Functional Immunology Applications In Viral Illness

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Affiliations and Declaration of Interest

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- Consultant to Pure Encapsulations, LLC
- Consultant to Calroy, LLC

Cogence

Why care about viral burdens?

Nuclear factor-*k*B — a pivotal transcription factor in chronic inflammatory diseases

N Engl J Med. 1997 Apr 10;336(15):1066-71. Barnes P, Karin M

TABLE 1. STIMULI THAT ACTIVATE NF-κB.

Cytokines
Tumor necrosis factor α
Interleukin-1β
Interleukin-17
Protein kinase C activators
Phorbol esters
Platelet-activating factor
Oxidants
Hydrogen peroxide
Ozone
Viruses
Rhinovirus
Influenzavirus
Epstein–Barr virus
Cytomegalovirus
Adenovirus
Immune stimuli
Phytohemagglutinin
Anti-CD3 antibodies (by means of T-lymphocyte activation)
Antigen
Other
Lipopolysaccharide
Ultraviolet radiation

Pathogen burden, cytomegalovirus infection and inflammatory markers in the risk of premature coronary artery disease in individuals of Indian origin.

Exp Clin Cardiol. 2012 Summer;17(2):63-8. Mundkur LA, Rao VS, Kakkar VV, et al.

"Coronary artery disease (CAD) occurs at an earlier age in South Asians compared with other ethnic groups. Infection and inflammation show a positive association with the disease…

…anti-CMV antibody levels were a significant risk factor for CAD occurrence… and recurrent cardiac events... Mean values of the inflammatory biomarkers IL-6 (P=0.035), fibrinogen (P=0.014), hsCRP (P=0.010) and secretory phospholipase A2 (P=0.002) increased with CMV antibody levels.

Pathogen burden, especially CMV infection in combination with inflammatory markers, is a significant predictor of CAD risk in the young Indian population."

Impact of pathogen burden in patients with coronary artery disease in relation to systemic inflammation and variation in genes encoding cytokines.

Am J Cardiol. 2003 Sep 1;92(5):515-21. Georges JL, Rupprecht HJ, Tiret L, et al.

"The number of infectious pathogens to which an individual has been exposed (pathogen burden) has been linked to the development and the prognosis of coronary artery disease (CAD)."

Clinical Pearl: Higher systemic pathogen burden → Greater systemic inflammation

Molecular mimicry as a mechanism of autoimmune disease.

Clin Rev Allergy Immunol. 2012 Feb;42(1):102-11. Cusick MF, Libbey JE, Fujinami RS.

Human Diseases	Target	T Cells/Ab	Human Antigen Mimicked	Organism
Spondyloarthropathies (SpAs), anklosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated SpA	Lumbar spine and sacroiliac joints	Abs	HLA-B27	*Klebsiella pneumoniae, Shigella, Chlamydia trachomatis* and other gram-negative bacteria
Antiphospholipid syndrome	Fetal loss and thromboembolic phenomena	Abs	β2-glycoprotein I	Bacteria, viruses, yeast, and tetanus toxin
Autoimmune chronic gastritis (AIG) (gastric atrophy, hypochloridria and pernicious anemia)	Stomach epithelium cells or parietal cell canaliculi	T cell/Abs	H^+, K^+-ATPase, parietal cell canaliculi	*Helicobacter pylori*
Cogan's syndrome	Eye and ear	Abs	SSA/Ro; (DEP-1/CD148); connexin 26	Reovirus III major core protein lambda 1
Autoimmune thrombocytopenic purpura	Platelet	Abs	Platelet; platelet-associated immuno-globulin G (PAIgG)	*Helicobacter pylori*
Behçet's disease	Eyes, skin, oral cavity, joints, genital system, CNS and blood vessels	T cell	HSP 60, HSP 65, HSP70, alpha-tropomyosin, S-antigens	Mycobacterial HSP, *Plasmodium falciparum*
Cardiomyopathy (myocarditis)	Heart	T cell/Abs	Cardiac myosin	Coxsackie virus, group A streptococci, chlamydia or *Trypanosoma cruzi*
Celiac sprue (celiac disease)	Small intestine	T cell	Transglutaminase	Gliadin (gluten), perinatal infections, adenovirus 12, hepatitis C virus (HCV)
Chagas disease	Heart	T cell	Cardiac myosin	*Trypanosoma cruzi* B13 protein
Chronic inflammatory demyelinating polyneuropathy	Schwann cells	Abs	Monosialoganglioside GM2	Melanoma, *Campylobacter jejuni*
Crohn's disease	Gastrointestinal tract	T cell	Unknown	Gram-positive bacterial peptidoglycans
Dermatomyositis (juvenile)	Skin and muscle	T cell	Skeletal myosin	*Streptococcus pyogenes* M5 protein
Essential mixed cryoglobulinemia	B cell	Abs	IgG-Fc	HCV
Guillain-Barré syndrome	Gangliosides and peripheral nerve	Abs	Peripheral nerve	*Campylobacter jejuni*
Insulin dependent diabetes (type I)	Pancreas	T cell	Islet antigens (GAD 65, proinsulin carboxypeptidase H)	Coxsackie B virus, rubella, rotavirus, herpes, rhinovirus, hantavirus, flavivirus and retrovirus
Systemic lupus erythematosus	Systemic	Abs	60 Kda Ro	Epstein-Barr virus (EBV nuclear antigen-1)
Multiple sclerosis	Myelin	T cell	Myelin basic protein	EBV, measles and HHV-6
Primary biliary cirrhosis	Liver (intrahepatic bile ducts)	Abs/B and T cell	PDE2, GP210, human pyruvate dehydrogenase complex-E2 (PDC-E2), HLA-DR	Gram-negative bacterium, *Escherichia coli, Helicobacter pylori, Pseudomonas*

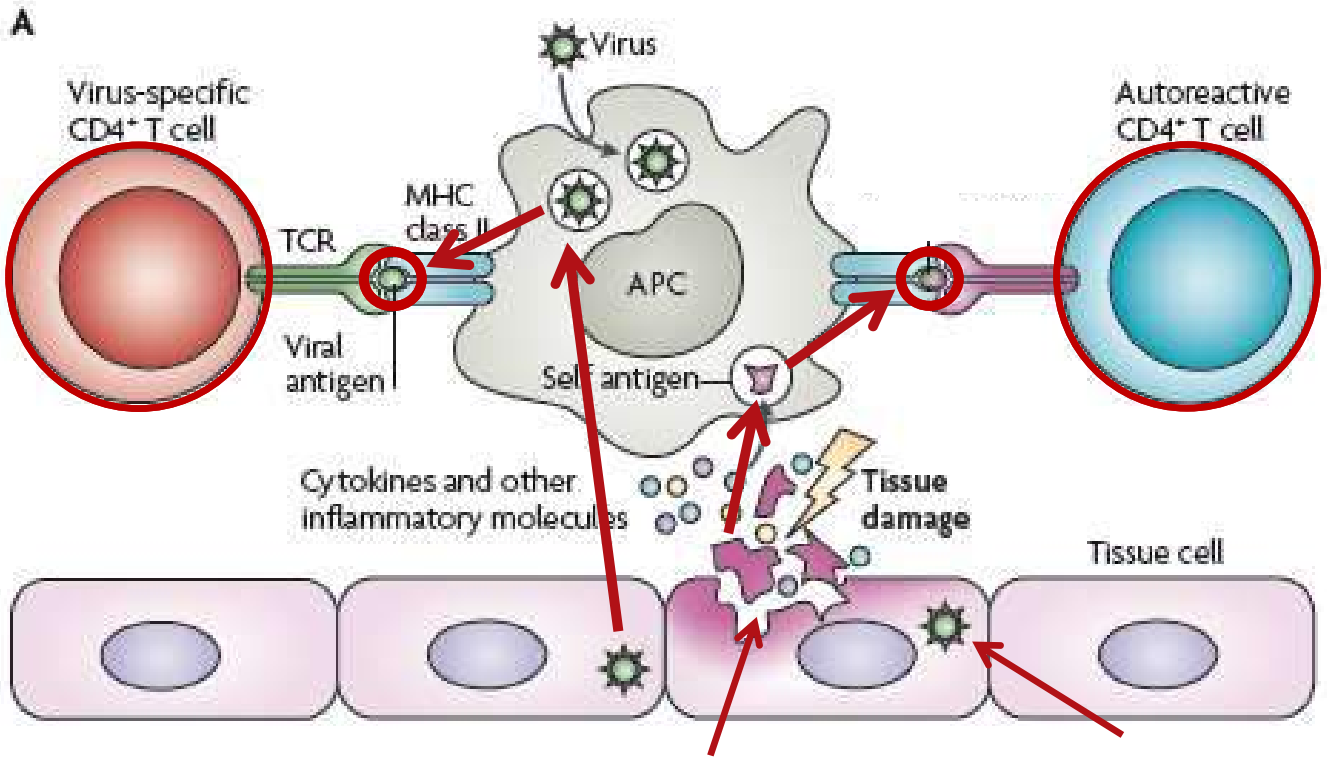
Revisiting the old link between infection and autoimmune disease with commensals and T helper 17 cells

Immunol Res. 2012 Dec;54(1-3):50-68. Blander JM, Torchinsky MB, et al.

Disease type or experimental model	Role of infection in onset of the disease and associated pathogens	Role of microbiota in onset of the disease and associated commensal species
GBS (peripheral nervous system)	Induction of autoimmunity (EBV, CMV, *Mycoplasma pneumoniae*, *Campylobacter jejuni*)	Not reported
Myocarditis	Induction of autoimmunity (B3 coxsackievirus and group A streptococci)	Not reported
MS, enchephalomyelitis and EAE (MOG + CFA, RR mice) (central nervous system)	Induction of autoimmunity (EBV, measles virus, HHV-6)	Induction of autoimmunity (SFB, MOG + CFA), Germ-free housing (MOG + CFA, RR mice) and antibiotic treatment (RR mice) are protective
Lyme arthritis	Induction of autoimmunity (*Borrelia burgdorferi*)	Not reported
Rheumatic fever	Induction of autoimmunity (*β-hemolytic Streptococci*)	Not reported
Clinical and experimental rheumatoid arthritis (*Il1rn*$^{-/-}$, K/BxN)	Induction of autoimmunity (Enteropathogenic bacteria, EBV, CMV and parvovirus in humans)	Induction of autoimmunity (*Lactobacillus bifidus*, *Il1rn*$^{-/-}$), SFB (K/BxN) Germ-free housing is protective (*Il1rn*$^{-/-}$, K/BxN)
Autoimmune gastritis	Induction of autoimmunity (*Helicobacter pylori*) *Aicda*$^{-/-}$ mice	No change in autoimmunity in germ-free conditions
Crohn's disease, DSS in ATG16L1^{HM} mice, Samp-I/Yit mice	Induction of Crohn's like symptoms in ATG16L1^{HM} mice after DSS treatment (murine norovirus)	Humans: Altered composition and activity of microbiota and response against commensal-derived antigens (invasive *escherichia coli*, *Pseudomonas fluorescence*) Mice: Germ-free housing (Samp-I/Yit) and antibiotic treatment (ATG16L1^{HM} mice) are protective
Ulcerative colitis, genetic models of colitis (C3H/HeJBir, *Il10*$^{-/-}$, Tg(ε26), *Il2*$^{-/-}$) and DSS treatment	Not reported	Humans: Composition and activity of microbiota and response against commensal-derived antigens Mice: Induction of colitis (*Bacteroidetes* (*Prevotellaceae*) and TM7) Protection of colitis (ASF, *Clostridium*, *Lactobacillus*, *Bacteroides fragilis*) Germ-free housing (*Il10*$^{-/-}$, Tg(ε26), *Il2*$^{-/-}$) is protective

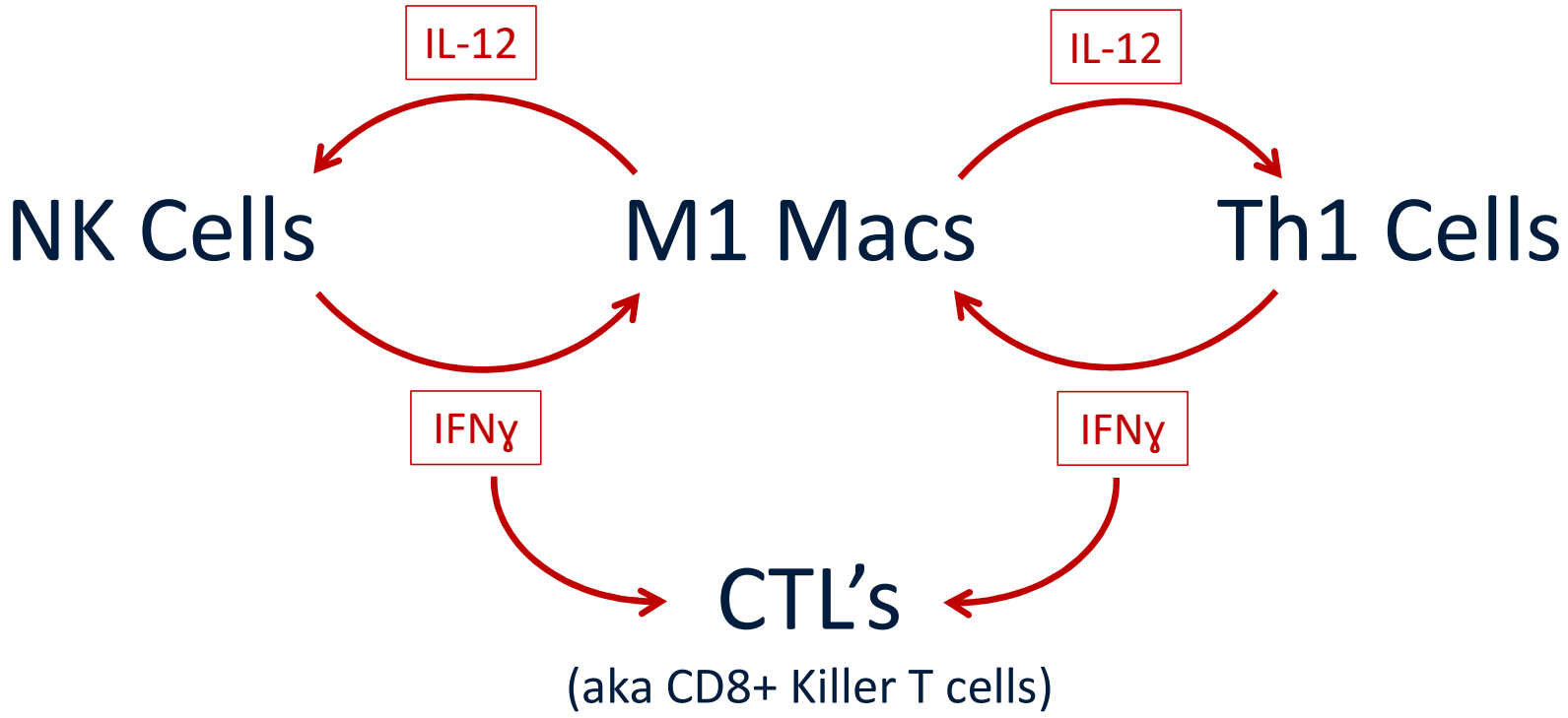
Antiviral immune responses: triggers of or triggered by autoimmunity?

Nat Rev Immunol. 2009 Apr;9(4):246-58, Münz C1, Lünemann JD, Getts MT, Miller SD



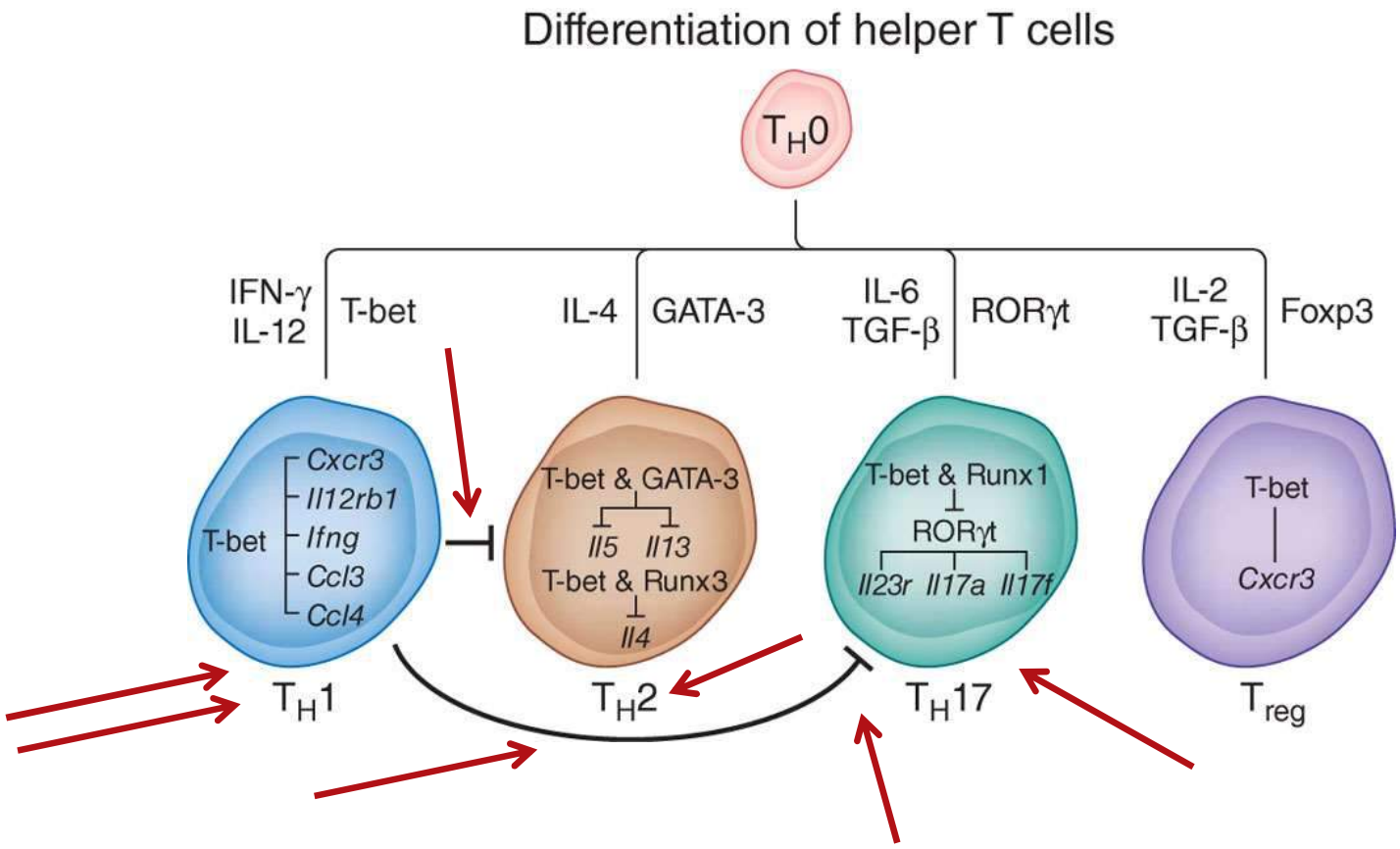
T Cell Polarization

Anti-Viral Immunology Basics



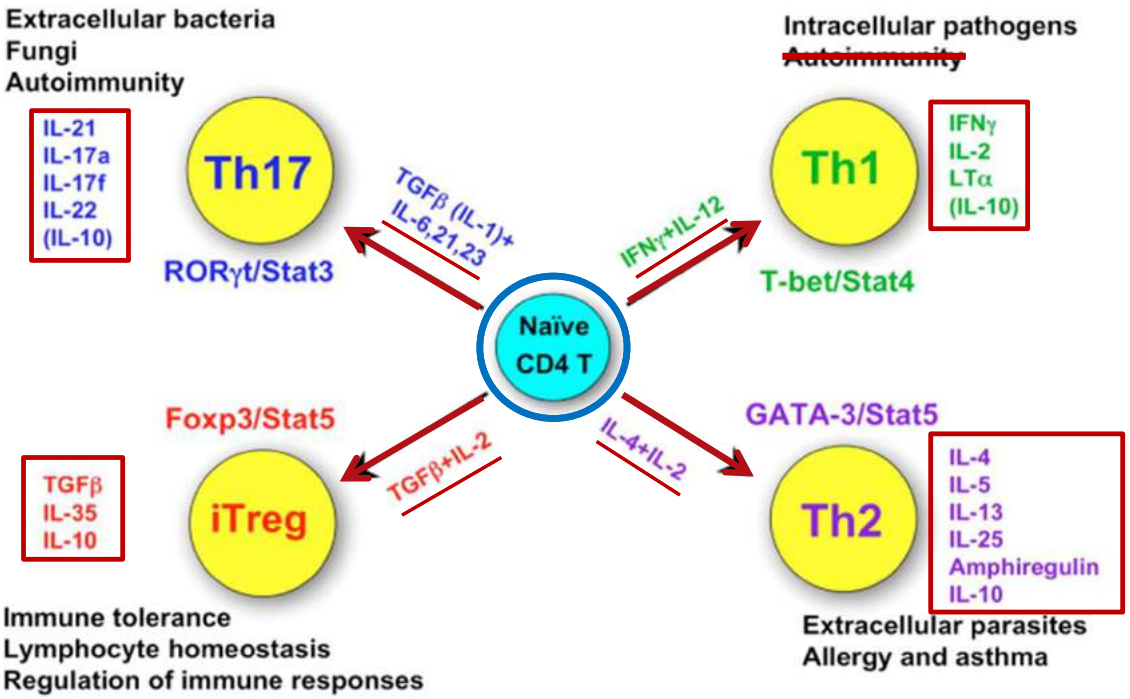
T-bet in disease

Nat Immunol. 2011 Jun 20;12(7):597-606, Lazarevic V, Glimcher LH



CD4 T cells: Fates, functions, and faults

Blood. 2008 Sep 1;112(5):1557-69, Zhu J, Paul WE



CD4 T cells: Fates, functions, and faults

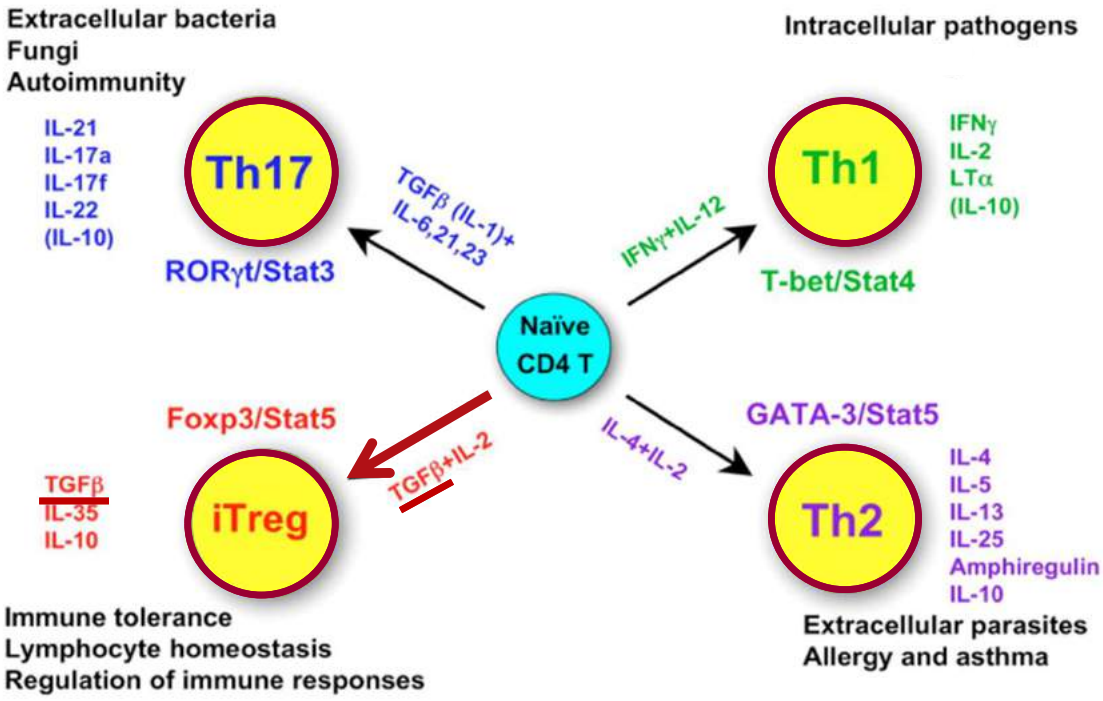
Blood. 2008 Sep 1;112(5):1557-69, Zhu J, Paul WE

Drive Autoimmune Tissue Destruction. **Always key in autoimmunity.**

High Neutrophil %, hsCRP (not always high)

Quiet ALL effector T cells.
Quiet autoimmunity.
Can be overactive in chronic infection.

High TGFβ suggests excess activity here, often driven by inflammation.



Kill Bacteria & Viruses.
Cancer surveillance. Low in chronic infection. Low in autoimmunity.

Total wbc's below 4 (not always). Can be high if monocytes >12%.

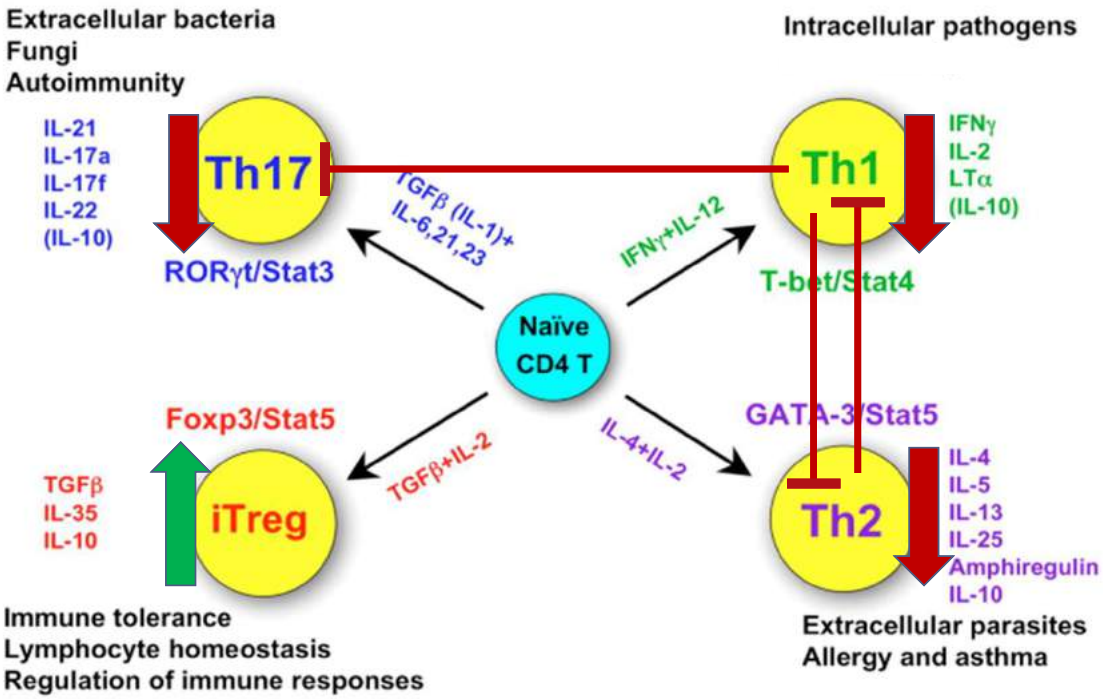
Kill parasites.
Expel pollen, etc.
Hollow space inflammation drives Th2 Dominance.

Eosinophils above 2%.
Mast cells & histamine.

CD4 T cells: Fates, functions, and faults

Blood. 2008 Sep 1;112(5):1557-69, Zhu J, Paul WE

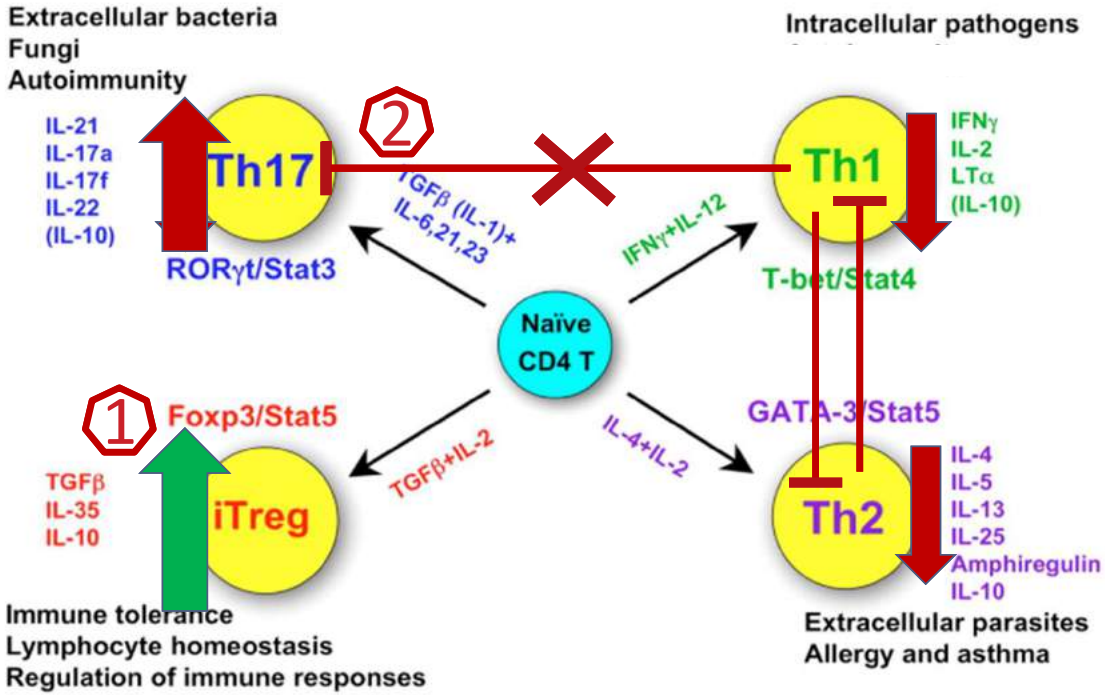
T Cell Inhibition Patterns



CD4 T cells: Fates, functions, and faults

Blood. 2008 Sep 1;112(5):1557-69, Zhu J, Paul WE

Two Ways to Quiet Autoimmunity

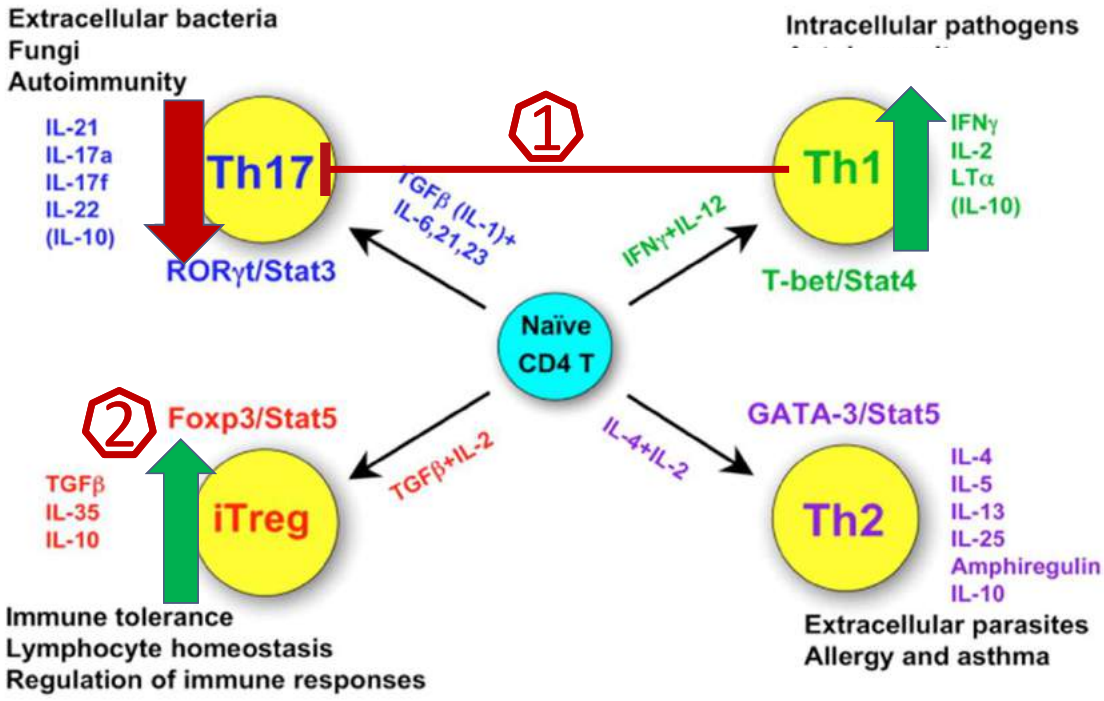


What we all tend to think we should do is…

CD4 T cells: Fates, functions, and faults

Blood. 2008 Sep 1;112(5):1557-69, Zhu J, Paul WE

The Correct Order…



Key: Keep the Th1 Response up while promoting immune tolerance.

Q: What else dumps Th1 response?

Once you've got the Th1 response supported…

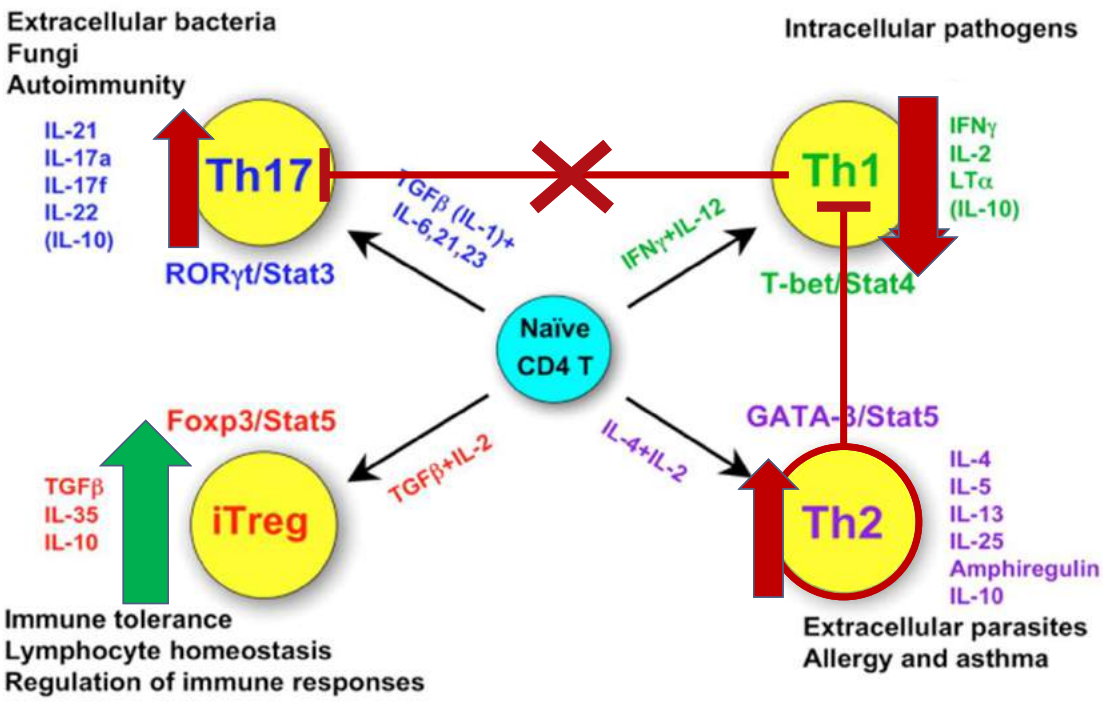
CD4 T cells: Fates, functions, and faults

Blood. 2008 Sep 1;112(5):1557-69, Zhu J, Paul WE

The Th2 Dominance Problem

Th2 Dominance

- Loss of Th1
- Th17 Activation
- Autoimmune Tissue Destruction



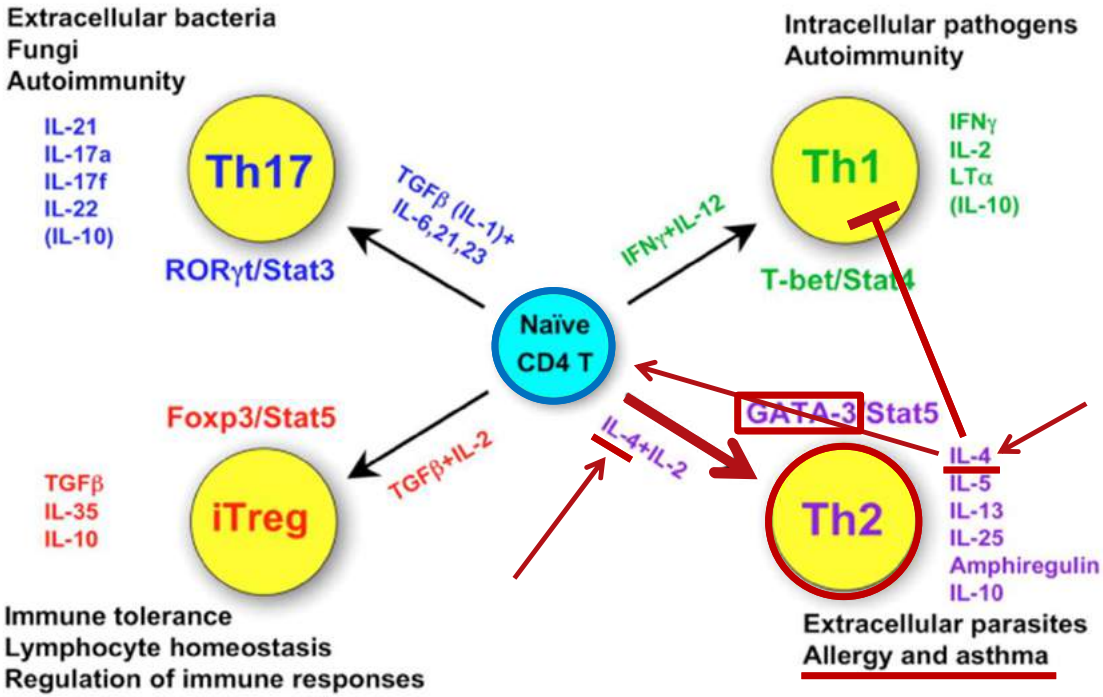
Factors That Increase Th2 Dominance:

- Inflammation
- Stress Chemistry
- Mold / Candida
- Pesticides
- Plastics (BPA, etc.)
- Head Injury
- Brain Inflammation
- Inflammation in **hollow spaces**
  - Intestines
  - Lungs
  - Sinuses
  - Vaginal Tract
  - Bladder

CD4 T cells: Fates, functions, and faults

Blood. 2008 Sep 1;112(5):1557-69, Zhu J, Paul WE

Th2 Self-Reinforcing Activation



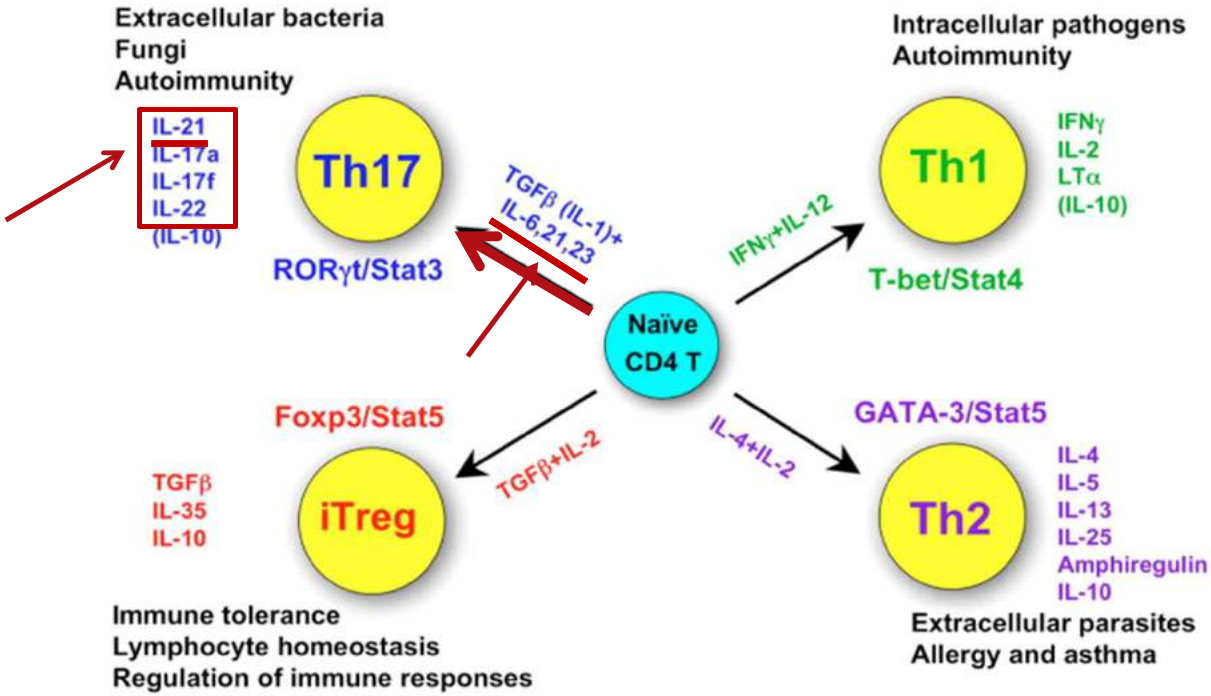
Clinical Targets to Modulate Th2 Response:

- IL-4
- GATA3
- Histamine

CD4 T cells: Fates, functions, and faults

Blood. 2008 Sep 1;112(5):1557-69, Zhu J, Paul WE

Th17 Self-Reinforcing Activation



CD4 T cells: Fates, functions, and faults

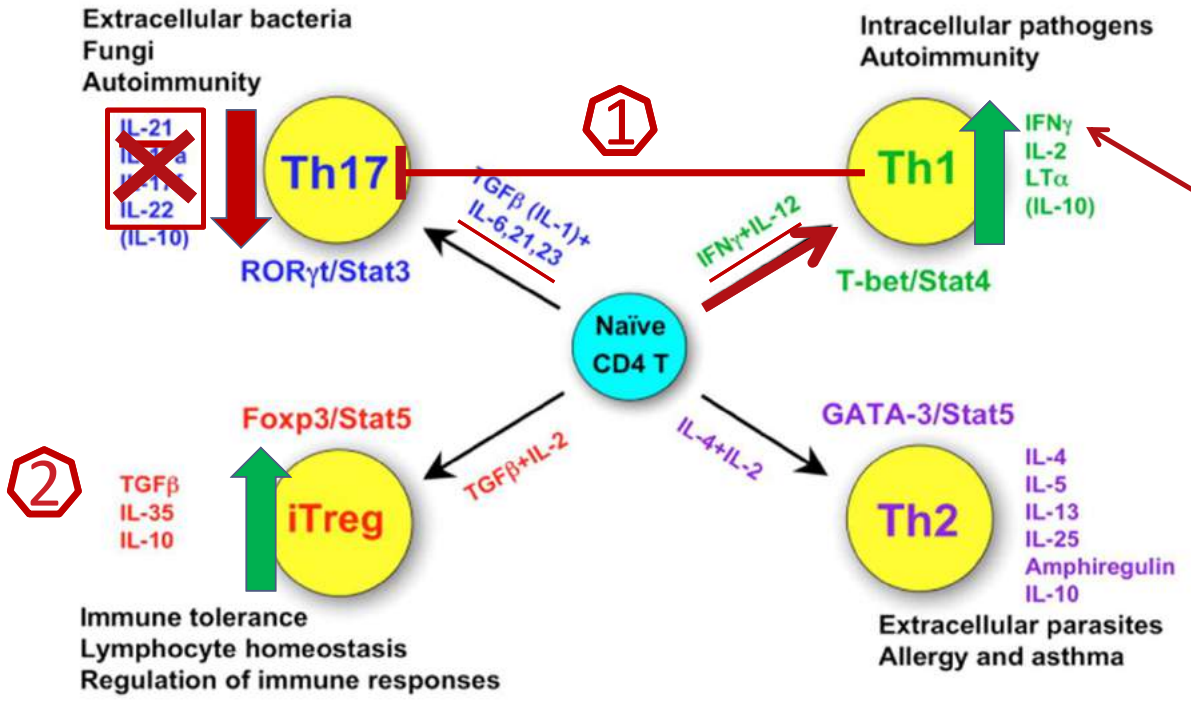
Blood. 2008 Sep 1;112(5):1557-69, Zhu J, Paul WE

Inhibiting Th17 Activation

Step 1:

Balance T Cell Polarization by:

1. **Supporting Th1 Response** *and*
2. **Modulating Th2 response**



Support Th1:

- IL-12
- IFNɣ

Modulate Th2:

- IL-4
- GATA3
- Histamine

A brief history of TH17, the first major revision in the TH1/TH2 hypothesis of T cell–mediated tissue damage

Nat Med. 2007 Feb;13(2):139-45, Steinman L

"T-helper type 1 (TH1) cells — long thought to mediate tissue damage—might be involved in the initiation of damage, but they do not sustain or play a decisive role in many commonly studied models of autoimmunity, allergy and microbial immunity.

A major role for the cytokine interleukin-17 (IL-17) has now been described in various models of immune-mediated tissue injury, including organ-specific autoimmunity in the brain, heart, synovium and intestines, allergic disorders of the lung and skin, and microbial infections of the intestines and the nervous system."

A brief history of TH17, the first major revision in the TH1/TH2 hypothesis of T cell–mediated tissue damage

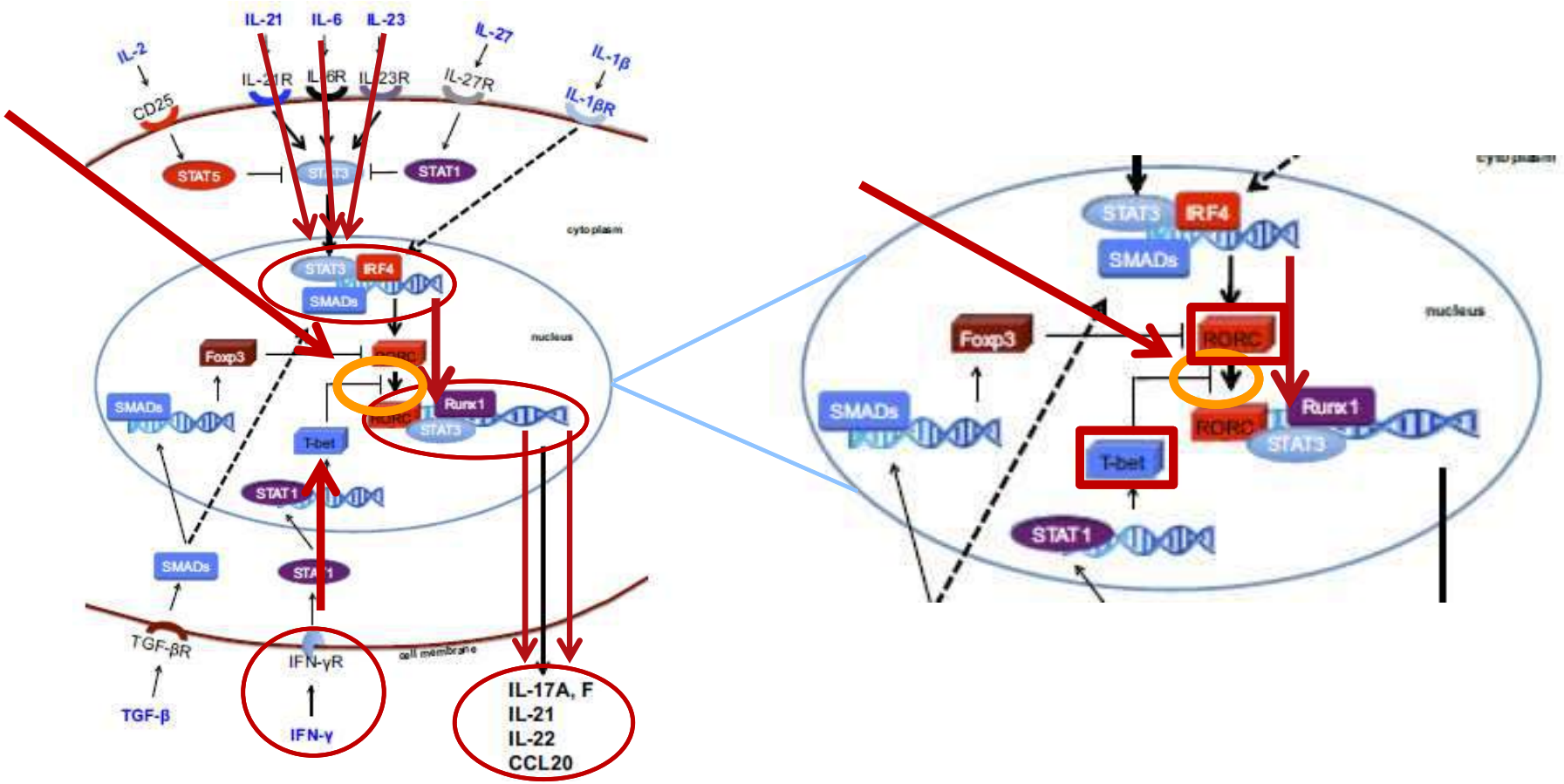
Nat Med. 2007 Feb;13(2):139-45, Steinman L

"A pathway named TH17 is now credited for causing and sustaining tissue damage in these diverse situations. The TH1 pathway antagonizes the TH17 pathway in an intricate fashion.

The evolution of our understanding of the TH17 pathway illuminates a shift in immunologists' perspectives regarding the basis of tissue damage, where for over 20 years the role of TH1 cells was considered paramount."

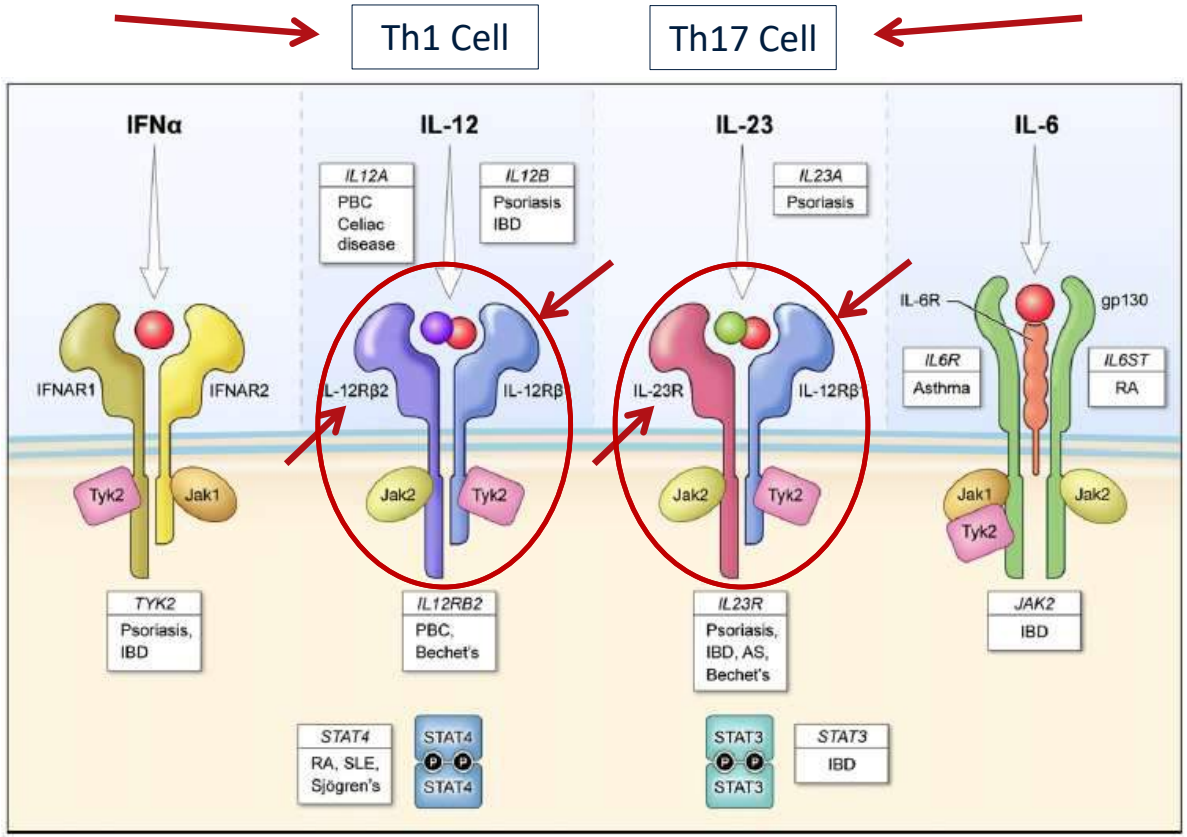
Th17 Cells - Biology, Pathogenesis of Autoimmune and Inflammatory Diseases, and Therapeutic Strategies

Am J Pathol. 2012 Jul;181(1):8-18, Maddur MS, Miossec P, Kaveri SV, Bayry J



JAK and STAT Signaling Molecules in Immunoregulation and Immune-Mediated Disease

Immunity. 2012 Apr 20;36(4):542-50, O'Shea JJ, Plenge R



Th17 Cells - Biology, Pathogenesis of Autoimmune and Inflammatory Diseases, and Therapeutic Strategies

Am J Pathol. 2012 Jul;181(1):8-18, Maddur MS, Miossec P, Kaveri SV, Bayry J

"Th17 cells are critical for the clearance of extracellular pathogens, including Candida and Klebsiella. However, under certain conditions, these cells and their effector molecules, such as IL-17, IL-21, IL-22, GM-CSF, and CCL20, are associated with the pathogenesis of several autoimmune and inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis, inflammatory bowel disease, and allergy and asthma."

Clinical Pearl: Th17 Cells are associated with the pathogenesis of many autoimmune diseases.

Clinical Pearl: Chronic hollow-space pathogen burdens like dysbiosis, sinusitis, chronic URI's, UTI's, etc. >>> persistent Th17 response >>> Autoimmune destruction…

Conflicting Clinical Goals

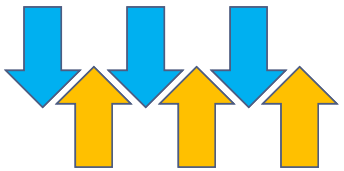
- Autoimmunity?
  - Dampen Autoimmune Attack (Quiet Down the Immune System)

- Infection?
  - Crank Up the Immune Response to Kill Pathogens

- Many autoimmune patients also carry chronic pathogen burdens.
  How do you quiet the immune system while activating the immune system?

Clinical Pearl:

Promoting tolerance alone won't work if there's a pathogen burden.
Killing pathogens alone won't work if you don't also promote tolerance.



TGFβ and

Myeloid Derived Suppressor Cells

TGF-β inhibits the activation and functions of NK cells by repressing the mTOR pathway.

Sci Signal. 2016 Feb 16;9(415):ra19. Viel S, Marçais A, et al.

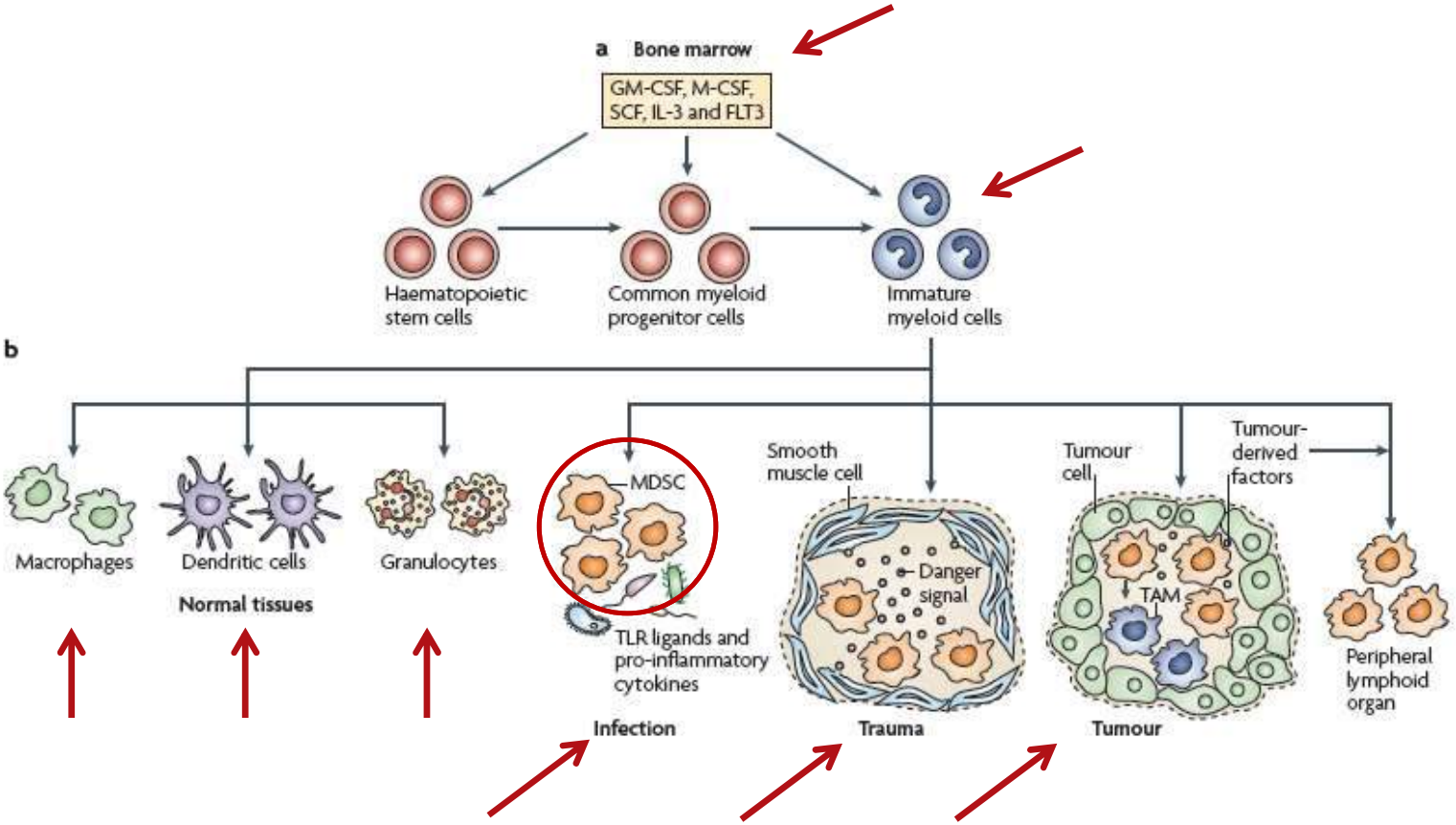
"TGF-β and the mTOR inhibitor rapamycin both reduced the metabolic activity and proliferation of NK cells and reduced the abundances of various NK cell receptors and the cytotoxic activity of NK cells."

Transforming Growth Factor β

- Robustly Tolerogenic
- Normal Housekeeping
  - > Mac phagocytosis of apoptotic neutrophils → TGFβ
    - Debris Clearance during cellular repair from injury or during infection
  - > Tregs
- Hypoxia
- NLRP3 inflammasome activation
  - > Key driver of inflammation and clotting mechanisms that also drives fibrosis in COVID-19
- MDSC's
  - > Copious TGFβ production
    - ROS production
    - Destruction of zeta chains = deactivation of NK cells and T cells (appears to affect Th1 most)
    - Th2 Dom >> ILC2 activation >> MDSC activation
    - Drives fibrosis

Myeloid-derived suppressor cells as regulators of the immune system

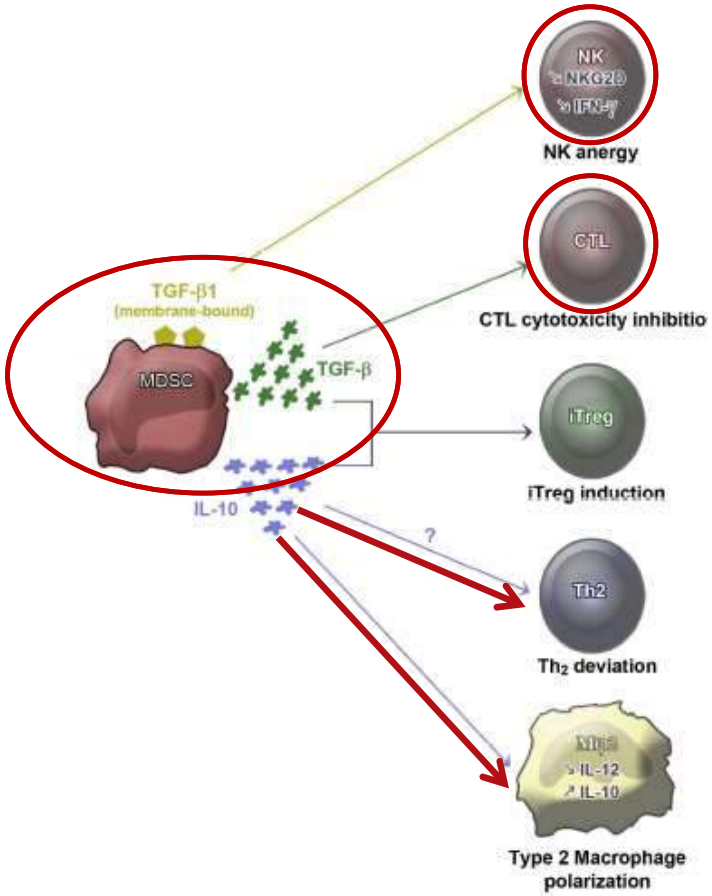
Nat Rev Immunol. 2009 Mar;9(3):162-74. Gabrilovich DI, Nagaraj S.



Myeloid derived suppressor cells: mechanisms of action and recent advances in their role in transplant tolerance

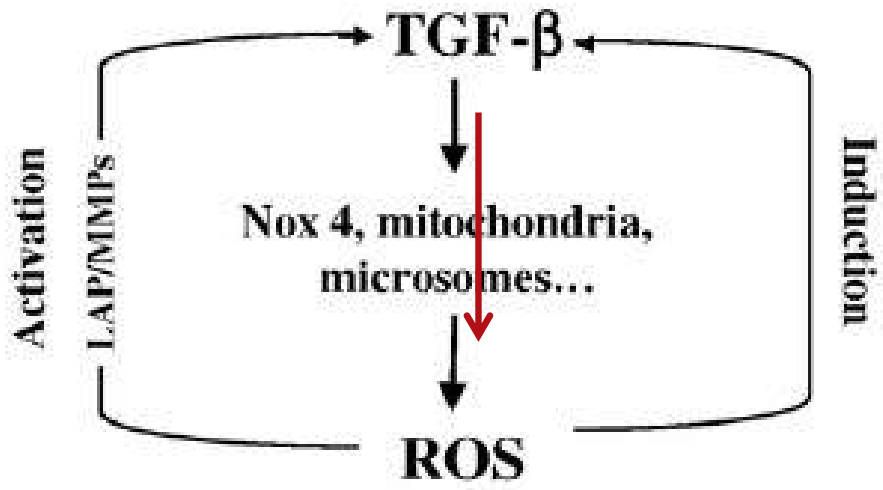
Front Immunol. 2012; 3: 208. Dilek N, Vuillefroy de Silly R, et al.

"Membrane-bound TGF-β1 leads to NK cell anergy, resulting in inhibition of NKG2D and IFN-γ expression."



Oxidative stress and glutathione in TGFβ-mediated fibrogenesis

Free Radical Biology & Medicine 48 (2010) 1–15. Liu RM, Gaston Pravia KA.



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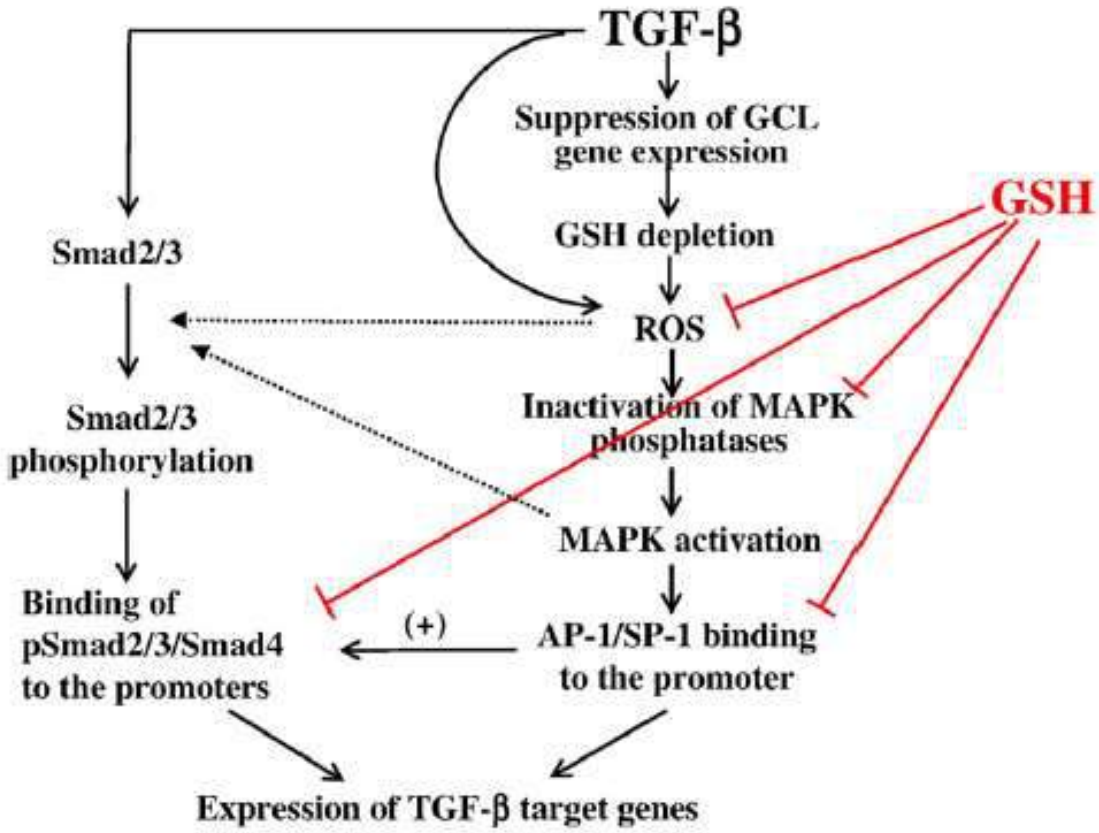


Antiviral and Immunomodulatory Properties of New Pro-Glutathione (GSH) Molecules

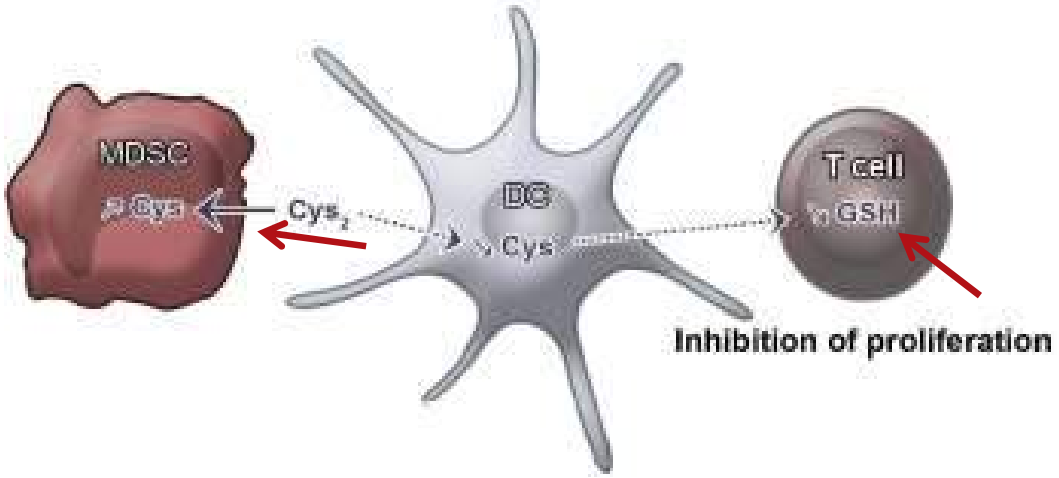
Curr Med Chem. 2006;13(15):1749-55, Fraternale A, Paoletti MF, Magnani M, et al.

"Many antioxidant molecules, such as GSH and N-acetylcysteine (NAC), have been demonstrated to inhibit in vitro and in vivo viral replication through different mechanisms of action. Accumulating evidence suggests that intracellular GSH levels in antigen-presenting cells such as macrophages, influence the Th1/Th2 cytokine response pattern, and more precisely, GSH depletion inhibits Th1-associated cytokine production and/or favours Th2 associated responses."

Myeloid derived suppressor cells: mechanisms of action and recent advances in their role in transplant tolerance

Front Immunol. 2012; 3: 208. Dilek N, Vuillefroy de Silly R, et al.

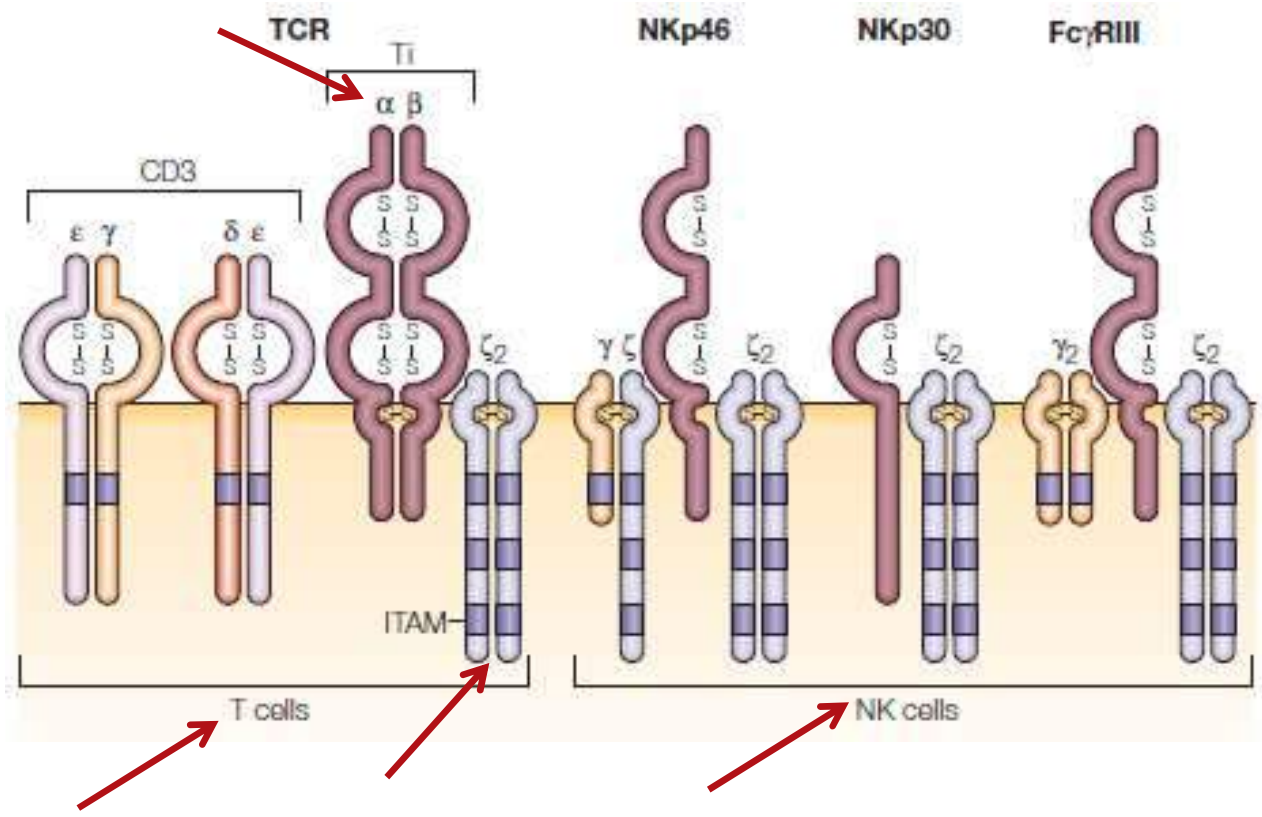
"MDSC compete with dendritic cells for Cys2 import from the extracellular milieu. This prevents DCs from providing sufficient Cys to T cells for GSH production, thus inhibiting T cell proliferation."



Clinical Pearl: Inflammation → MDSC's → CYS Diversion from DC's → Loss of T cell glutathione → Loss of Th1 Status → Th2 Dominance → Expansion of Pathogen Burden → Inflammation

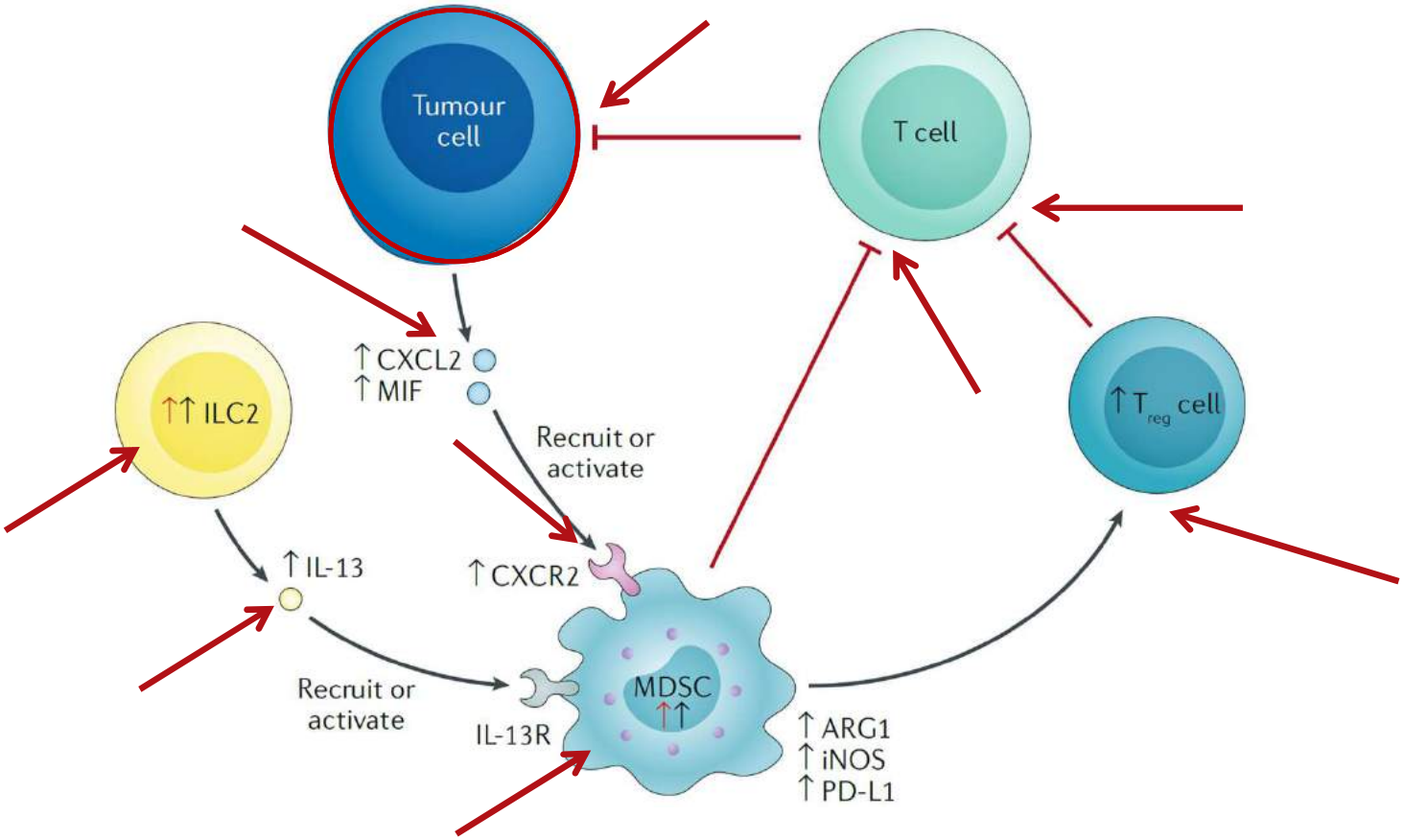
TCR ζ-Chain downregulation: curtailing an excessive inflammatory immune response

Nat Rev Immunol. 2004 Sep;4(9):675-87. Baniyash M.



The multifaceted immune regulation of bladder cancer

Nat Rev Urol. 2019 Oct;16(10):613-630. Schneider AK, Chevalier MF, Derré L.



Why is Th2 Dominance So Common:

Seven Key Ways to Lose Your Th1 Status

Progress and problems in understanding and managing primary Epstein-Barr virus infections.

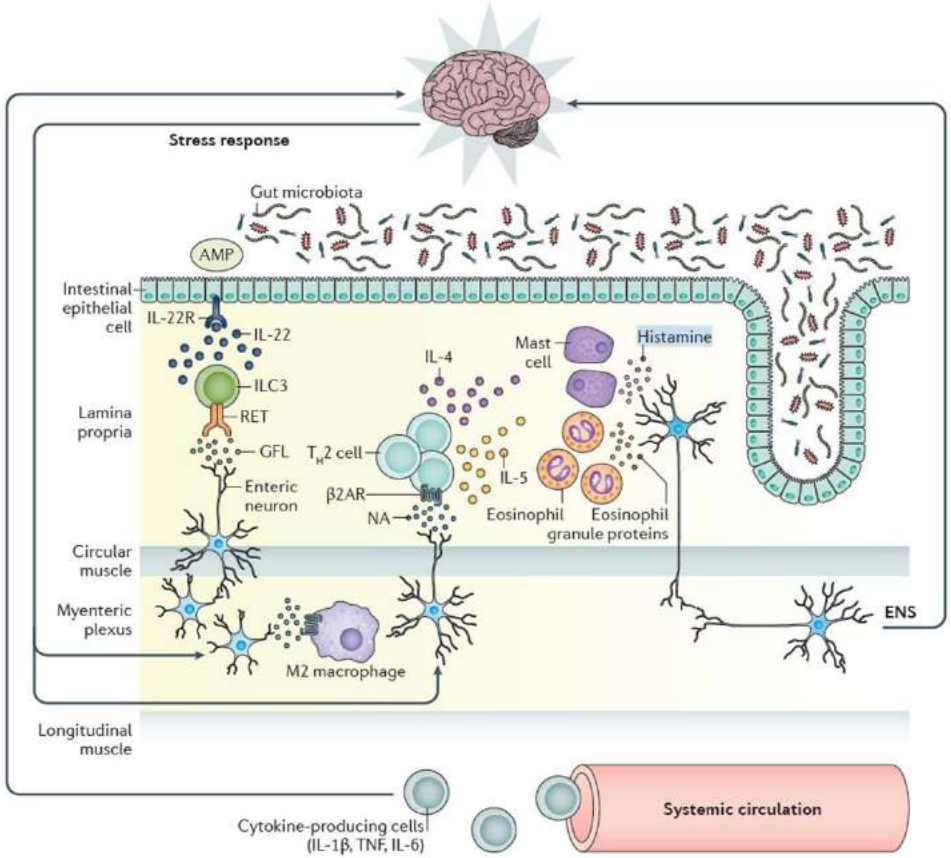
Clin Microbiol Rev. 2011 Jan;24(1):193-209. Odumade OA, Hogquist KA, Balfour HH Jr.

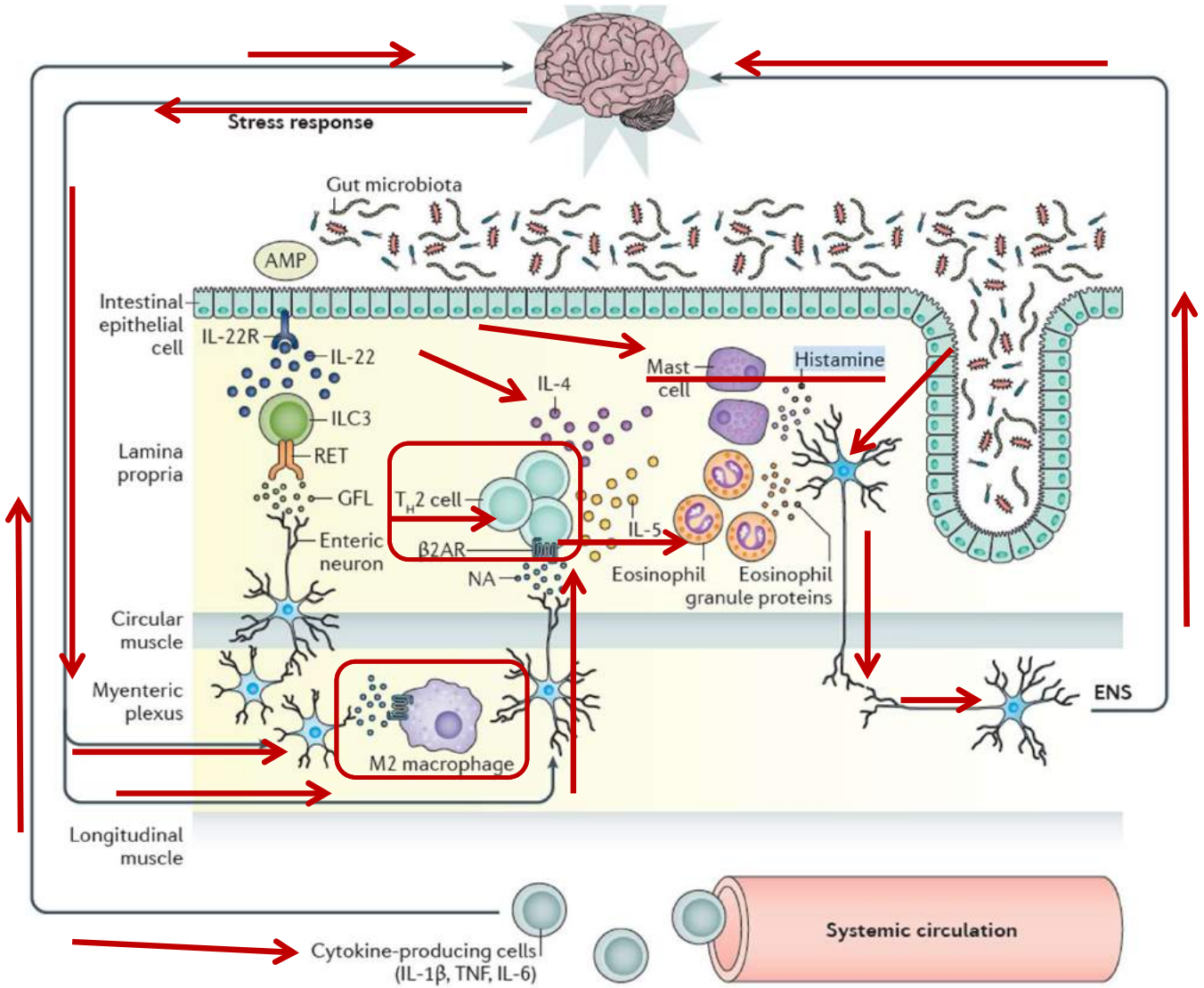
"Epstein-Barr virus (EBV) is a gammaherpesvirus that infects a large fraction of the human population. Primary infection is often asymptomatic but results in lifelong infection, which is kept in check by the host immune system. In some cases, primary infection can result in infectious mononucleosis. Furthermore, when host-virus balance is not achieved, the virus can drive potentially lethal lymphoproliferation and lymphomagenesis. In this review, we describe the biology of EBV and the host immune response."

Clinical Pearl: If you've got a background of viral infection that is jus sitting there, but then you lose your Th1 response, it can bloom out…

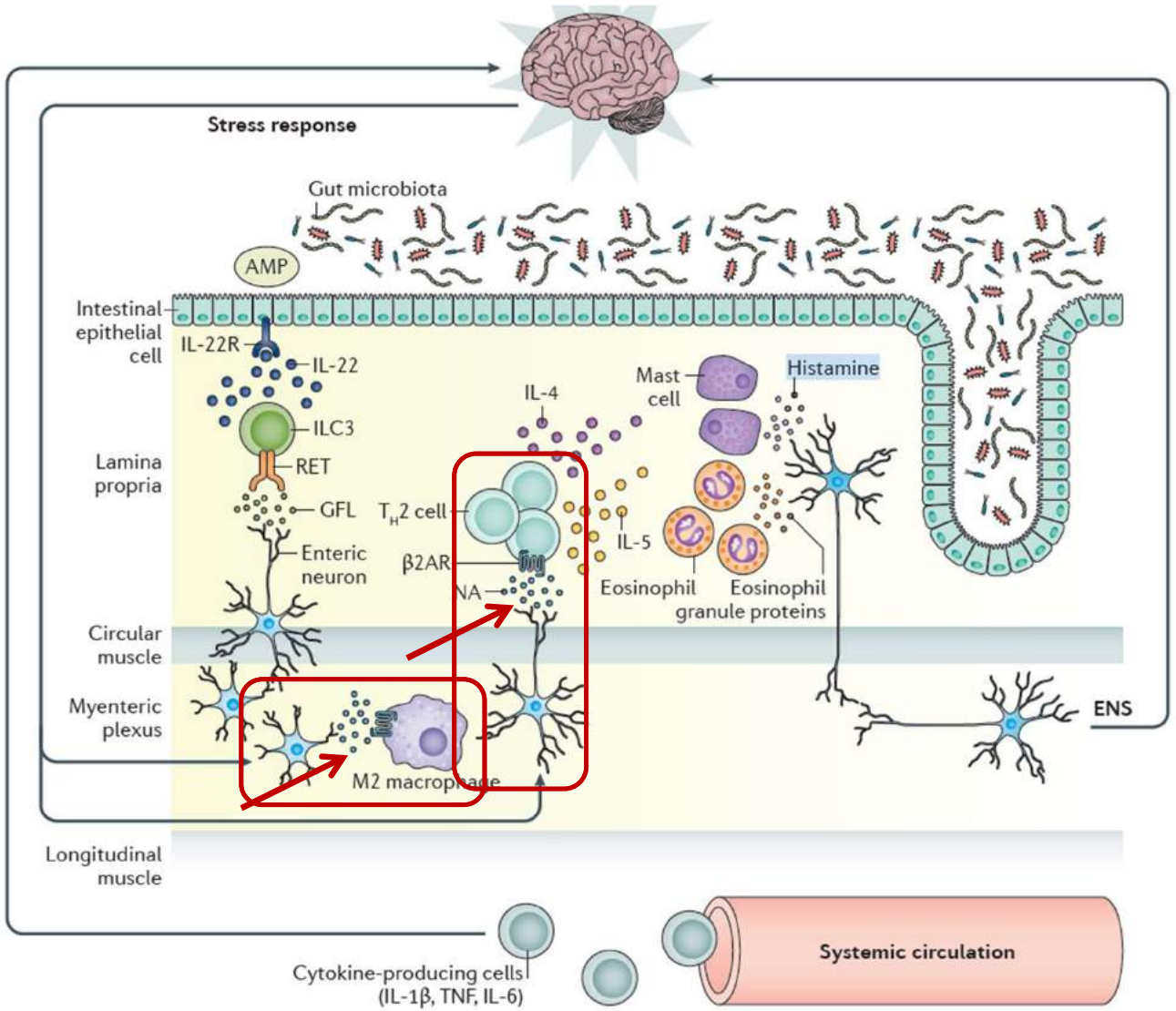
The mucosal immune system: master regulator of bidirectional gut-brain communications

Nat Rev Gastroenterol Hepatol. 2017 Mar;14(3):143-159. Powell N, Walker MM, Talley NJ.





Nat Rev Gastroenterol Hepatol. 2017 Mar;14(3):143-159. Powell N, et al.



Nat Rev Gastroenterol Hepatol. 2017 Mar;14(3):143-159. Powell N, et al.

Th2 cell development and function

Nat Rev Immunol. 2018 Feb;18(2):121-133. Walker JA, McKenzie ANJ.

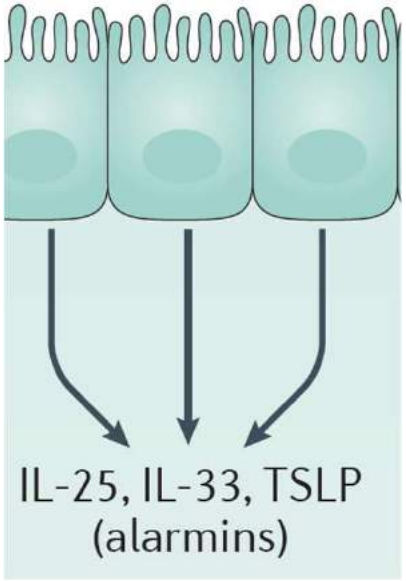
Intestinal Epithelial Inflammation

↓

IL-33, TSLP

↓

Mast Cell Degranulation



IgE and mast cells in allergic disease

Nat Med. 2012 May 4;18(5):693-704. Galli SJ1, Tsai M.

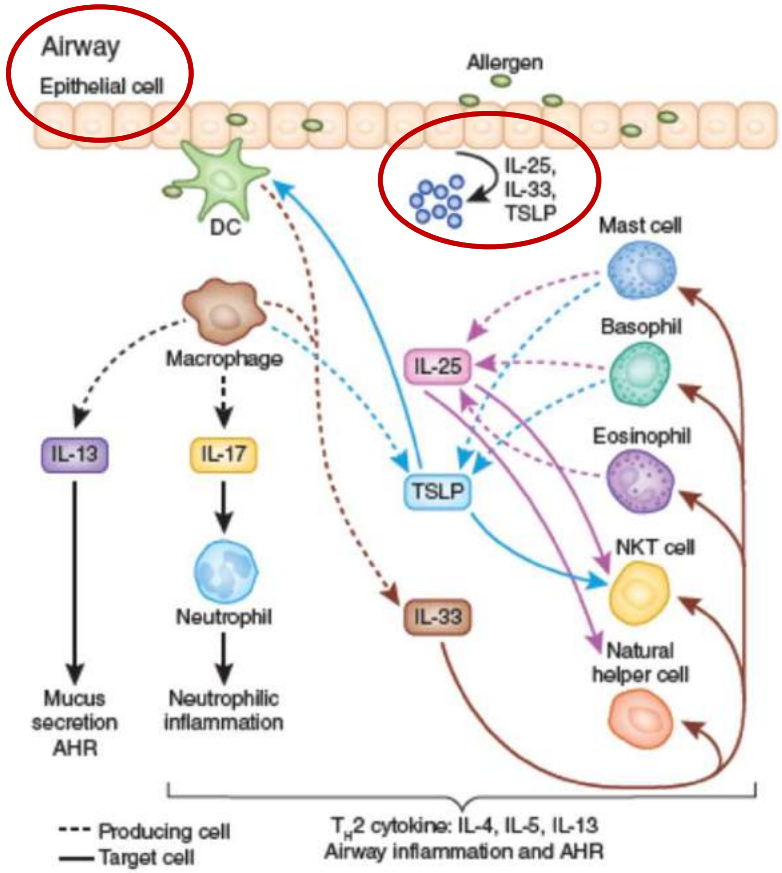
"…both IgE and mast cells are also key drivers of the long-term pathophysiological changes and tissue remodeling associated with chronic allergic inflammation in asthma and other settings. Such potential roles include IgE-dependent regulation of mast-cell functions, actions of IgE that are largely independent of mast cells and roles of mast cells that do not directly involve IgE…

Many additional stimuli can directly activate mast cells and, in some cases, also enhance IgE-dependent mast cell activation, including adenosine, S1P, thymic stromal lymphopoietin (TSLP), IL-33 and many other cytokines, as well as proteases, inflammatory mediators, products of complement activation and exogenous agents, including bacterial toxins."

Clinical Pearl: Patients with mast cell issues will NOT necessarily have high IgE.

The many paths to asthma: phenotype shaped by innate and adaptive immunity

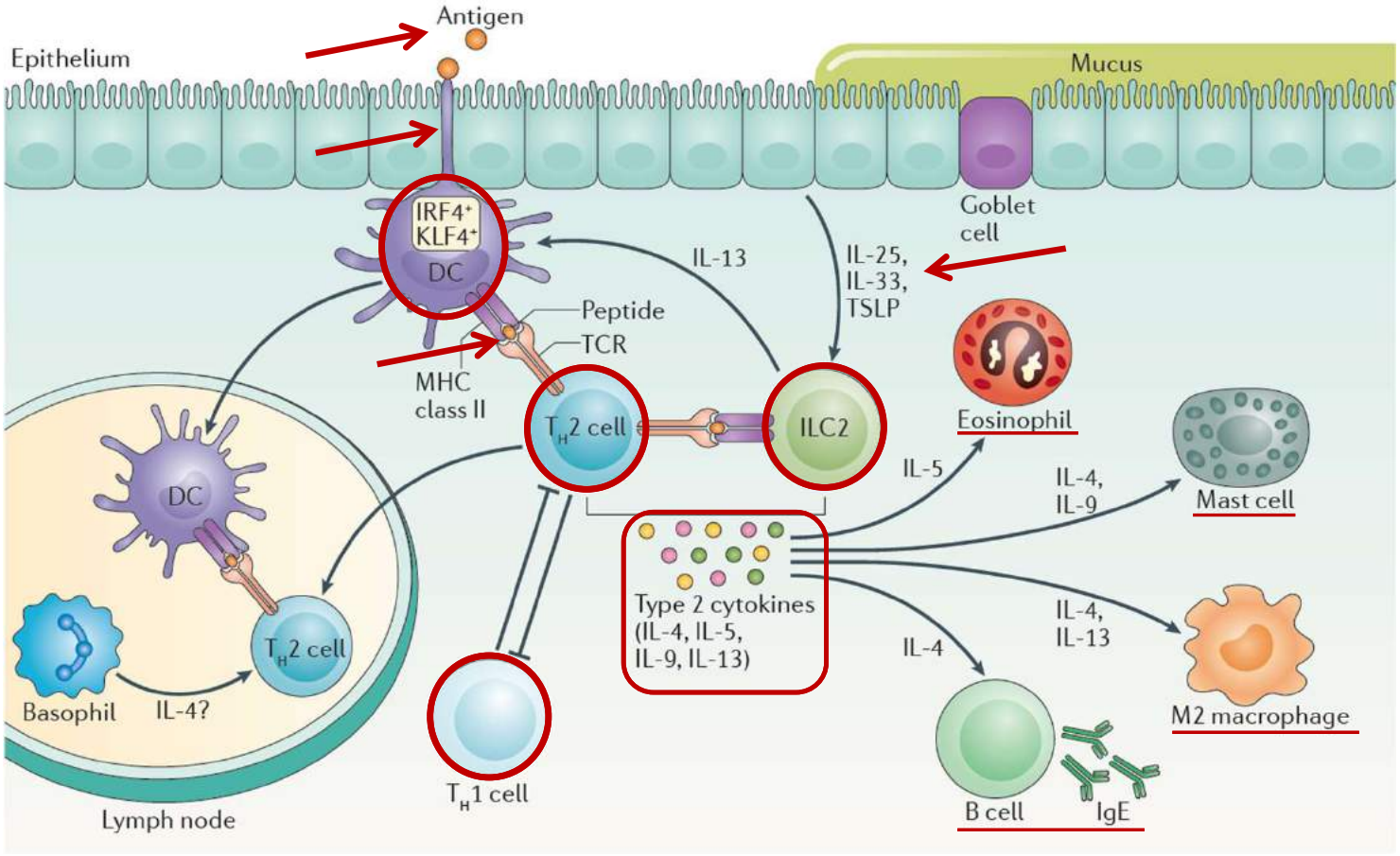
Nat Immunol. 2010 Jul; 11(7): 577–584. Kim HY, et al



Th2 cell development and function

Nat Rev Immunol. 2018 Feb;18(2):121-133. Walker JA, McKenzie ANJ.

Key here is the ILC2's… See how they're promoted by epithelial cells? When GI gets inflamed, this is driven. What do ILC2's do?



Age-related impaired type 1 T cell responses to influenza

J Immunol. 2004 Mar 15;172(6):3437-46. Deng Y, Jing Y, Campbell AE, Gravenstein S.

"The objective of this study was to analyze the changes in the type 1 T cell response, including the CD4+ Th1 and CD8+ T cell responses, to influenza in the elderly compared with those in young adults. PBMC activated ex vivo with influenza virus exhibited an age-related decline in type 1 T cell response, shown by the decline in the frequency of IFN-gamma-secreting memory T cells specific for influenza (IFN-gamma+ ISMT) using ELISPOT or intracellular cytokine staining.

…Taken together, these data demonstrate that there is a decline in the type 1 T cell response to influenza with age that may help explain the age-related decline in vaccine efficacy and the increases in influenza morbidity and mortality."

Age-related change in peripheral blood T-lymphocyte subpopulations and cytomegalovirus infection in the very old: the Swedish longitudinal OCTO immune study

Mech Ageing Dev. 2000 Dec 20;121(1-3):187-201. Olsson J, Wikby A, et al.

"The prevalence of individuals with CMV-IgG antibodies in the very old individuals was 90% (89 individuals out of 98) at Time 1 (1989), 88% (59 individuals out of 67) at Time 3 (1991) and 95% (19 individuals out of 20) at Time 4 (1997). The prevalence of individuals with CMV-IgG antibodies in the middle-aged at these times were relatively consistent at 67% (10 out of 15), 67% (10 out of 15) and 65% (10 out of 14)."

Interactions between corticosteroids and beta-adrenergic agonists in asthma disease induction, progression, and exacerbation.

Am J Respir Crit Care Med. 2000 Mar;161(3 Pt 2):S188-96. Anderson, GP.

"The ability of corticosteroids to effectively suppress IL-12 production has been widely overlooked. These observations are important because they raise the possibility that early intervention with current asthma therapy of β-agonist and steroids, while it will effectively control overt symptoms and inflammation, may "hard wire" immune deviation toward Th2 responses."

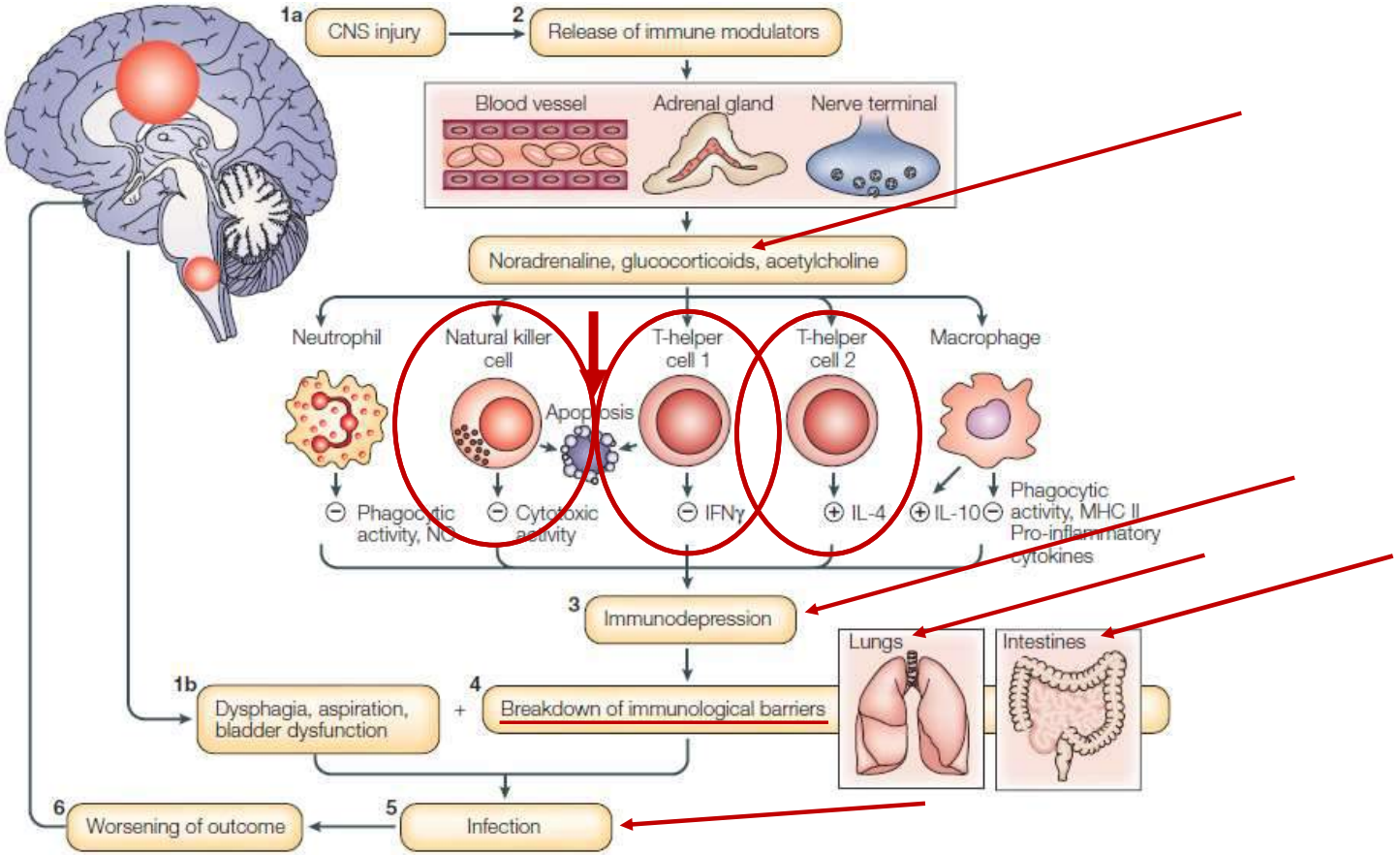
Academic stress-induced changes in Th1- and Th2-cytokine response.

Saudi Pharm J. 2017 Dec;25(8):1237-1247. Assaf AM, Al-Abbassi R, Al-Binni M.

"Psychological stress stimulates physiological responses releasing catecholamines and corticoids, which act via corresponding receptors on immune cells, producing a shift in the cytokine balance. These responses are variable depending on the nature of stressors. The effect of the academic stress on the production of the Th1-cytokines (TNF-α, IFN-γ, IL-1β, IL-2, IL-6 and IL-8) and Th2-cytokines (IL-1ra, IL-4, IL-5 and IL-10) on 35 medical/health sciences students after completing their questionnaires was investigated. Blood samples were taken at three stages; baseline stage at the beginning, midterm and final academic examination stages. Plasma cortisol and cytokines were measured during the three stages. The last two stages were compared with the baseline non-stress period. Results of the stress induced during the final examination stage were the highest with a significant increase in cortisol release, IL-4, IL-5 and IL-1ra release with a shift in Th1:Th2 cytokines balance towards Th2."

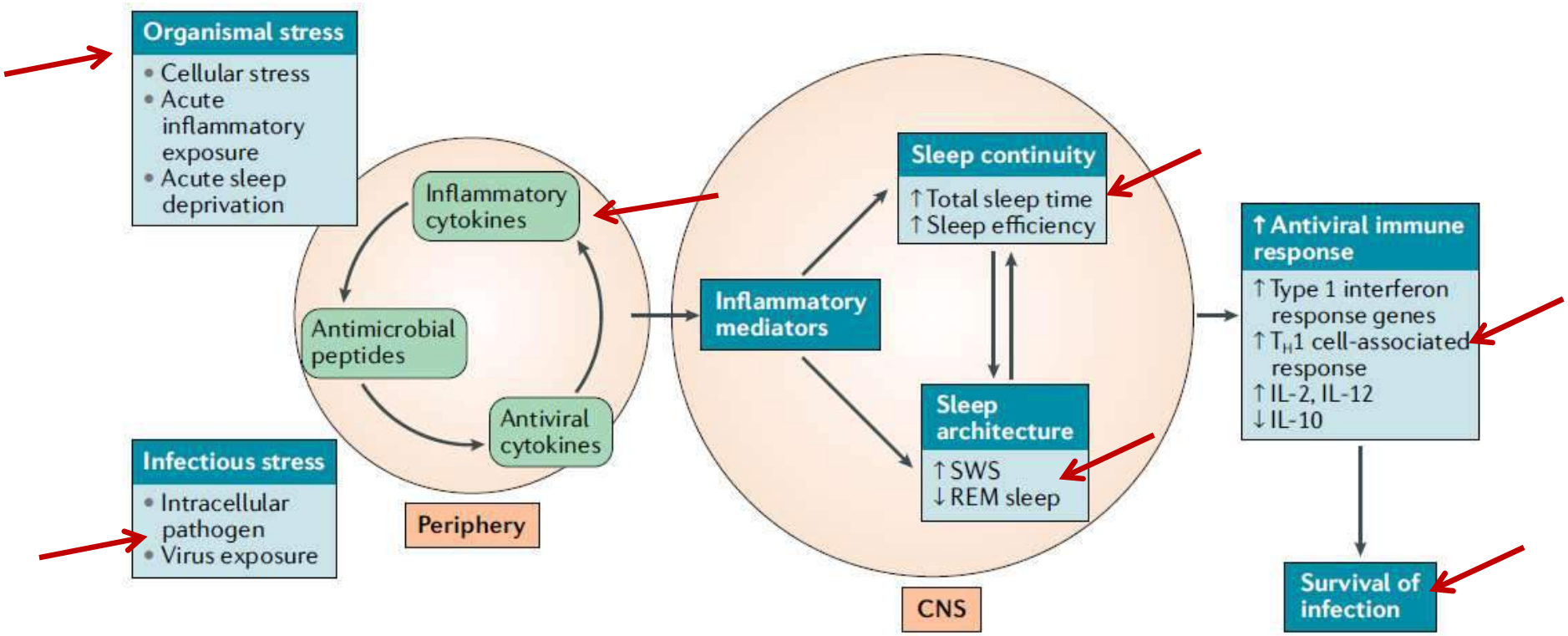
Central nervous system injury-induced immune deficiency syndrome

Nat Rev Neurosci. 2005 Oct;6(10):775-86. Meisel C, et al



Sleep and inflammation: partners in sickness and in health.

Nat Rev Immunol. 2019 Nov;19(11):702-715. Irwin MR.



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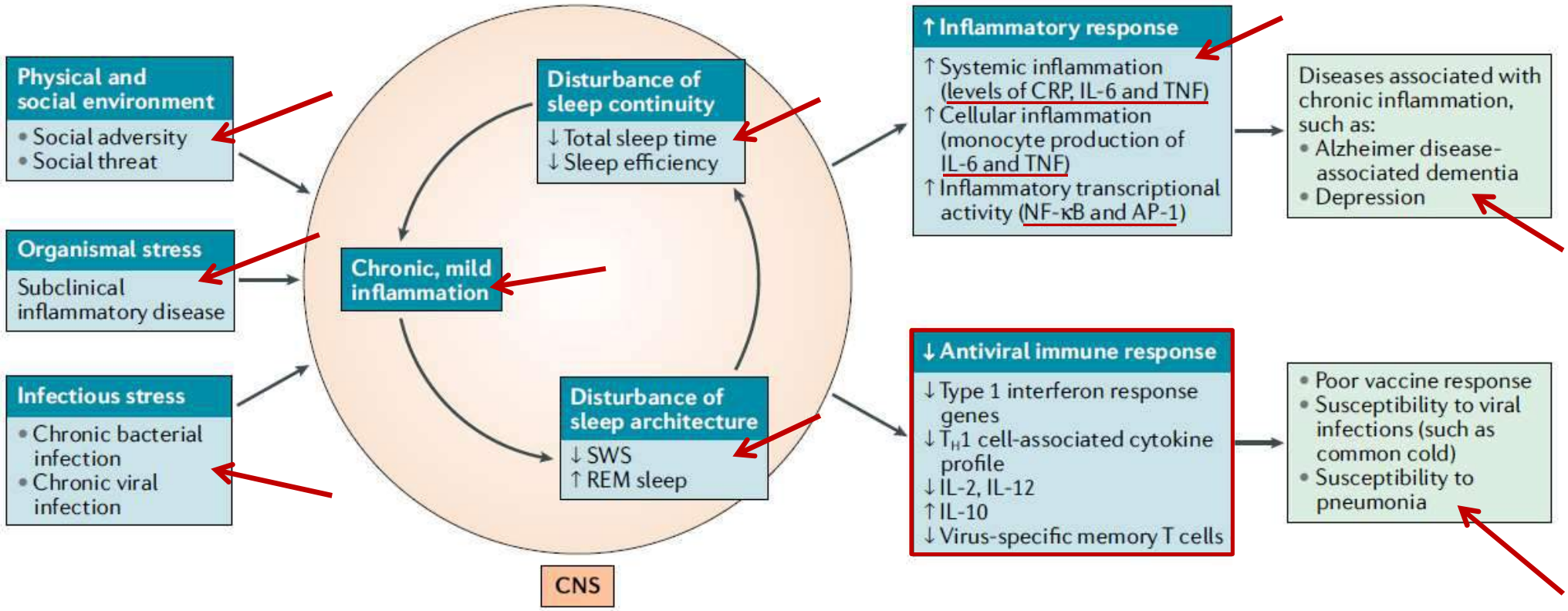

The endocrine disruptors nonylphenol and octylphenol exert direct effects on T cells to suppress Th1 development and enhance Th2 development

Immunol Lett. 2004 Jun 15;94(1-2):135-9, Iwata M, Eshima Y, Kagechika H, Miyaura H

"We chose alkylphenols that have been widely used as plastic additives and surfactants, and some of them are recognized as xenoestrogens. We examined whether they exert direct effects on T cells to suppress or enhance Th1/Th2 development.

…1–10M of p-n-nonylphenol suppressed Th1 development and enhanced Th2 development, whereas estrogen by itself failed to affect Th1/Th2 development. p-n-Octylphenol elicited similar effects, but 4-nonylphenol and p-t-octylphenol elicited much weaker effects. p-n-Dodecylphenol or p-n-octylbenzene failed to affect Th1/Th2 development. Thus, the length and branching of the alkyl side chain appeared to affect the activity."

Endocrine disruptors that deplete glutathione levels in APC promote Th2 polarization in mice leading to the exacerbation of airway inflammation

Eur J Immunol. 2006 May;36(5):1199-209, Kato T, Tada-Oikawa S, Kuribayashi K, et al.

"Endocrine-disrupting chemicals (EDC) are ubiquitous in environment and may have various undesirable effects on human health… In the present study, we have shown that some EDC [benzophenone, p-octylphenol, and tributyltin chloride (TBT)] promoted strong Th2 polarization via suppression and augmentation of Th1 and Th2 development, respectively, from naive CD4+ T cells primed with anti-CD3 and splenic antigen-presenting cells (APC). The effect was indicated to be indirect via suppression of IL-12 production and augmentation of IL-10 production of APC, which are critical for the Th1 and Th2 development, respectively."

Endocrine disruptors that deplete glutathione levels in APC promote Th2 polarization in mice leading to the exacerbation of airway inflammation

Eur J Immunol. 2006 May;36(5):1199-209, Kato T, Tada-Oikawa S, Kuribayashi K, et al.

"Such modulation of cytokine production by EDC was associated with reduction of intracellular glutathione levels in APC. IL-10 deprivation or the addition of N-acetylcysteine, which replenishes intracellular glutathione level during priming, cancelled the effect of EDC on the promotion of Th2 polarization.

Clinical Pearl:

Endocrine Disrupting Chemicals >> ↓ Glutathione > ↓ IL-12 > ↓ Th1 Response >> ↑ Th2

Steve – 72 y. o. male – with GI sx.

FM Symptom Inventory –

- S/P bypass surgery after years of normal annual executive workups
- Lives on a golf course
- GI Bloating and discomfort
- Hx of high stress

Labs Include:
ASCA 37.6 H; ANCA 93.3 H;

Viral loads:
HSV1 IgG 42.3 H; (42x the range)
EBV VCA IgG >600, EBNA 362, EBV EA 9.3;
CMV IgG 8.4 H; (>10x the range)

Pesticide Exposure >> Loss of Th1 >> Expansion of Viral Loads >> Inflammation >> CAD Inflammation + Expanded Viral Loads >> Autoimmunity (IBD)

Cogence

Monocyte recruitment during infection and inflammation.

Nat Rev Immunol. 2011 Oct 10;11(11):762-74. Shi C, Pamer EG.

"Aspergillus fumigatus is an inhaled fungal pathogen that can cause invasive infections in immunocompromised patients. A. fumigatus spores are common in the environment and are inhaled on a daily basis. In some individuals, A. fumigatus induces TH2 cell responses that exacerbate asthma and lead to allergic bronchopulmonary aspergillosis."

Staphylococcal enterotoxin B increases TIM4 expression in human dendritic cells that drives naïve CD4 T cells to differentiate into Th2 cells.

Mol Immunol. 2007 Jul;44(14):3580-7. Liu T, et al.

"Here we report that a significant increase in TIM4 expression in human DCs was observed in response to Staphylococcal enterotoxin B (SEB) stimulation via Toll-like receptor (TLR)2 and nucleotide-binding oligomerization domain (NOD)1 pathway. Coculture SEB-conditioned DCs with naïve CD4 T cells induced Th2 responses that could be abolished using TLR2 or NOD1 or TIM4 or TIM1 with counterpart antibodies or RNA interference. The results demonstrate that Staphylococcus aureus derived SEB promotes the TIM4 production in human DCs. The interaction between TIM4 and TIM1 drives naïve CD4 T cells to develop to Th2 cells."

Interplay between Candida albicans and the mammalian innate host defense.

Infect Immun. 2012 Apr;80(4):1304-13. Cheng SC, Joosten LA, Kullberg BJ, Netea MG.

"Recently, we have also reported the active role played by soluble factors released by C. albicans.

…the conditioned medium downregulated host IFN-γ synthesis yet upregulated IL-10 production, thus shifting the T helper cell response from a beneficial Th1 response to a detrimental Th2 response."

How does this apply to COVID-19?

If you've spent your professional life working with chronically ill patients,
the potential for a fast shift toward imminent demise risks leaving you flat footed.
Don't let it do that.

The usual cycle of giving the patient instructions and
having them check back with you in a few weeks
to see how they did with your instructions
does not apply here.

Cogence

Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery

Yanuck SF, Pizzorno J, Messier H, Fitzgerald KN. IMJC, April 2020.

Four Phases of COVID-19

Clinicians will encounter patients in one of four phases of COVID-19, each requiring its own focus.

- **Prevention** - support is focused on immune surveillance efficiency and reduction of baseline levels of inflammation, to improve outcomes if the patient becomes infected,
- **Infection** - support emphasizes immune activity against infection,
- **Escalating Inflammation** - support is focused on anti-inflammatory measures, and
- **Recovery** - support is focused on resolving inflammation, inhibiting fibrosis and other forms of tissue damage, curtailing losses of function, and restoring and reoptimizing function.

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Yanuck SF, Pizzorno J, Messier H, Fitzgerald KN. IMJC, April 2020.

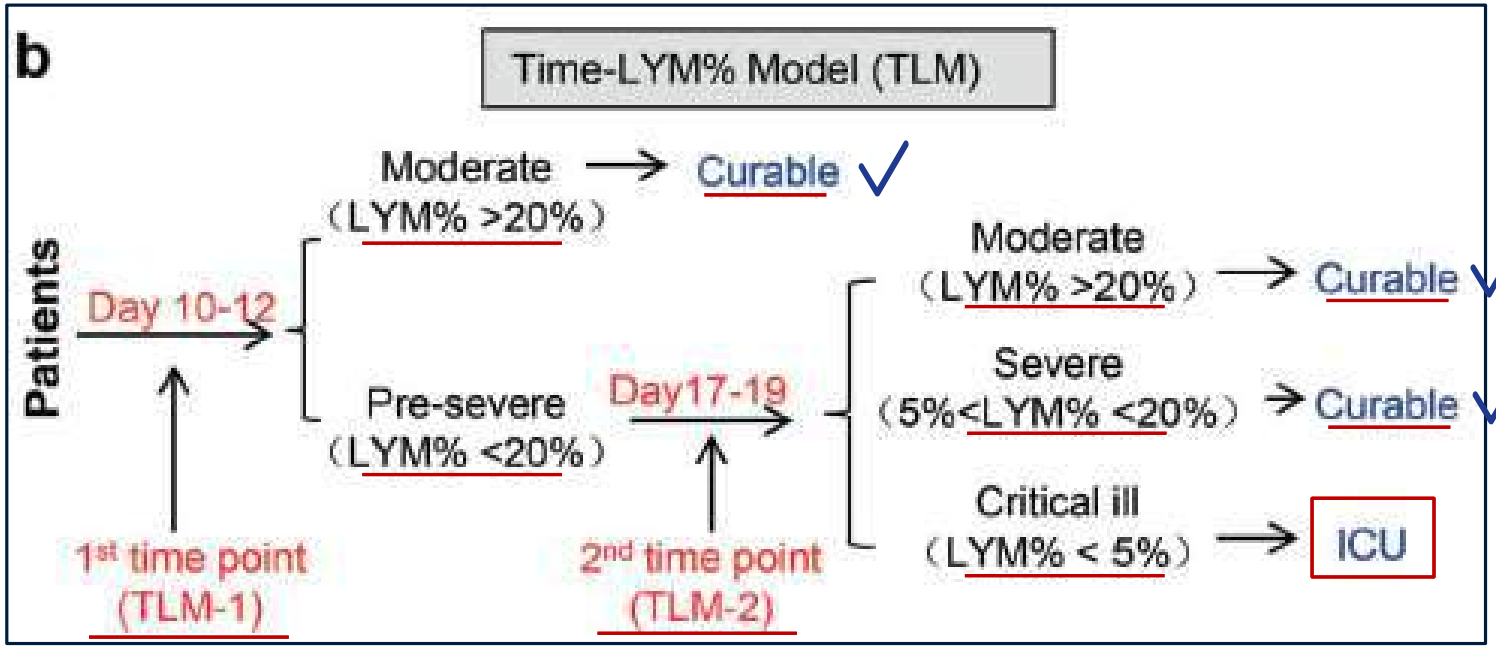
"Emerging evidence in COVID-19 suggests that the SARS-CoV-2 virus may both evade the innate immune response and kill macrophages. Delayed innate immune response and a depleted population of macrophages can theoretically result in a blunted antigen presentation, delaying and diminishing activation of the adaptive immune response. Thus, one clinical strategy involves supporting patient innate and adaptive immune responses early in the time course of illness, with the goal of improving the timeliness, readiness, and robustness of both the innate and adaptive immune responses."

Early Risk = virus delays / kills macs

>> virus gets ahead and immune system can't catch up.

Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study.

Signal Transduct Target Ther. 2020 Mar 27;5:33. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al.



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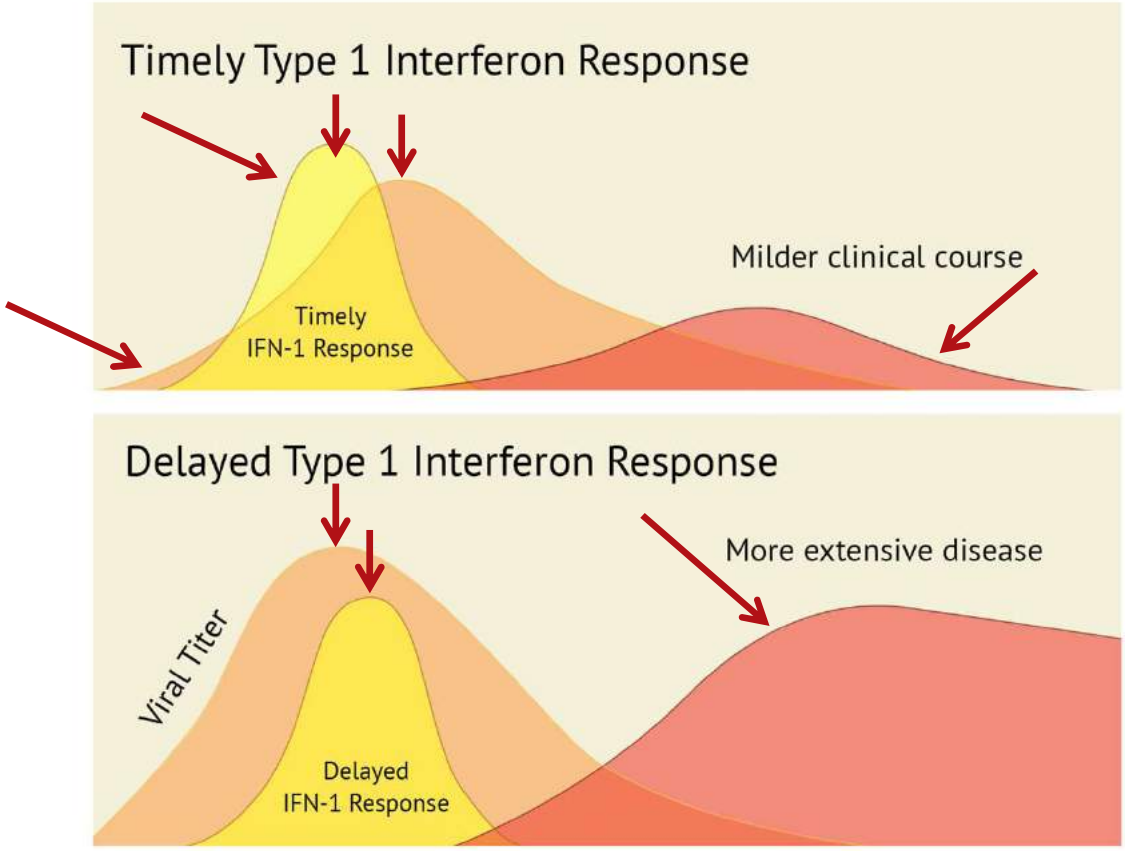

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Yanuck SF, Pizzorno J, Messier H, Fitzgerald KN. IMJC, April 2020.

"At the other end of the disease pathology spectrum, risk of fatality in COVID-19 is driven by excessive and persistent upregulation of inflammatory mechanisms associated with cytokine storm. Thus, the second clinical strategy is to prevent or mitigate excessive inflammatory response to prevent the cytokine storm associated with high mortality risk."

Late Risk = Inflammation & ROS Activation

>> Clotting / Thick Mucous / Sepsis >> Microvascular damage to epithelia & endothelia

>> organ damage / death or fibrotic sequelae

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Early Risk = virus delays / kills macs

>> virus gets ahead and immune system can't catch up.

Early Goal >> Mac / NK / Th1 Activation

Late Risk = Inflammation & ROS Activation

>> Clotting / Thick Mucous / Sepsis >> Microvascular damage to epithelia & endothelia >> organ damage / death or fibrotic sequelae

Late Goal >> Reduce Inflammation / ROS / Neutrophils / Fibrosis

Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery

Yanuck SF, Pizzorno J, Messier H, Fitzgerald KN. IMJC, April 2020.

"…every immune response against pathogens carries with it, inherently, an incremental increase in inflammatory cytokine activation.

…Any and all methods of stimulating, activating and enhancing the immune system's ability to recognize and kill any pathogen, including the SARS-CoV-2 virus, will of necessity involve the immune system generating a cellular and biochemical response, not limited to but including appropriate production of inflammatory cytokines."

Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery

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Adequate activation >> appropriate immune response
>> pathogen eradication & triggering of resolution phase chemistry >> resolution

Excessive activation >> epithelial & endothelial tissue damage
>> DAMPs/PAMPs >> further inflammatory cytokine generation
>> increased influx of immune elements (neutrophils, macrophages, etc.)
>> more damage >> loop (failure of resolution)

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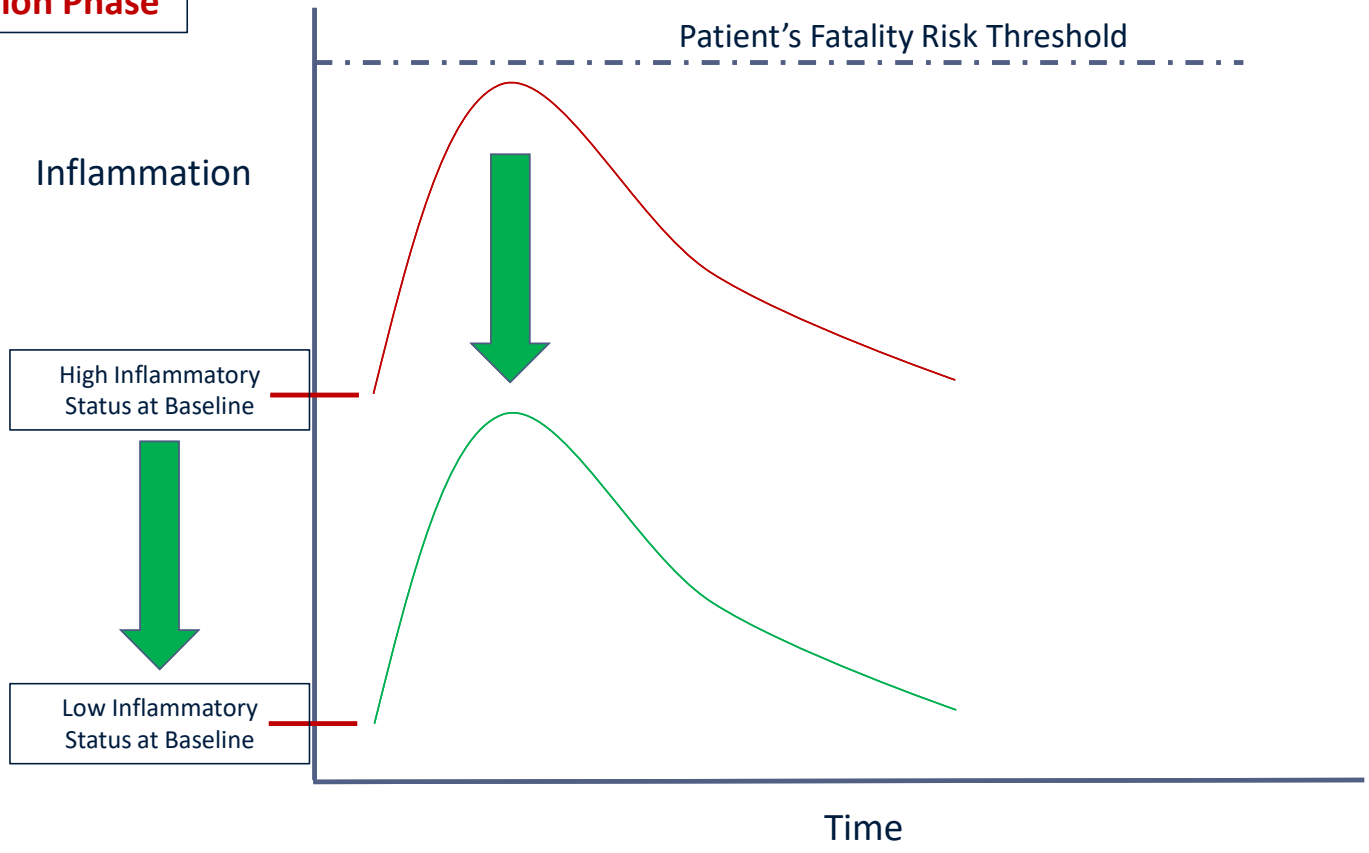
Prevention Phase

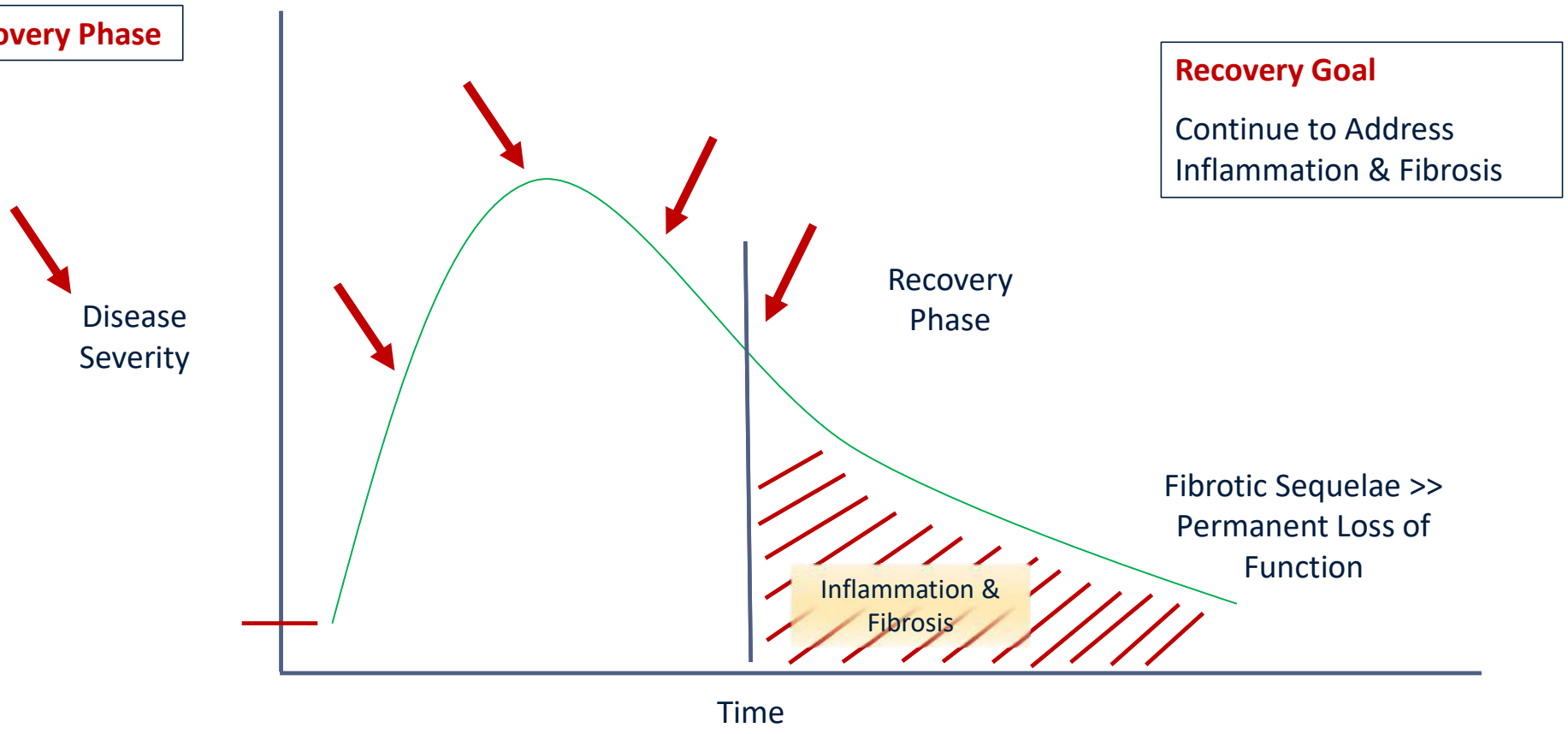


Prevention Goal

Eliminate Non-Purposeful Inflammation

Recovery

Recovery Phase



Recovery Goal

Continue to Address Inflammation & Fibrosis

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"Disease sequelae, including persistent organ dysfunction, are a significant concern, particularly related to acute lung injury and fibrosis. In SARS-CoV-1, 20% of recovered patients had fibrotic disease nine months post infection. Given the apparent role of the NLRP3 inflammasome in COVID-19, and the role of NLRP3 in driving TGFβ-mediated fibrosis mentioned already, it becomes essential to attend to the patient's potential need for persistent downregulation of inflammasome biology, with the goal of mitigating risk of additional consequences from non-lethal but nonetheless life changing sequelae related to lingering inflammatory and fibrotic effects that occur in the tail of the curve after the crescendo of disease has passed. As mentioned above, because patients have been observed to relapse into the Escalating Inflammation Phase, it is essential for clinical surveillance to continue well into what may appear to be the Recovery phase."

Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery

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"These Phases and their corresponding clinical imperatives are interconnected and bidirectional. There is both a sequencing as the patient transitions between them and an order of importance of tactics to address each of them, addressed in the tables that describe the tactics. If the patient becomes infected, the very same clinical goals that are appropriate to the Prevention Phase (avoiding infection and early virus clearance) will continue to apply as in the Infection Phase. The key tactical transition occurs if the patient enters the Escalating Inflammation Phase."

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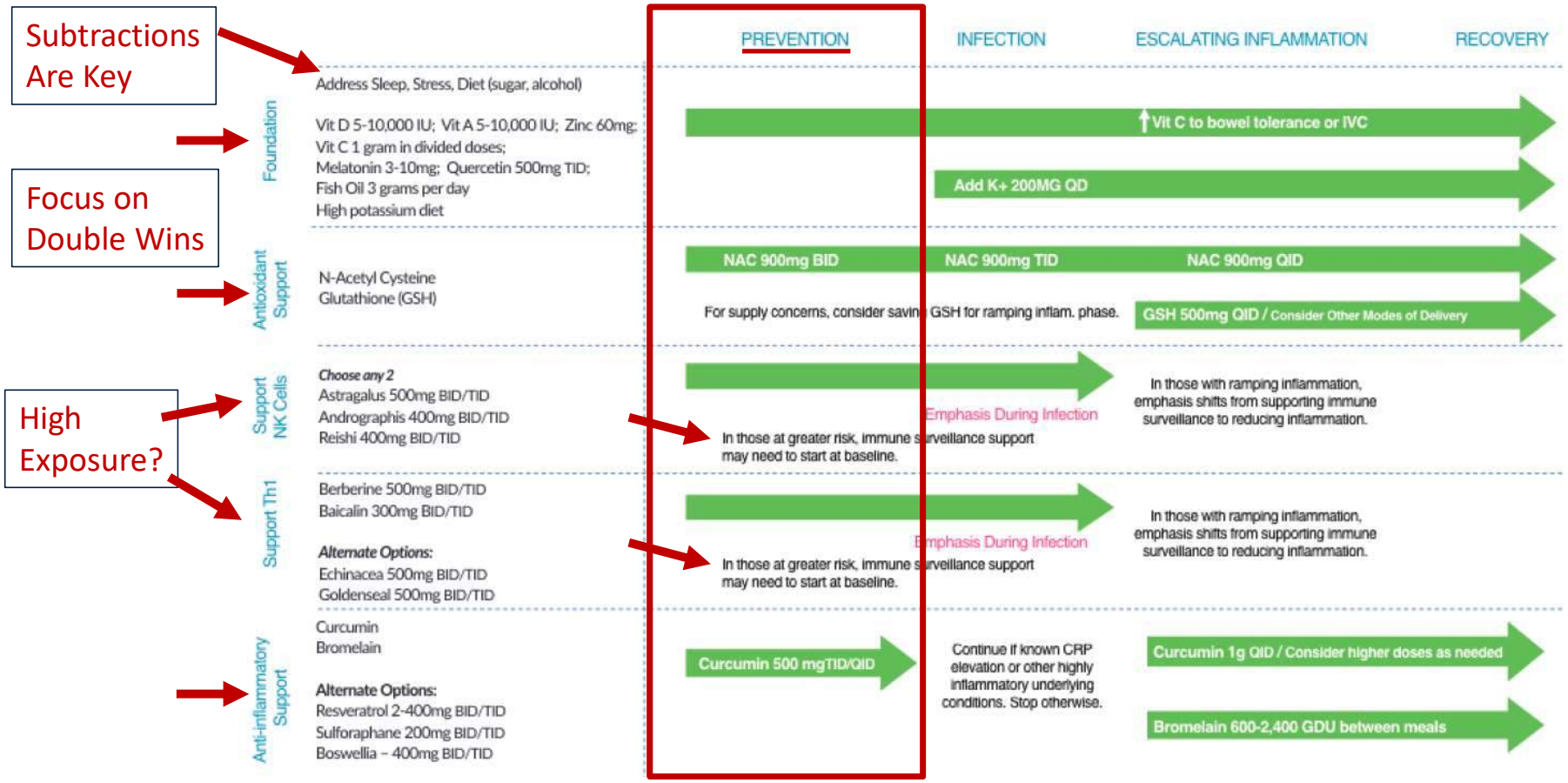

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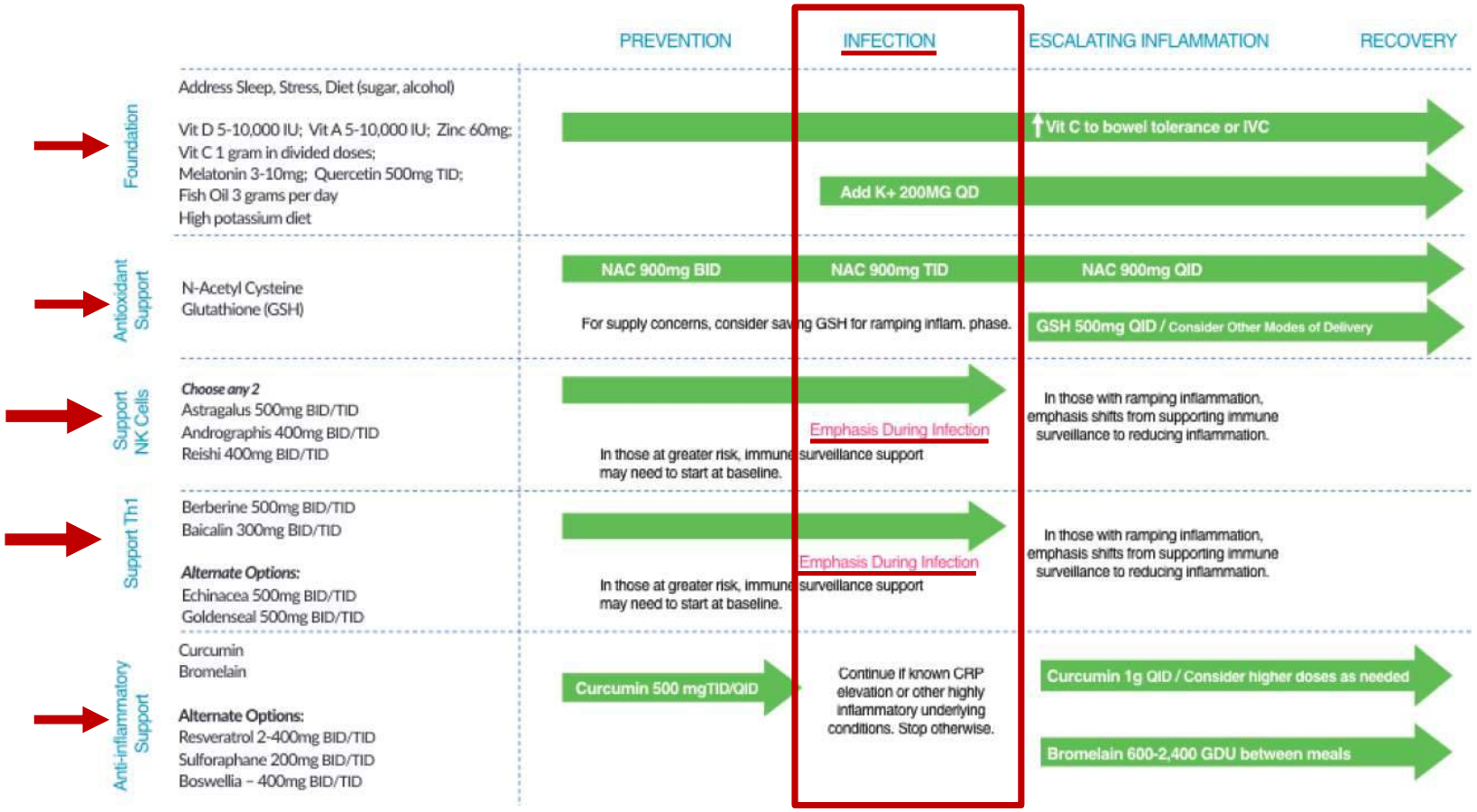

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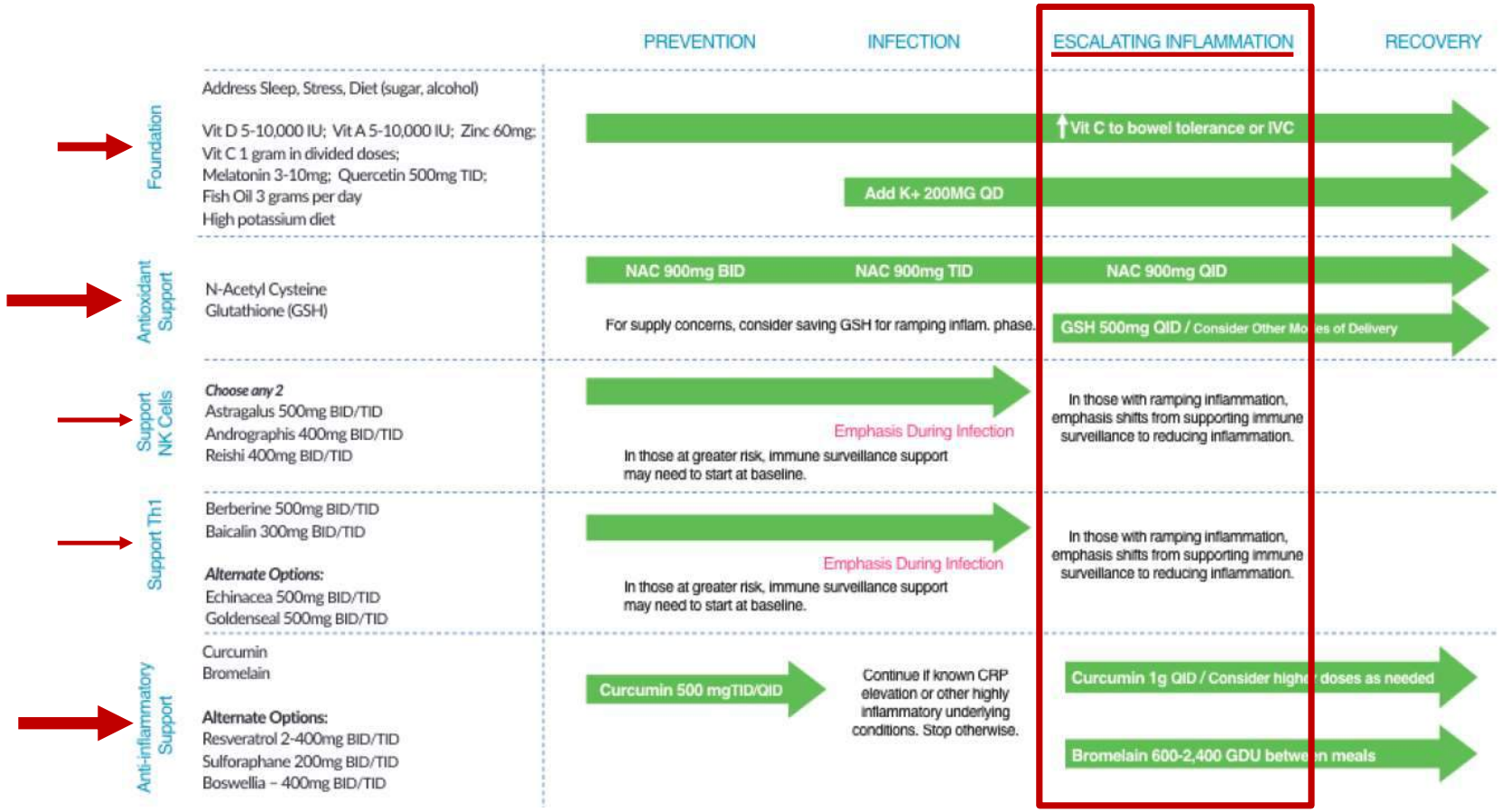

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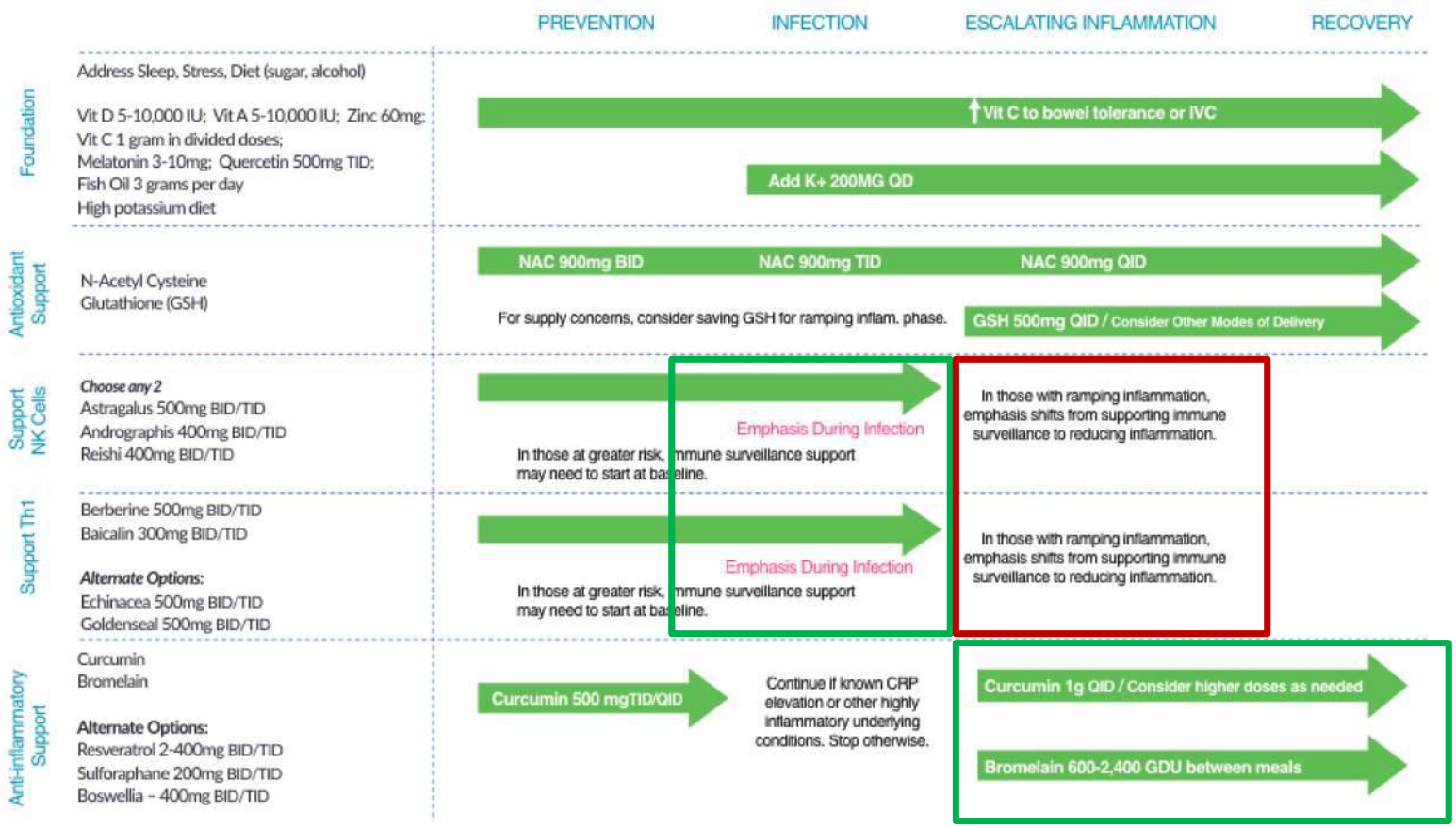

Assessing Viral Burdens

Cytomegalovirus Antibody Level and Mortality Among Community-Dwelling Older Adults With Stable Cardiovascular Disease

JAMA. 2009 Jan 28;301(4):380-2. Strandberg TE, Pitkala KH, Tilvis RS.

"These findings support an independent association between CMV IgG antibody level and 7-year mortality in community-living older adults. The association was independent of *H pylori* infection and C-reactive protein level, suggesting a specific effect of CMV rather than infection or inflammation. Study limitations include all participants having a history of stable cardiovascular disease, which may limit the generalizability. Also, we measured anti-CMV antibody titers, not viral load."

Evaluating the performance of the focus HerpeSelect® HSV-2 IgG in veterans with chronic hepatitis C infection.

J Med Virol. 2015 Aug;87(8):1377-81. Burton M, Van Wagoner NJ, Hook EW 3rd.

"Epidemiologic links between chronic hepatitis C and herpes simplex type-2 infection have been suggested; however, type-specific tests for HSV-2 infection have not been validated in patients with chronic hepatitis C infection. The Focus HerpeSelect(®) HSV-2 IgG (Cypress, California) assay and the Biokit HSV-2 rapid assay (Biokit USA, Lexington, MA) were performed on serum samples obtained from 84 veterans with chronic hepatitis C who demonstrated a previously positive HSV-2 serologic test in their medical records. Using the Biokit HSV-2 as the comparator assay, the positive predictive value, and specificity for the HerpeSelect(®) HSV-2 assay were 62.1% (95%CI: 49.3-73.8) and 41.9% (95%CI: 27.0-57.9), respectively. Increasing the HerpeSelect(®) HSV-2 index value defining a positive test result from >1.1 to ≥2.89 increased the assay's specificity to 97.7% (95%CI: 87.7-99.6) and the positive predictive value to 94.1%(95%CI: 71.2-99.0)."

Use of valganciclovir in patients with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein-Barr Virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue.

J Clin Virol. 2006 Dec;37 Suppl 1:S33-8. Kogelnik AM, Loomis K, Montoya JG, et al.

"We sought to determine whether elevated antibodies to EBV and HHV-6 indicated chronic viral activation in patients with CNS dysfunction and if their symptoms could be improved by suppressing viral activity with oral valganciclovir.

Patients with high IgG antibody titers against HHV-6 and EBV who were suffering from central nervous system dysfunction and debilitating fatigue for more than one year (median 3 years, range 1-8 years) were treated with 6 months of valganciclovir in an open label study."

"Nine out of 12 (75%) patients experienced near resolution of their symptoms, allowing them all to return to the workforce or full time activities."

Use of valganciclovir in patients with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein-Barr Virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue.

J Clin Virol. 2006 Dec;37 Suppl 1:S33-8. Kogelnik AM, Loomis K, Montoya JG, et al.

"Since HHV-6 is typically acquired by the age of two and EBV is generally acquired in early childhood or as a young adult, we interpreted the elevated titers as a sign of reactivated rather than primary infection. The antibody titers of the patients were considerably higher than those in 12 healthy controls, tested in the same laboratory."

""Molecular assays available in clinical laboratories were not informative. None of the responding patients was positive for HHV-6 or EBV DNA using an assay capable of detecting as few as 200 copies/ml. DNA of these viruses is typically detected only during a primary or acute infection."

Clinical Approach

Clinical Approach

- Address factors that promote Th2 dominance
- Support healthy Th1 Cell status
  - Berberine
  - Baicalin (Chinese skullcap)
  - Sulforaphane
  - Ginger
- Support healthy NK Cell status
  - Reishi (Ganoderma)
  - Andrographis
  - Astragalus
  - Vitamin C
  - Black Currant Seed Oil
- Downregulate Excessive TGFβ
  - Glutathione
  - Reduce Th2 response / ILC2 activation of MDSC's
  - NLRP3 inhibition: resveratrol, berberine, curcumin, sulforaphane, low glycemic diet, etc.

Functional Immunology Applications In Viral Illness

Samuel F. Yanuck, DC, FACFN, FIAMA

CEO, Director of Education, Cogence Immunology

Adjunct Assistant Professor
Department of Physical Medicine and Rehabilitation
University of North Carolina School of Medicine

Clinic Director, The Yanuck Center for Life & Health