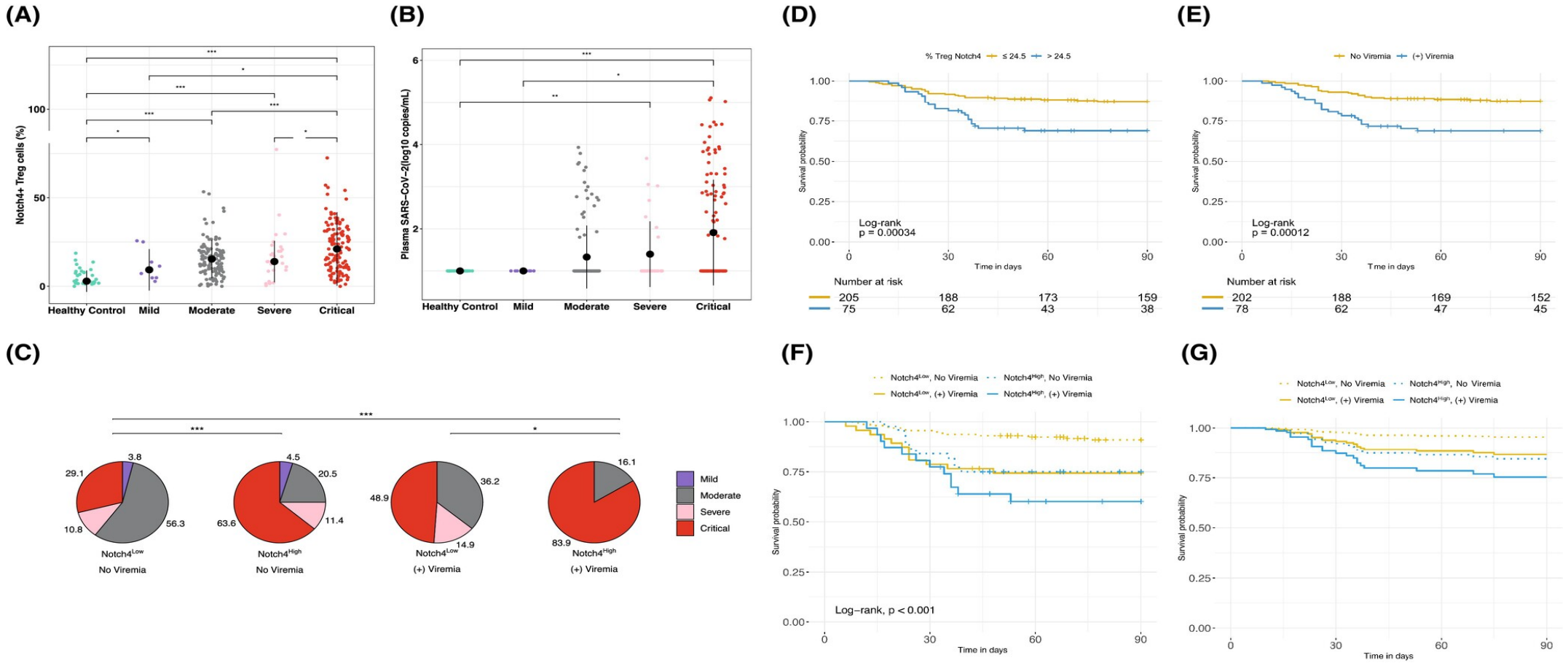


Immunity
Article

CellPress

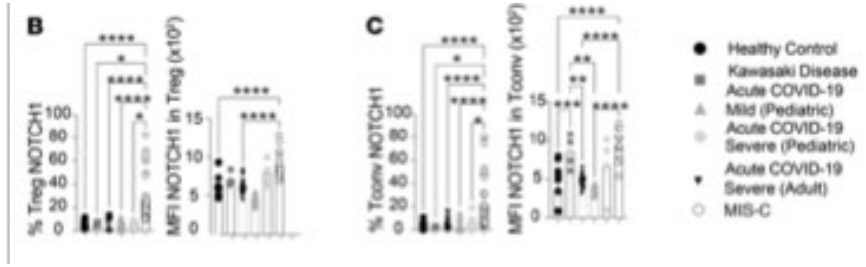


Numero di Treg Notch4+ e persistenza viremia condizionano la sopravvivenza dei pazienti con SARS-COVID19 correlata.

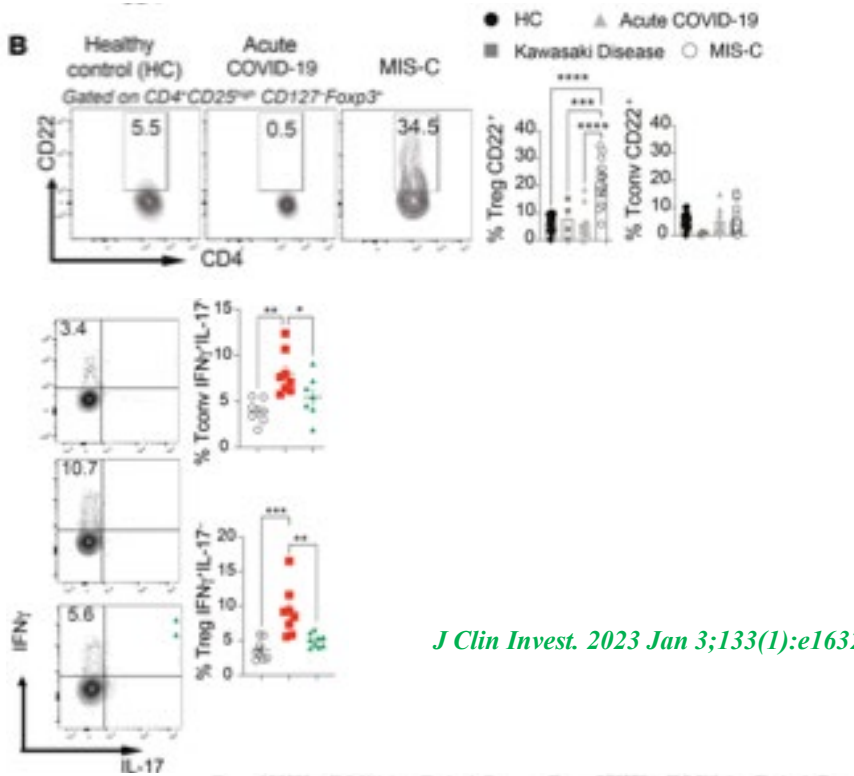


Allergy, Volume: 80, Issue: 2, Pages: 557-569, First published: 03 October 2024, DOI: (10.1111/all.16333)

Notch1+Treg supportano l'infiammazione in pazienti pediatrici Covid

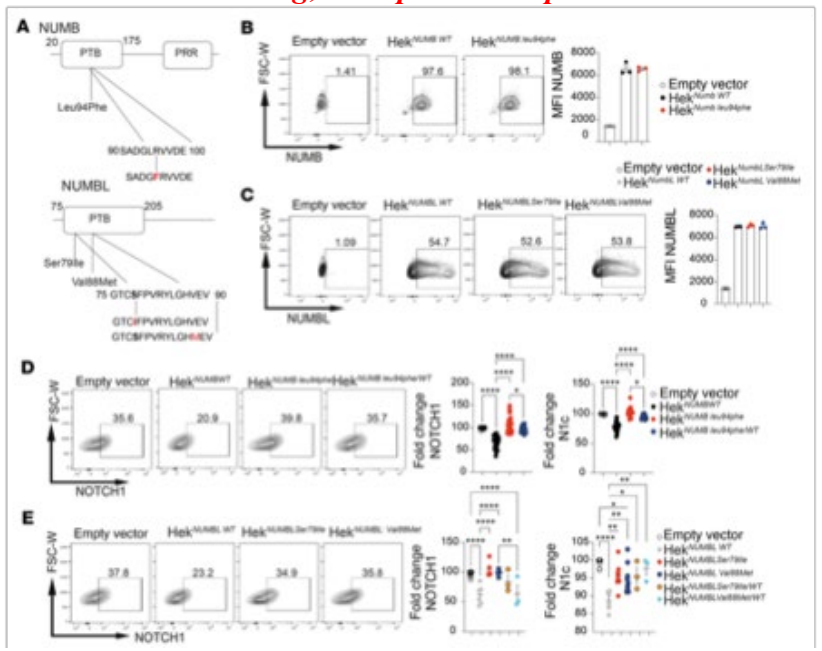


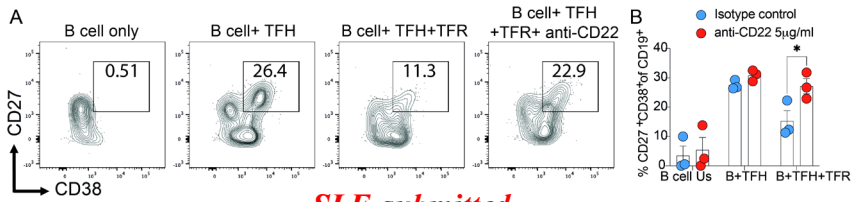
Notch1 destabilizza la funzione regolatoria delle Treg via CD22



J Clin Invest. 2023 Jan 3;133(1):e163235.

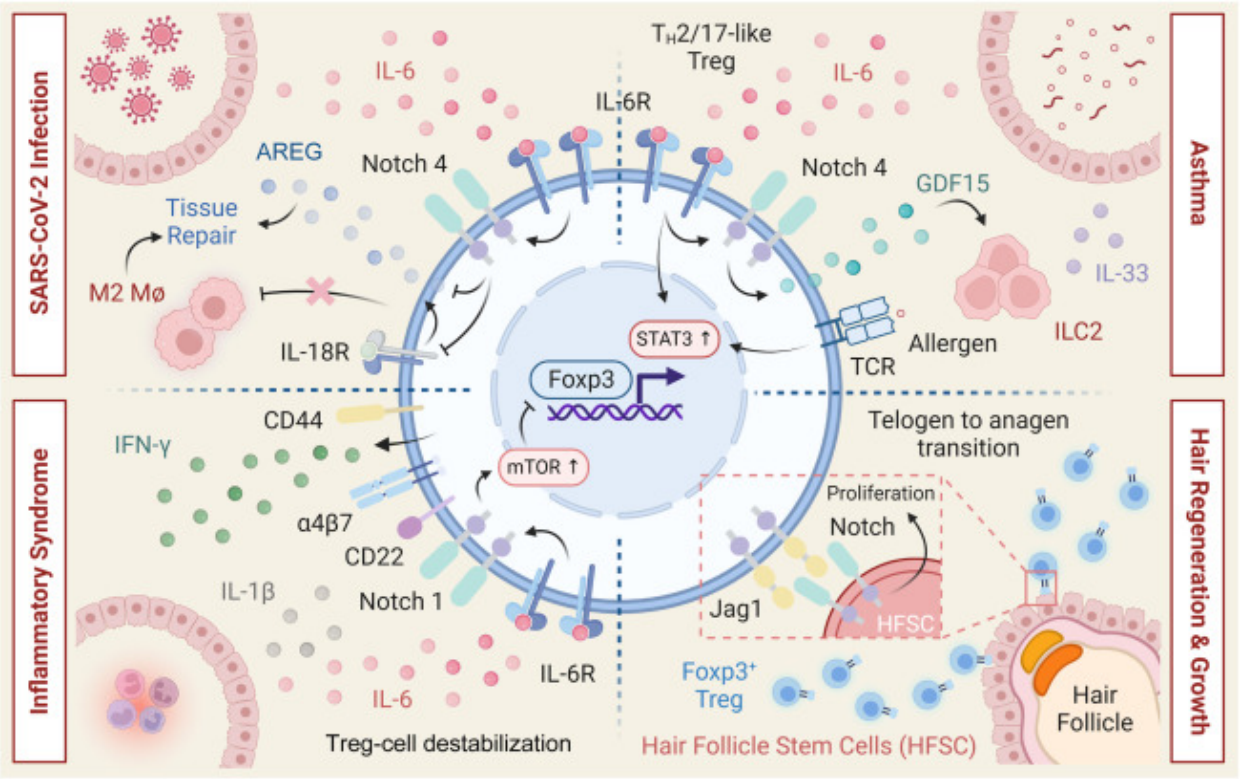
Mutazioni in due geni del pathway di Notch favoriscono l'iperattivazione dell'asse e destabilizzano ulteriormente la funzione modulatoria delle Treg; sono presenti in pazienti con vasculiti





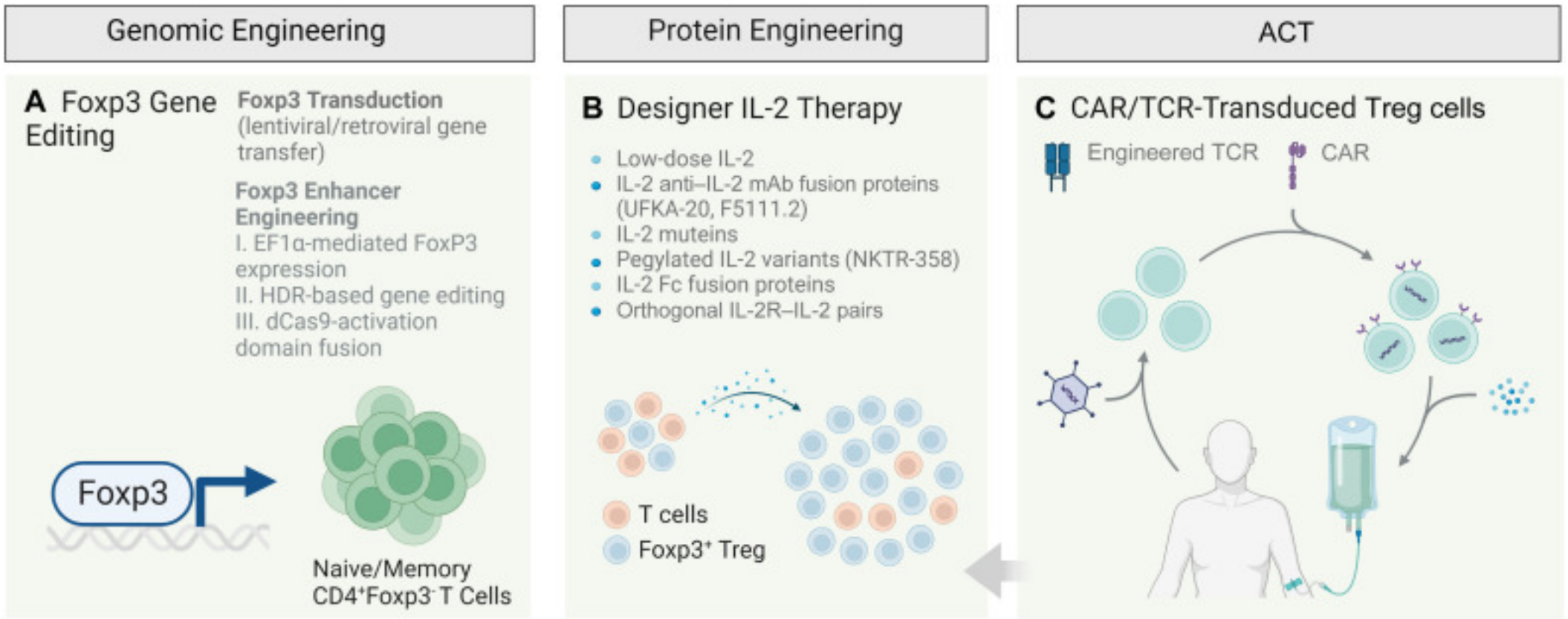
SLE-submitted

Multiple Sclerosis



Espressione di specifico Notch receptor sulle Treg ne permette, nei differenti tessuti, il legame con «danger signals» tessutali.

Il legame Notchr con il ligando può innescare una cascata di segnali in grado di sovvertire la funzione delle Treg portando ad un aumento dell'infiammazione.


Genomic Engineering
Protein Engineering
ACT
A Foxp3 Gene Editing
Foxp3 Transduction (lentiviral/retroviral gene transfer)
Foxp3 Enhancer Engineering
I. EF1α-mediated FoxP3 expression
II. HDR-based gene editing
III. dCas9-activation domain fusion
Foxp3
Naive/Memory CD4+Foxp3- T Cells
B Designer IL-2 Therapy
Low-dose IL-2
IL-2 anti–IL-2 mAb fusion proteins (UFKA-20, F5111.2)
IL-2 muteins
Pegylated IL-2 variants (NKTR-358)
IL-2 Fc fusion proteins
Orthogonal IL-2R–IL-2 pairs
T cells
Foxp3+ Treg
C CAR/TCR-Transduced Treg cells
Engineered TCR
CAR

Willy Gepts; Pathologic Anatomy of the Pancreas in Juvenile Diabetes Mellitus. ***Diabetes*** 1965; 14 (10): 619–633.

Cahill GF Jr, McDevitt HO. Insulin-dependent diabetes mellitus: the initial lesion. ***N Engl J Med***. 1981;304(24):1454-65.

Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. ***Lancet*** 1974;2(7892):1279-83.

Bottazzo GF. Lawrence lecture. Death of a beta cell: homicide or suicide?
Diabet Med. 1986 Mar;3(2):119-30

ER Stress

Results from high demand for protein production and secretion (i.e insulin, chromogranin A).

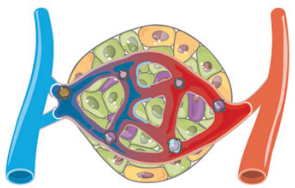
Unresolved ER stress causes accumulation of misfolded proteins, dysregulated PTMs, and the formation of HIPs.

Oxidative Stress

Low levels of catalase, glutathione peroxidase, and peroxiredoxin contribute to ROS imbalance.

Prolonged oxidative stress leads to increased levels of ROS reduced insulin secretion, and cell death.

High Vascularity



Dense network of islet vasculature is required for distribution of synthesized proteins into the bloodstream.

Provides easy access to inflammatory immune cells and potentially harmful cytokines.

La produzione di anticorpi antigene specifici è indirizzata dalle cellule T

NATURE VOL. 314 11 APRIL 1985

Antigen-specific interaction between T and B cells

Antonio Lanzavecchia

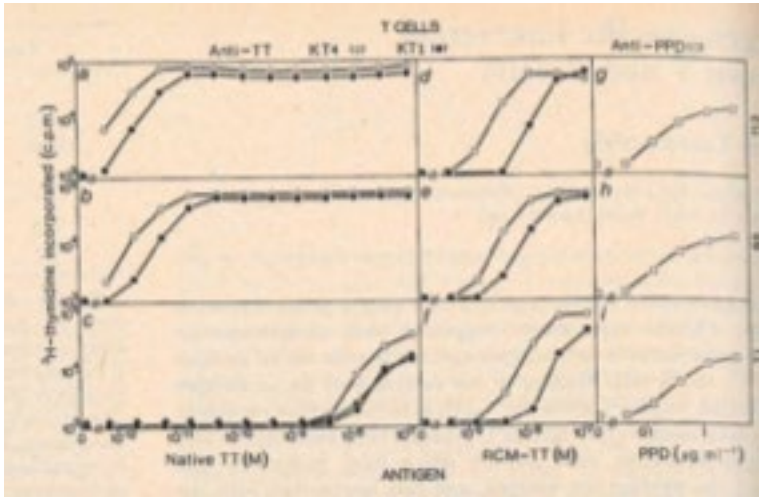
Basel Institute for Immunology, Grenzacherstrasse 487, Postfach CH-4005, Basel, Switzerland

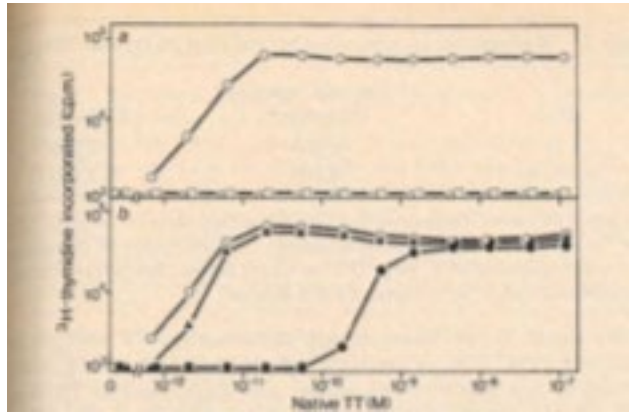
Table 1 Antigen binding by antigen-specific B cells

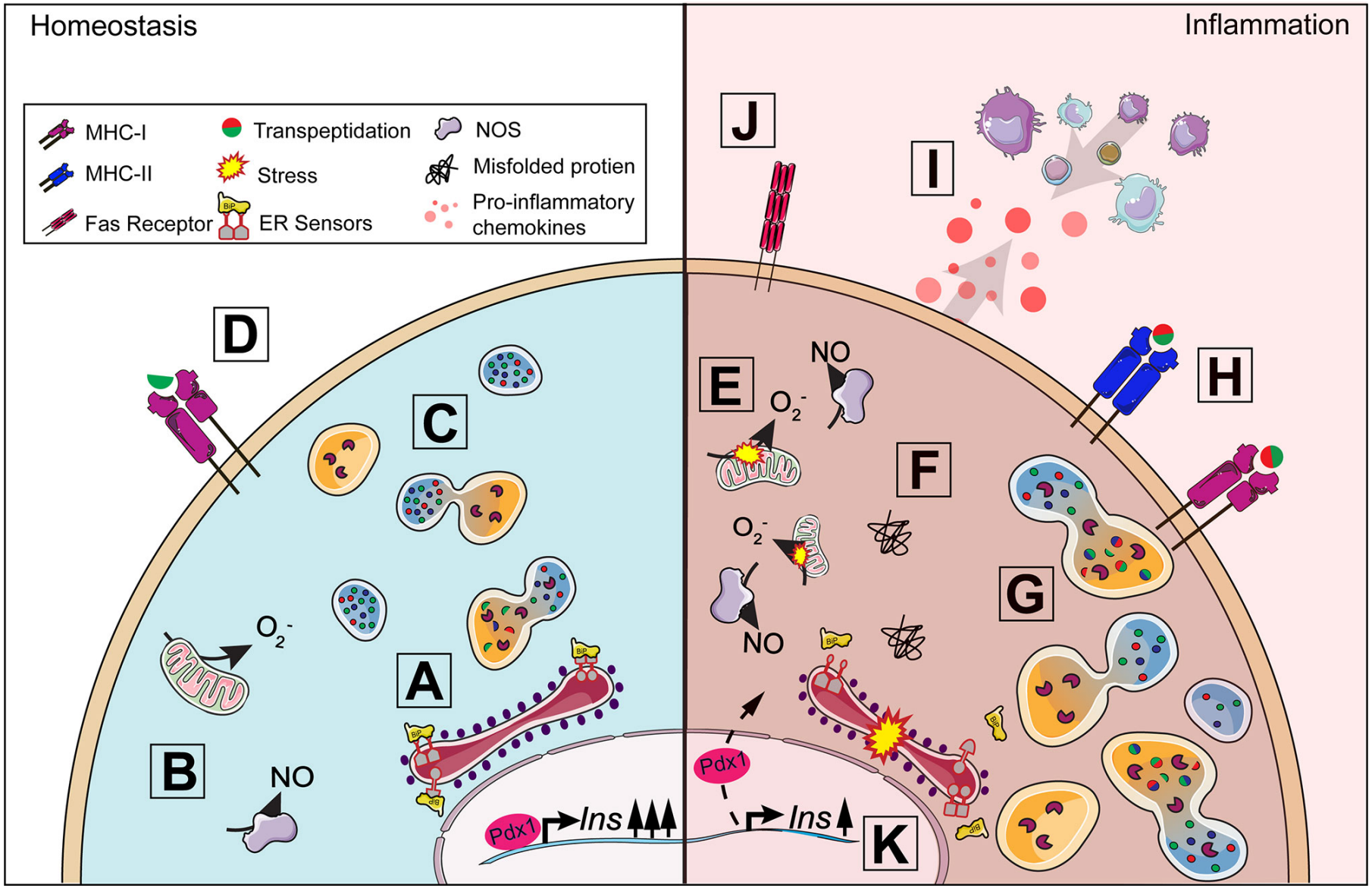
B-cell clone	^{125}I-TT bound per 10^6 cells (c.p.m.)	k ($l\,mol^{-1}$)	No. of sites per cell
11.3	43,529 (1,039)	5×10^7	10^5
8.5	26,834 (593)	2×10^8	2×10^4
4.2	21,067 (912)	5×10^7	5×10^4
7.1	841 (730)	ND	ND

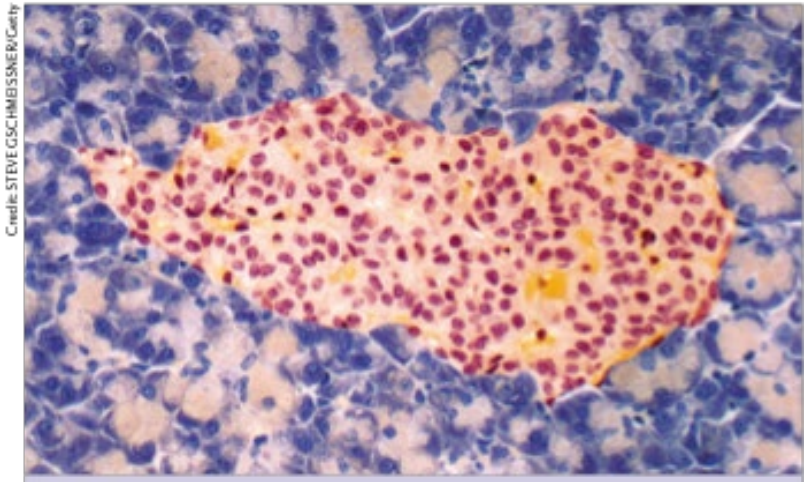
Table 2 Antigen presentation by specific B cells requires intracellular antigen processing

Expt 1: Treatment of B cells before washing	Added in culture	^{3}H-thymidine incorporated (c.p.m.) by T-cell clone KT2	KT4	AK3
—	—	161	138	32,625
TT	—	8,578	36,853	33,499
Anti-Ig, TT	—	979	6,985	33,029
Anti-Ig, TT	TT	8,552	36,491	ND
TT, anti-Ig	—	5,984	28,616	ND
TT	Anti-Ig	8,425	33,890	ND
Expt 2: Treatment of B cells before fixation				
—	—	127	214	21,779
—	TT	148	171	22,532
TT	—	12,373	79,175	21,708
Chloroquine + TT	—	220	962	21,582






Homeostasis
Inflammation
MHC-I
MHC-II
Fas Receptor
Transpeptidation
Stress
ER Sensors
NOS
Misfolded protien
Pro-inflammatory chemokines
A
B
C
D
E
F
G
H
I
J
K
O_2^-
NO
Pdx1
Ins
BiP



Credit: STEVE GSCHMEISSNER/Getty

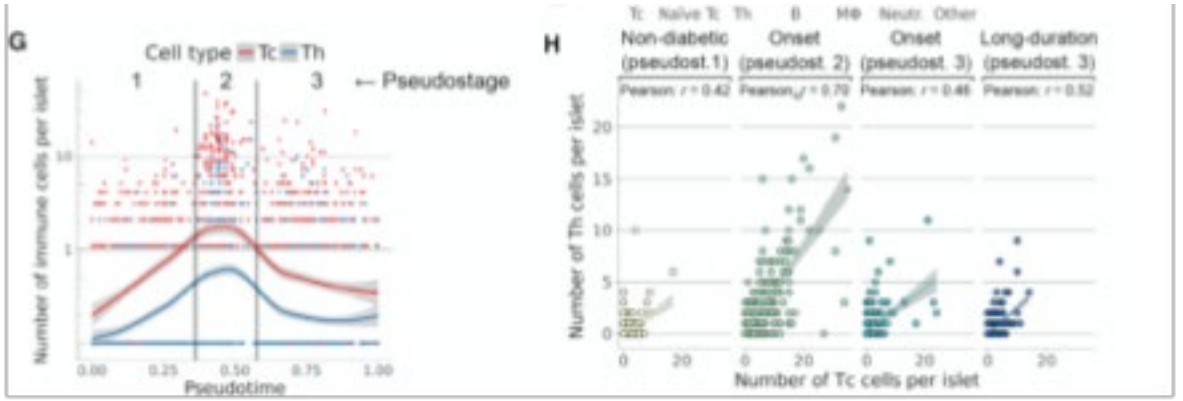
DIABETES

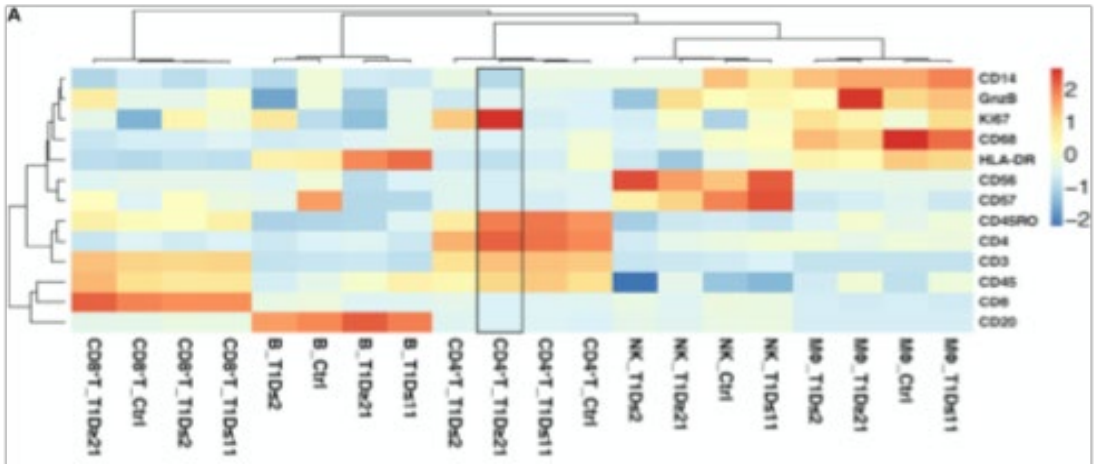
The reconstructed natural history of type 1 diabetes mellitus

Paolo Pozzilli and Alberto Signore

The causes of type 1 diabetes mellitus (T1DM) are unclear; however, a general consensus exists that T1DM is a T cell-mediated autoimmune disease characterized by the selective destruction of insulin-secreting β-cells. Now, two imaging mass cytometry studies of human pancreatic tissue illuminate new biology in the pathogenesis of T1DM.

Refers to Damond, N. K. et al. A map of human type 1 diabetes progression by imaging mass cytometry. Cell Metab. https://doi.org/10.1016/j.cmet.2018.11.014 (2019) | Wang, Y. J. et al. Multiplexed in situ imaging mass cytometry analysis of the human endocrine pancreas and immune system in type 1 diabetes. Cell Metab. https://doi.org/10.1016/j.cmet.2019.01.003 (2019).





THE LANCET, JULY 7, 1984

PATHOGENESIS OF INSULIN-DEPENDENT DIABETES: A ROLE FOR ACTIVATED T LYMPHOCYTES

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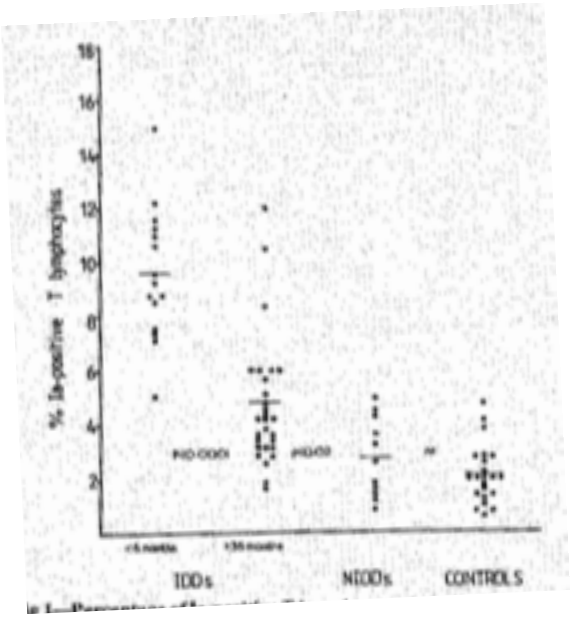
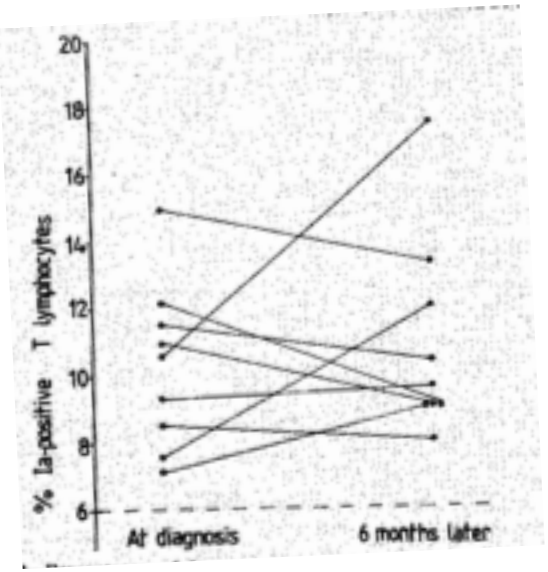
non-insulin-dependent.[16] 15 of the insulin-dependent diabetics were tested within 6 months of diagnosis; the other 28 had been diabetic for more than 3 years. 9 of the 15 newly diagnosed patients were retested after 6 months.

Seven pairs of identical twins discordant for insulin-dependent diabetes were studied; in each pair the diabetic twin had been diabetic for less than 5 years.[17] All the unaffected twins had normal oral glucose tolerance and glycosylated haemoglobin (HbA_1) levels when first studied.

Methods





La rottura della tolleranza in età adulta è una conseguenza della rottura della tolleranza periferica, conseguenza di fattori differenti che possono coesistere (antigeni nuovi per il nostro sistema immune, interazioni con l'ambiente, tumori…..)

La presenza isolata di autoanticorpi non significa necessariamente che siamo di fronte ad una malattia autoimmune

Considerate gli anticorpi anche come marcatori di memoria immunologica e componenti importanti della regolazione, anche quando diretti contro il self, regolazione a volte infruttuosa (vedi ad esempio Fattore Reumatoide, o anticorpi antivirus in alcune forme di vasculite) che finisce per contribuire al danno

Necessità di integrare il Sistema Immunitario nel «Modulo di Controllo», endocrino e SN

We are looking for the opportunity to give a closer look to break of tolerance in type I diabetes

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Mehdi Benamar PhD

Boston Children's Hospital
Until every child is well™

HARVARD MEDICAL SCHOOL

Paola Contini PhD

Claudia Angelini PhD

My personal system of Tolerance to environment