Clinical Management of the "Infected & Autoimmune" Conundrum in Autoimmune Encephalopathies

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Most Autoimmune Encephalitis Patients… have Autoimmunity *and* Infection

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.

What to Expect…

"If only I could find the magic key..."

What to Expect…

"What parts do I need to build this engine..."

Carburetor, spark plugs, engine block, pistons, steering wheel, brakes, transmission, etc...

Clinical Pearl:
You must address the patient at the level of complexity that matches their pattern of illness.

Outline of Key Factors

- Autoimmune – Inflammation Co-Activation
  - Impact of Inflammation on Autoimmune Flare Activation
  - Impact of Inflammation on Neuron-Microglial Cell Interactions
    - Microglia Munching Neurons
    - Microglia as APC's
- T Cell Polarization
  - Quieting Autoimmune-Mediated Tissue Destruction
  - Increasing Pathogen Surveillance
  - The Classic Mistake
- Applications

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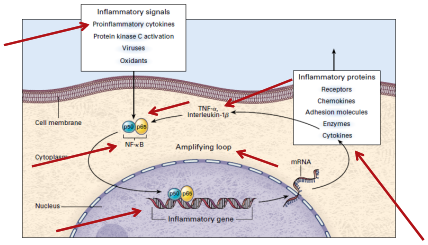
Core Connections of Inflammation & Autoimmunity

NFκB ↔ STAT3

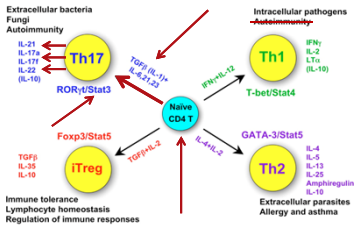
Nuclear factor-*k*B — a pivotal transcription factor in chronic inflammatory diseases

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



CD4 T cells: Fates, functions, and faults

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



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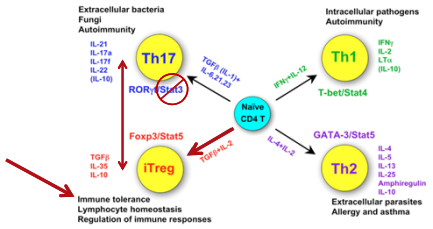
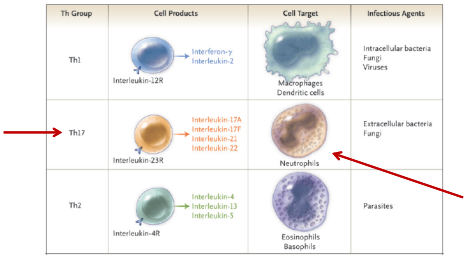


Interleukin-17 and Type 17 Helper T Cells

N Engl J Med 2009;361:888-98, Miossec P, Korn T, Kuchroo VK



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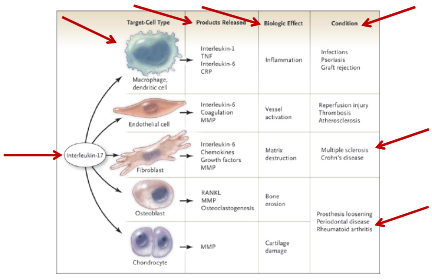


The Role of an NFκB-STAT3 Signaling Axis in Regulating the Induction and Maintenance of the Pluripotent State

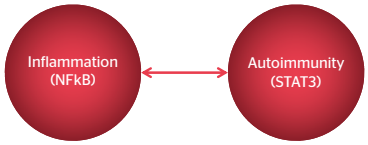
Chapter from: Pluripotent Stem Cell Biology - Advances in Mechanisms, Methods and Models
by Jasmin Roya Agarwal and Elias T. Zambidis

"Synergistic NFκB and STAT3 signaling

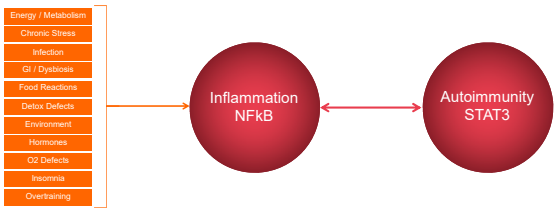
The NFκB and STAT3 pathways are closely interconnected in regulating immune responses…

Un-phosphorylated STAT3 that accumulates in the cell can bind to un-phosphorylated NFκB in competition with IκB. **The resulting STAT3/NFκB dimer localizes to the nucleus to induce NFκB-dependent gene expression."**

Key Opportunities for Intervention: NFkB and STAT3



The Cascade…



Main Points so far…

- NFkB and STAT3 both drive inflammatory tissue destruction
- NFkB and STAT3 are co-activators
- Blocking STAT3 Promotes Treg's → Tolerance

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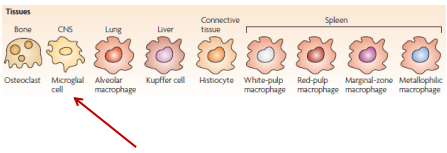
Neuron-Microglial Interactions

Exploring the Full Range of Macrophage Activation

Nature Reviews Immunology. 2008 Dec;30:958-969.



Exploring the Full Range of Macrophage Activation

Nature Reviews Immunology. 2008 Dec;30:958-969.

"Macrophages display **remarkable plasticity** and can change their physiology in response to environmental cues. These changes can give rise to different populations of cells with distinct functions."

Microglial phagocytosis of live neurons

Nat Rev Neurosci. 2014 Apr;15(4):209-16. Brown GC, Neher JJ.

"Microglia, the brain's professional phagocytes, can **remove dead and dying neurons** as well as synapses and the processes of live neurons."

Sculpture

Microglial phagocytosis of live neurons

Nat Rev Neurosci. 2014 Apr;15(4):209-16. Brown GC, Neher JJ.

"However, we and others have recently shown that **microglia can also execute neuronal death by phagocytosing stressed-but-viable neurons** — a process that we have termed phagoptosis. In this Progress article, we discuss evidence suggesting that **phagoptosis may contribute to neuronal loss during brain development, inflammation, ischaemia and neurodegeneration.**"

Ice Sculpture

Neuronal 'On' and 'Off' Signals Control Microglia

Trends in Neurosciences. 2007 Oct;30(11):596-602. Biber K, Neumann H, Inoue K, Boddeke HW.

"…neurons are not merely passive targets of microglia but rather control microglia activity…

'Off' signals constitutively keep microglia in their resting state and antagonize pro-inflammatory activity. 'On' signals are inducible, and include purines, chemokines, glutamate. Thus, neurons should be envisaged as key immune modulators in the brain."

Neuronal 'On' and 'Off' Signals Control Microglia

Trends in Neurosciences. 2007 Oct;30(11):596-602. Biber K, Neumann H, Inoue K, Boddeke HW.

OFF Signals	Signal	Effect
Released	TGFβ	Inhibition of effector T cells; Promotion of immune tolerance & inflammatory resolution; loss of anti-pathogenic vigilance
	CD22	Inhibition of B cell activity
	CX3CL1	Inhibition of microglial neurotoxicity
	Neurotransmitters	Multiple functions
	NGF	Nerve growth factor
	BDNF	Brain derived neurotrophic factor
	NT-3	Neurotrophin-3
Membrane Bound	CD200	Inhibition of glial inflammation
	CD22	Inhibition of B cell activity
	CD47	Inhibition of glial inflammation
	CX3CL1	Inhibition of microglial neurotoxicity

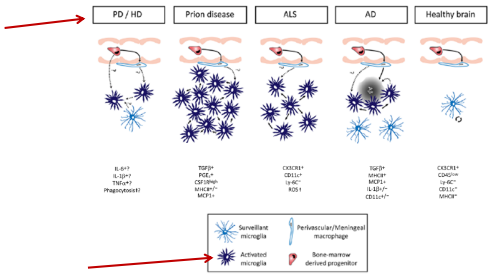
Neuronal 'On' and 'Off' Signals Control Microglia

Trends in Neurosciences. 2007 Oct;30(11):596-602. Biber K, Neumann H, Inoue K, Boddeke HW.

ON Signals	Signal	Effect
Released	CCL21	Glial chemoattraction
	CXCL10	Glial chemoattraction
	ATP & UTP	Glial chemoattraction & IL-1β release
	Glutamate	TNFα release & Neuroexcitotoxicity
	MMP3	Induces glial release of TNFα, IL-1β, IL-6 (inflammatory)
Membrane Bound	TREM2 ligand	Promotes glial phagocytosis of neurons

Microglial Dynamics and Role in the Healthy and Diseased Brain

The Neuroscientist 2015, Vol. 21(2) 169–184. Gomez-Nicola D, Perry VH.



Microglia in neurodegenerative disease

Nat. Rev. Neurol. Mar 2010;6:193-201. Perry VH, Nicoll JA, Holmes C.

"Microglia, the resident macrophages of the CNS, jury and disease, altering their morphology and phenotype to adopt a so-called activated state in response to pathophysiological brain insults…

Microglial phenotype is also modified by systemic infection or inflammation…

The fact that diseases with a chronic systemic inflammatory component are risk factors for Alzheimer disease implies that crosstalk occurs between systemic inflammation and microglia in the CNS."

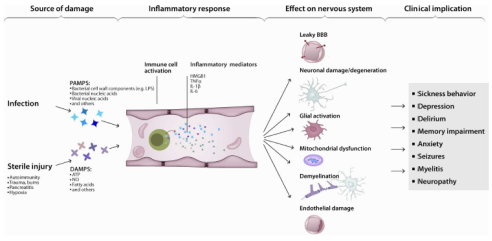
Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy – A unifying hypothesis

Surg. Neurol. Int 2011;2:107. Blaylock RL, Maroon J.

"IL-1β has been shown to be the main activator of microglia during brain disturbances and **systemic IL-1β can cause CNS inflammation** once it enters the brain, thus linking systemic inflammation and immune activation with worsening of brain pathology and pre-existing neurodegeneration."

Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration

Front Cell Neurosci. 2015 Feb 2;9:28. Sankowski R, Mader S, Valdés-Ferrer SI.



Regulation of innate immune responses in the brain

Nat Rev Immunol. 2009 Jun;9(6):429-39. Rivest S.

"A single systemic injection of **LPS** (1 mg/kg intraperitoneally) results in the robust induction of **expression in microglial cells of genes that encode pro-inflammatory cytokines and chemokines,** as well as proteins of the complement system."

Regulation of innate immune responses in the brain

Nat Rev Immunol. 2009 Jun;9(6):429-39. Rivest S.

"Systemic LPS injection induces the expression of *Cd14* and *Tlr2* mRNA… in a pattern that closely relates to the **induction of tumour necrosis factor (TNF) expression in the brain,** which mediates parenchymal responses. Autocrine and paracrine effects of TNF on the upregulation of expression of these innate immune receptors and other genes in the CNS have been described; **microglial cells do not respond to systemic LPS when TNF is neutralized in the CNS** and the direct administration of TNF to the CNS is a strong trigger of the innate immune response in the brain."

Regulation of innate immune responses in the brain

Nat Rev Immunol. 2009 Jun;9(6):429-39. Rivest S.

"Without the rapid clearance of myelin debris or toxic elements from the brain, microglial cells can react differently and mount a pro-inflammatory response that is detrimental for neurons, resulting in demyelination, synaptic dysfunction and ultimately neurodegeneration. Microglial cells are therefore at the forefront of the defence mechanisms that could set the conditions for repair or contribute to neuronal damage."

Regulation of innate immune responses in the brain

Nat Rev Immunol. 2009 Jun;9(6):429-39. Rivest S.

"By contrast, TNF- and IL-1β-deficient mice rapidly succumb to HSV encephalitis. These results indicate that an inflammatory response (mediated by TNF and IL-1β) is initially required to restrict the first stages of viral replication, but that this response must be subsequently suppressed (for example, by glucocorticoids) to avoid severe neuronal damage."

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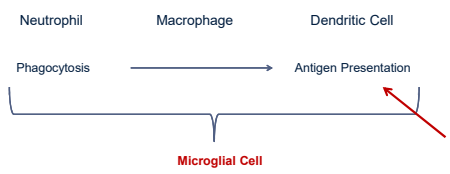
With Neuroinflammation, Microglial Cells Become *Antigen Presenting Cells*

Microglial Cell Functions



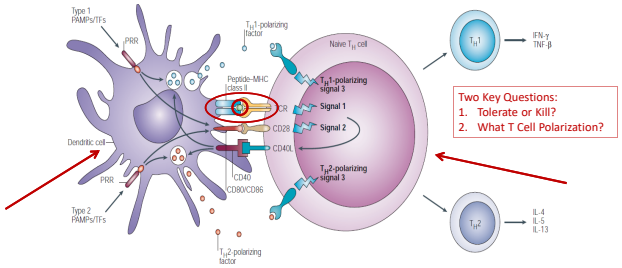
Control of Glial Immune Function by Neurons

Glia 2001; 36:191-199. Neumann H.

"…in a variety of inflammatory and neurodegenerative diseases, including MS, infections, trauma, stroke, neoplasia, and Alzheimer's disease, **glial cells such as microglia gain antigen-presenting capacity through the expression of MHC molecules."**

Dendritic-cell control of pathogen-driven T-cell polarization

Nat Rev Immunol. 2003 Dec;3(12):984-93, Kapsenberg ML.



Two Key Questions:
1. Tolerate or Kill?
2. What T Cell Polarization?

The Multiple Roles of the Innate Immune System in the Regulation of Apoptosis and Inflammation in the Brain

J Neuropathol Exp Neurol. 2009 March;68(3):217-226. Griffiths MR, Gasque P, Neal JW.

"Phagocytosis of apoptotic cells is a nonphlogistic (i.e. non-inflammatory) process that provides immune regulation through anti-inflammatory cytokines and regulatory T cells.

Neurons and glia express cellular death signals, including tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and TNF receptor (TNFR), through which they can **trigger apoptosis in T cells and other infiltrating cells."**

The Multiple Roles of the Innate Immune System in the Regulation of Apoptosis and Inflammation in the Brain

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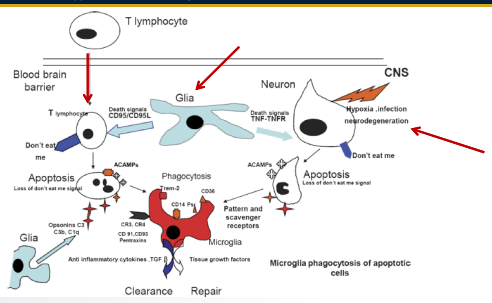

Glial Cells Suppress Postencephalitic CD8+ T Lymphocytes Through PD-L1

Glia. 2014 Oct;62(10):1582-94.

"Engagement of the programmed death (PD)-1 receptor on activated cells by its ligand (PD-L1) is a mechanism for suppression of activated T-lymphocytes. Microglia, the resident inflammatory cells of the brain, are important for pathogen detection and initiation of innate immunity, however, a novel role for these cells as immune regulators has also emerged. **PD-L1 on microglia has been shown to negatively regulate T-cell activation in models of multiple sclerosis and acute viral encephalitis."**

Glial Cells Suppress Postencephalitic CD8+ T Lymphocytes Through PD-L1

Glia. 2014 Oct;62(10):1582-94.

"In this study, we investigated the role of glial cell PD-L1 in controlling **encephalitogenic CD8+ T-lymphocytes, which infiltrate the brain to manage viral infection, but remain to produce chronic neuroinflammation.** Using a model of chronic neuroinflammation following murine cytomegalovirus (MCMV)-induced encephalitis, we found that CD8+ T-cells persisting within the brain expressed PD-1. Conversely, activated microglia expressed PD-L1. In vitro, primary murine microglia, which express low basal levels of PD-L1, upregulated the co-inhibitory ligand on IFN-γ-treatment."

Microglia

- **Normal / Non-inflamed Brain:**
  Phagocytic Macrophage Functions…
  - Repair damaged neurons
  - Phagocytize apoptotic neurons
  - Inhibit inflammation
  - Kill infectious agents
  - Induce apoptosis in invading T cells

Microglia

- **Inflamed Brain:**
  Aggressive Phagocytosis &
  Antigen Presenting Cell Functions
  - Phagocytize viable neurons
  - Express MHC II
  - Present fragments of neuronal debris to invading T cells
  - Promote autoimmune process in brain

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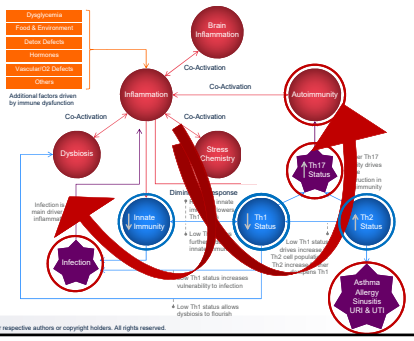
T Cell Polarization Patterns, Autoimmunity, and Pathogen Killing

Identifying the Primary Drivers of Chronic Illness



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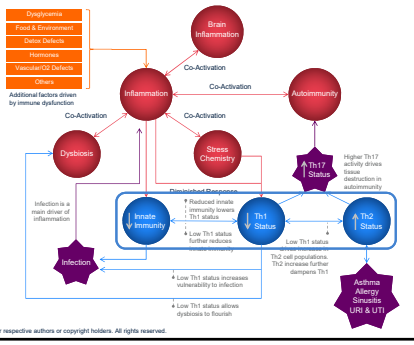

Key

- Core immune dysfunctions of chronic illness
- Key immune system changes they cause
- Key immune consequences of those changes
- Additional factors driving immune dysfunction

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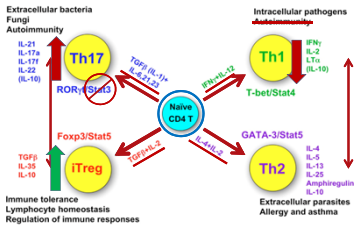
Why Care About T Cell Polarization?

- Determines the Style of Immune Response
- Proper T Cell Polarization Patterning is Required for:
  - Killing Tissue Infections
  - Killing Hollow Organ Infection (GI, Sinus, Lung, Bladder, Vaginal Tract)
  - Quieting Autoimmunity
  - Resolving Inflammation
- Dysfunction Drives Disease

CD4 T cells: Fates, functions, and faults

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

QUICK OVERVIEW…



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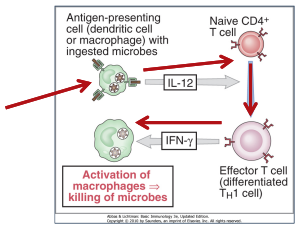
Th1 Response

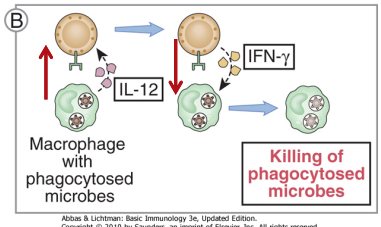
Th1 Cell ↔ Mac Co-activation Loop

↑ Th1 → IFNɣ ↔ IL-12 → ↑ Th1



Th1 Cell ↔ Mac & Mac ↔ NK Cell Co-activation Loops

↑ Th1 → IFNɣ ↔ IL-12 → ↑ Th1



Abbas & Lichtman: Basic Immunology 3e, Updated Edition.
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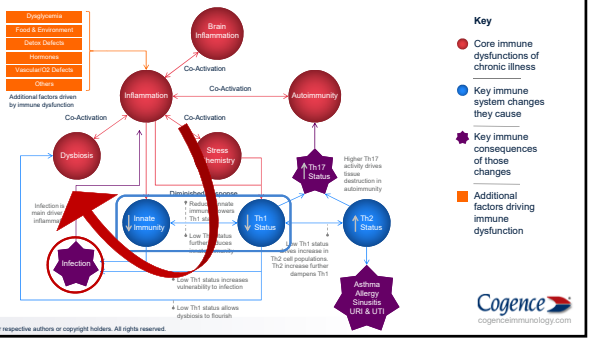
Identifying the Primary Drivers of Chronic Illness



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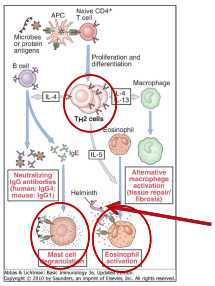
Th2 Response

Basic Immunology

Abbas & Lichtman 3e 2010



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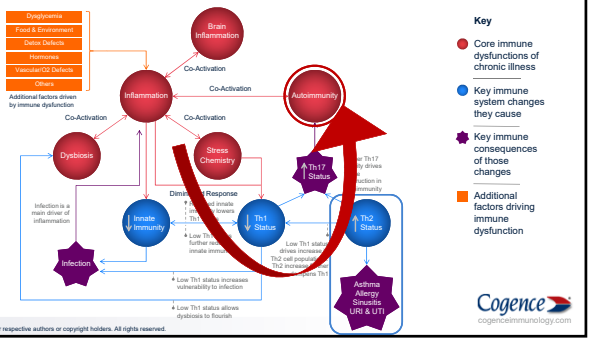
Identifying the Primary Drivers of Chronic Illness



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Th17 Response

57

Th17 Cells

- Mucosal immunity
- Autoimmune tissue destruction
- Inflammatory promotion

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

Am J Pathol. 2012 Jul;181(1):8-18, Meddur 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."**

Basic Immunology

Abbas & Lichtman 3e 2010

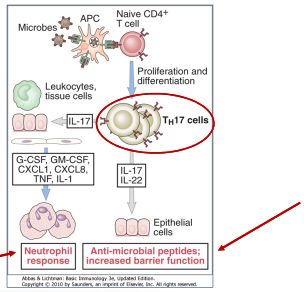
High neutrophils on CBC?

Could be fighting infection…

Could be Th17 driven AI flare…

And

If they're fighting infection all the time, it will drive autoimmune tissue destruction…



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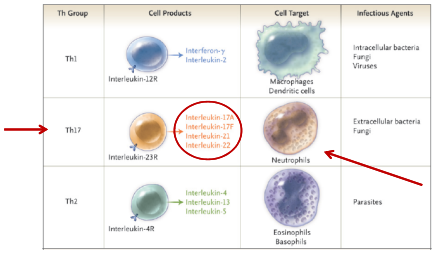

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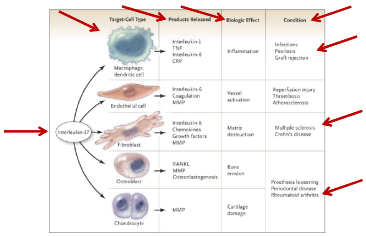

Group A Streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells.

J Clin Invest. 2016 Jan;126(1):303-17. Dileepan T, Smith ED, Latimer E, Harley E, Agalliu D, Cleary PP, et al.

"Group A streptococcal (GAS) infection induces the production of Abs that cross-react with host neuronal proteins, and these anti-GAS mimetic Abs are associated with autoimmune diseases of the CNS. However, the mechanisms that allow these Abs to cross the blood-brain barrier (BBB) and induce neuropathology remain unresolved. We have previously shown that **GAS infection in mouse models induces a robust Th17 response in nasal-associated lymphoid tissue (NALT).** Here, we identified GAS-specific Th17 cells in tonsils of humans naturally exposed to GAS, prompting us to explore whether GAS-specific CD4+ T cells home to mouse brains following i.n. infection."

Group A Streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells.

J Clin Invest. 2016 Jan;126(1):303-17. Dileepan T, Smith ED, Latimer E, Harley E, Agalliu D, Cleary PP, et al.

"Intranasal challenge of repeatedly GAS-inoculated mice promoted migration of GAS-specific Th17 cells from NALT into the brain, BBB breakdown, serum IgG deposition, microglial activation, and loss of excitatory synaptic proteins under conditions in which **no viable bacteria were detected in CNS tissue. CD4+ T cells were predominantly located in the olfactory bulb (OB) and in other brain regions that receive direct input from the OB.** Together, these findings provide insight into the immunopathology of neuropsychiatric complications that are associated with GAS infections and suggest that crosstalk between the CNS and cellular immunity may be a general mechanism by which infectious agents exacerbate symptoms associated with other CNS autoimmune disorders."

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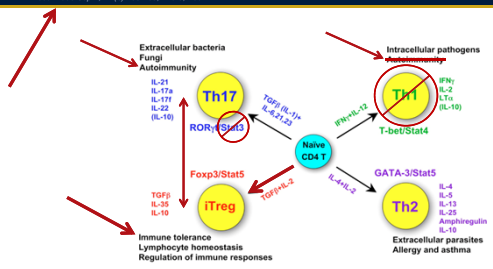
Th1 Cytokines Inhibit Th17 & Th2 Cell Activity

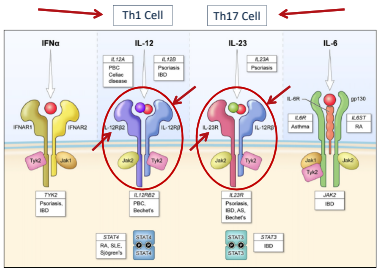
CD4 T cells: Fates, functions, and faults

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



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:

It's essential to address hollow-space pathogens like dysbiosis, sinusitis, chronic URI's, UTI's, etc. Hollow Space chronic pathogen burden → persistent Th17 response → Autoimmune destruction…

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."**

Clinical Pearl:
The TH1 pathway antagonizes the TH17 pathway.

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

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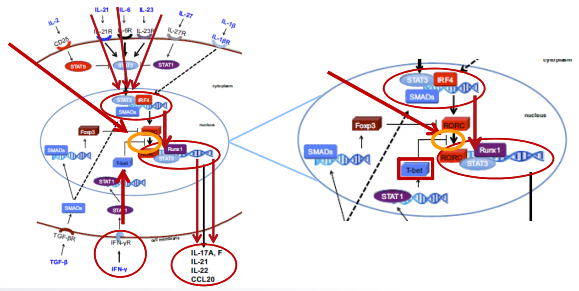
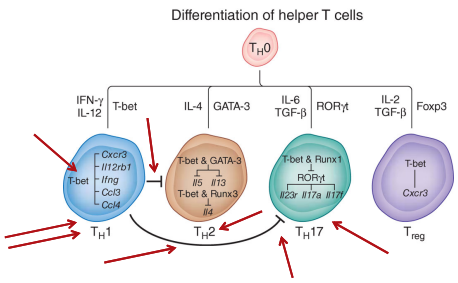
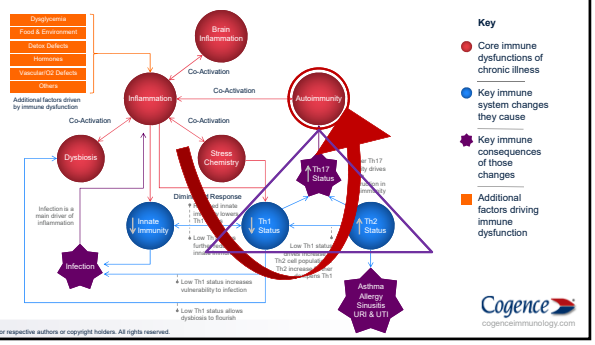


T-bet in disease

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



Identifying the Primary Drivers of Chronic Illness



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Indications of Th1 and Th17 responses in cerebrospinal fluid from patients with Lyme neuroborreliosis: a large retrospective study.

J Neuroinflammation. 2011 Apr 20;8:36. Henningsson AJ, Tjernberg I, Malmvall BE, Forsberg P, Ernerudh J.

"Previous studies indicate that **successful resolution of Lyme neuroborreliosis (NB)** is associated with a **strong T helper (Th) 1-type cytokine response in the cerebrospinal fluid (CSF) followed by a down-regulating Th2 response,** whereas the role of the recently discovered Th17 cytokine response is unknown.

To investigate the relative contribution of different Th associated cytokine/chemokine responses, we used a multiple bead array to measure the levels of CXCL10 (Th1 marker), CCL22 (Th2 marker), IL-17 (Th17 marker) and CXCL8 (general inflammation marker), in serum and in CSF from untreated patients with confirmed NB (n = 133), and non-NB patients (n = 96), and related the findings to clinical data. Samples from patients with possible early NB (n = 15) and possible late NB (n = 19) were also analysed, as well as samples from an additional control group with orthopaedic patients (n = 17), where CSF was obtained at spinal anaesthesia."

Indications of Th1 and Th17 responses in cerebrospinal fluid from patients with Lyme neuroborreliosis: a large retrospective study.

J Neuroinflammation. 2011 Apr 20;8:36. Henningsson AJ, Tjernberg I, Malmvall BE, Forsberg P, Ernerudh J.

"The most prominent differences across groups were found in the CSF. IL-17 was elevated in CSF in 49% of the patients with confirmed NB, but was not detectable in the other groups. Patients with confirmed NB and possible early NB had significantly higher CSF levels of CXCL10, CCL22 and CXCL8 compared to both the non-NB group and the control group ($p < 0.0001$ for all comparisons). Patients in the early NB group, showing a short duration of symptoms, had lower CCL22 levels in CSF than did the confirmed NB group ($p < 0.0001$). Furthermore, patients within the confirmed NB group showing a duration of symptoms <2 weeks, tended to have lower CCL22 levels in CSF than did those with longer symptom duration ($p = 0.023$). Cytokine/chemokine levels were not correlated with clinical parameters or to levels of anti-Borrelia-antibodies.

Our results support the notion that **early NB is dominated by a Th1-type response, eventually accompanied by a Th2 response. Interestingly, IL-17 was increased exclusively in CSF from patients with confirmed NB,** suggesting a hitherto unknown role for Th17 in NB. However, for conclusive evidence, future prospective studies are needed."

Th1-Th17 Ratio as a New Insight in Rheumatoid Arthritis Disease.

Iran J Allergy Asthma Immunol. 2018 Feb;17(1):68-77. Bazzazi H, Aghaei M, Yazdani Y, et al.

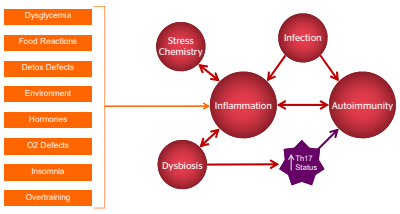
"The Th17, Th1 and dual Th17/Th1 cells are important players in rheumatoid arthritis (RA) disease. To assess their roles, the frequency and impact of these cells were investigated in patients with different disease activity. In 14 new cases and 41 established RA patients in comparison with 22 healthy controls, the percentages of **Th17, Th1 and dual Th17/Th1 cells** were determined by flow-cytometry and their correlations were investigated with disease activity score (DAS28). Moreover, **serum levels of IL-6 and IL-17 as inducer and functional cytokines for Th17 were investigated.** Finally, serum levels of anti citrullinated protein antibody (ACPA) and rheumatoid factor (RF) were assessed."

Th1-Th17 Ratio as a New Insight in Rheumatoid Arthritis Disease.

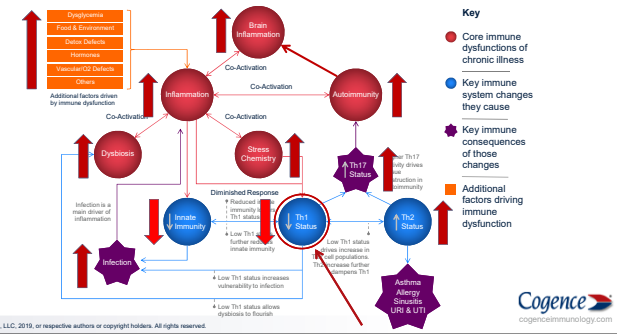
Iran J Allergy Asthma Immunol. 2018 Feb;17(1):68-77. Bazzazi H, Aghaei M, Yazdani Y, et al.

"Percentage of **Th17 cells in RA patients were increased** in comparison with healthy controls ($p<0.01$). In correlation with this finding, IL-17 and IL-6 cytokines in RA patients also increased ($p<0.01$). The **Th1 cells in RA patients were less than healthy group ($p<0.05$) and showed negative correlation with disease activity** ($r=-0.328$, $p<0.01$). **Dual Th17/Th1 cell only in new cases of RA were more than healthy control groups** ($p<0.01$). The **Th1/Th17 ratio in RA patients** is statistically different with healthy control group ($p<0.01$) and it has **negative correlation with disease activity** ($r=-264$, $p<0.05$). The levels of ACPA and RF were increased with disease progression. Decreasing of Th1/Th17 ratio in RA patient suggested a new paradigm in the field of autoimmune disease and indicated that imbalance or plasticity between these subsets can be important in progress, diagnosis and therapy of RA disease."

Clinical Application Summary



Identifying the Primary Drivers of Chronic Illness



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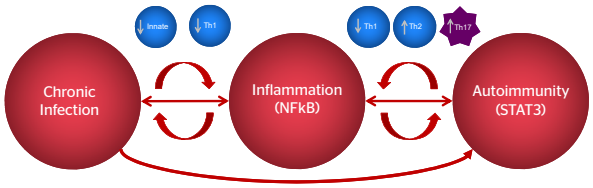
Key Opportunities for Intervention



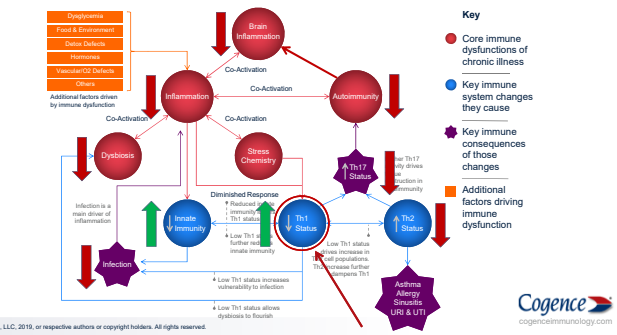
Pathogen burden, cytomegalovirus infection and inflammatory markers in the risk of premature coronary artery disease in individuals of Indian origin.

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

The Role of an NFκB-STAT3 Signaling Axis in Regulating the Induction and Maintenance of the Pluripotent State

Jasmin Roya Agarwal and Elias T. Zambidis
Chapter 1 in "Pluripotent Stem Cell Biology - Advances in Mechanisms, Methods and Models" edited by Atwood C and Meethal SV, ISBN 978-952-51-1580-8, Published: July 2, 2014. Open Access.

Identifying the Primary Drivers of Chronic Illness



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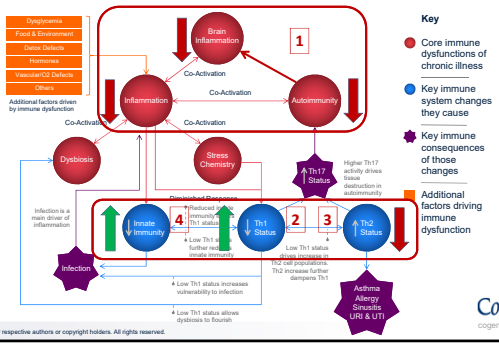
Identifying the Primary Drivers of Chronic Illness



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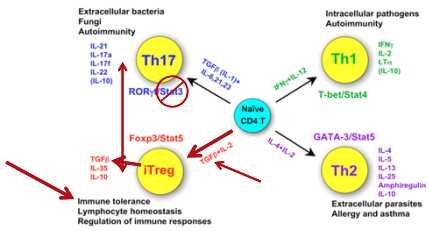
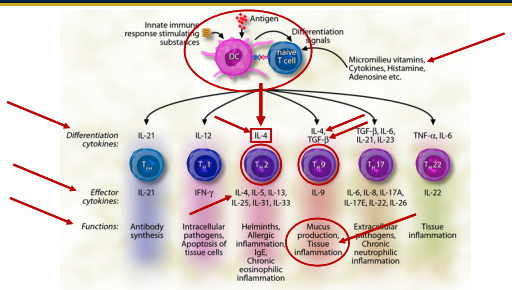
CD4 T cells: Fates, functions, and faults

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



Sensing the outside world: TSLP regulates barrier immunity.

Nat Immunol. 2010 Apr;11(4):289-93. Ziegler SF, Artis D.



Conflicting Clinical Goals

- Autoimmunity?
  - Inhibit NFkB-STAT3 Axis, Support Th1, Modulate Th2

- Infection?
  - Support Th1 and Innate Immune Response, Inhibit Th2

The Key Mistake to Avoid:
If you inhibit the NFkB-STAT3 axis in a Th2 Dominant patient, they will get worse!
You must modulate the Th2 dominance first!

Application

- Inhibit NFkB-STAT3 Coactivation:
  - Resveratrol, Curcumin, Sulforaphane, Quercetin, Black Ginger, D, A
- Support Th1:
  - Berberine, Chinese Skullcap (baicalin), Ginger, Sulforaphane
- Support Innate Immune Response:
  - Andrographis, Astragalus, Reishi (ganoderma)
- Modulate (downregulate) Th2:
  - Perilla, Astragalus, NAC, Quercetin

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Key Clinical Immunology Building Blocks

In Preparation for the IFM Immune APM 2019

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