IMMUNOSUPPRESSANTS VS IMMUNOMODULATORS:
A RHEUMATOLOGY PERSPECTIVE

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DISCLOSURES

- I have no relevant financial disclosures.
- As a rheumatologist, most of my examples are "off-label".

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OBJECTIVES

- Inform a basic understanding of the human immune system.
- Discuss differences in mechanism of action of different therapies that affect the immune system.
- Form a practical working definition of immunomodulators and immunosuppressants.

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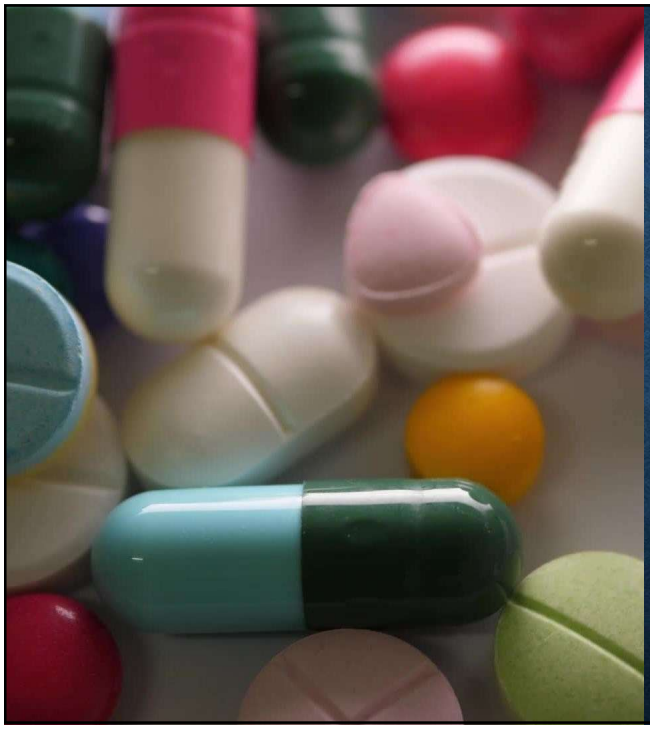

A FEW QUESTIONS TO PONDER

- What is the difference between an immunosuppressant and an immunomodulator?

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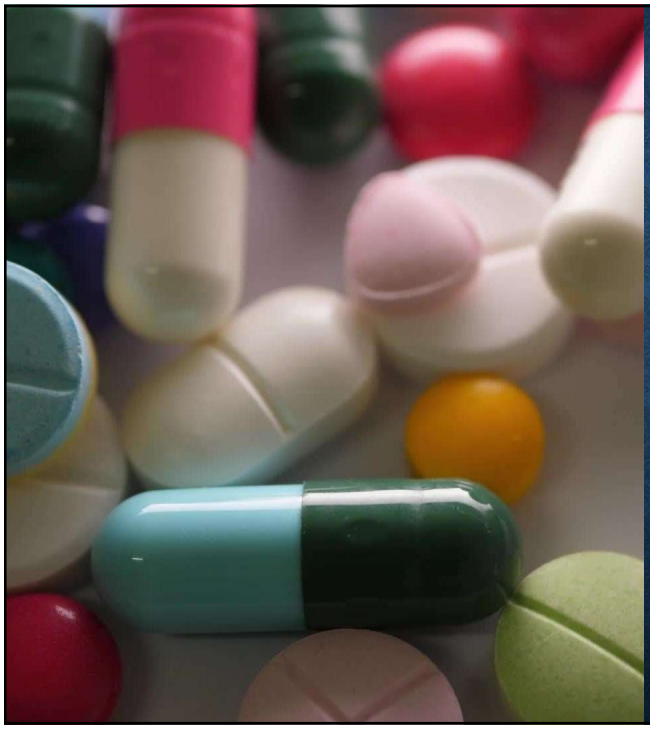

A FEW QUESTIONS TO PONDER

- Which poses a higher risk of infection for a patient, immunosuppressants or immunomodulators?

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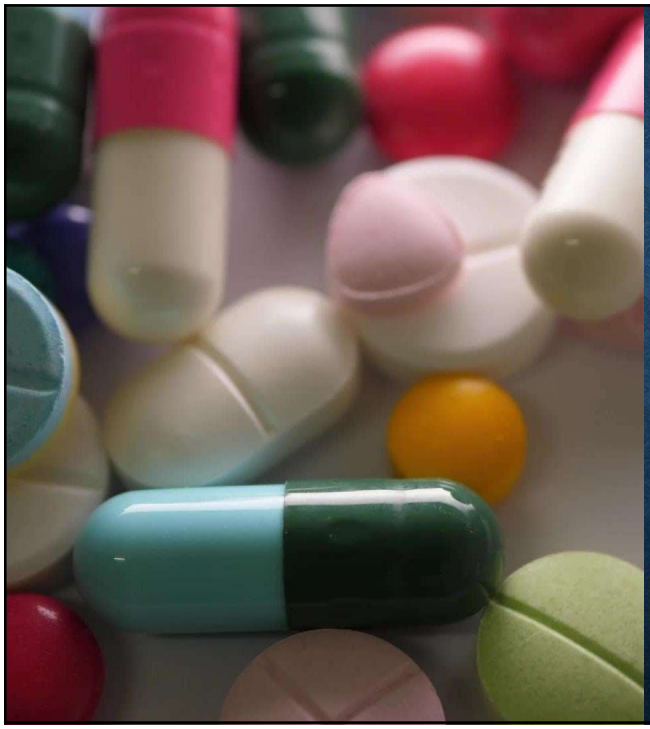

A FEW QUESTIONS TO PONDER

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  - C) adalimumab
  - D) anakinra
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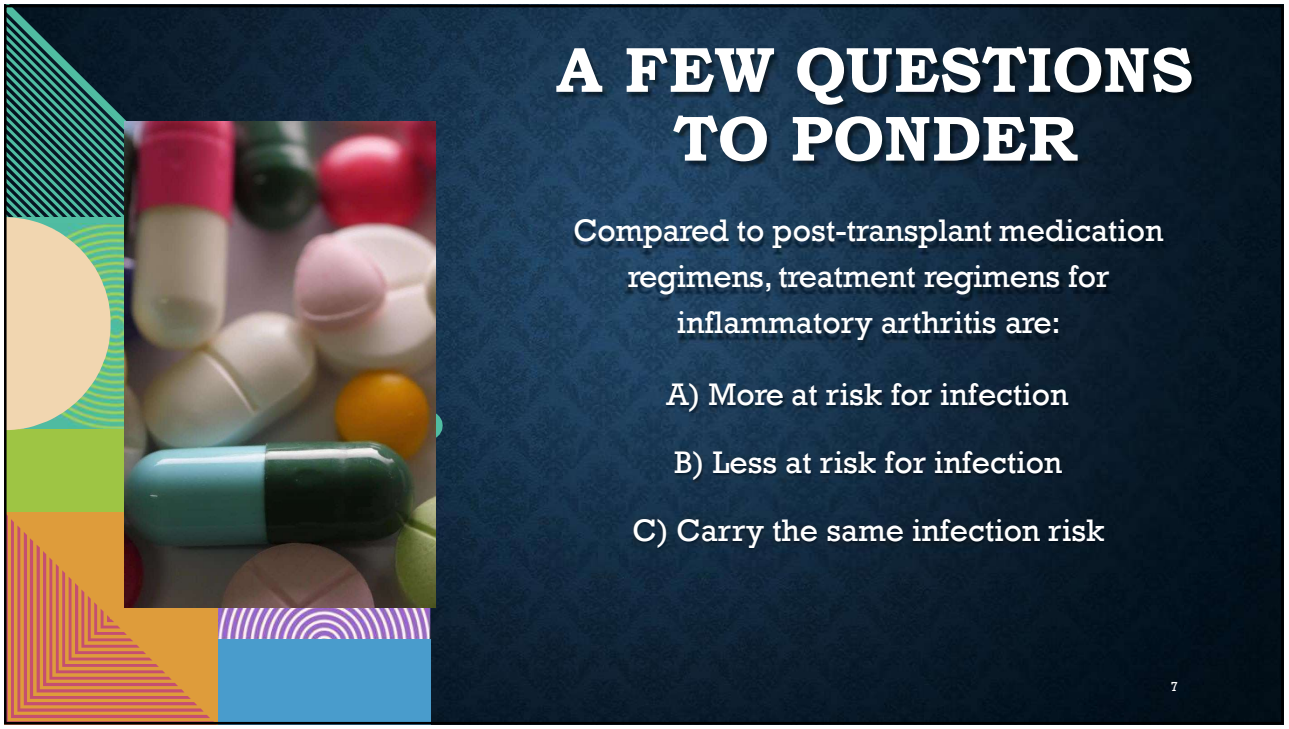
A FEW QUESTIONS TO PONDER
Compared to post-transplant medication regimens, treatment regimens for inflammatory arthritis are:
A) More at risk for infection
B) Less at risk for infection
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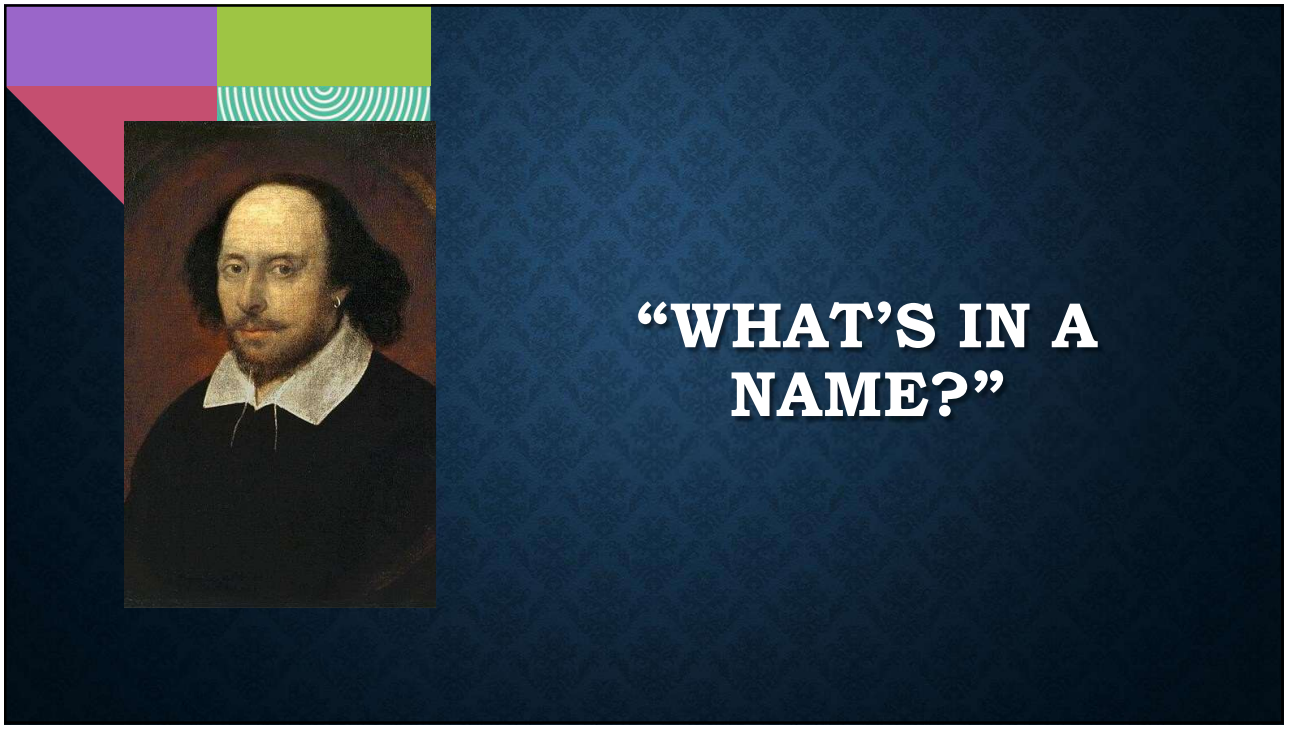
"WHAT'S IN A NAME?"

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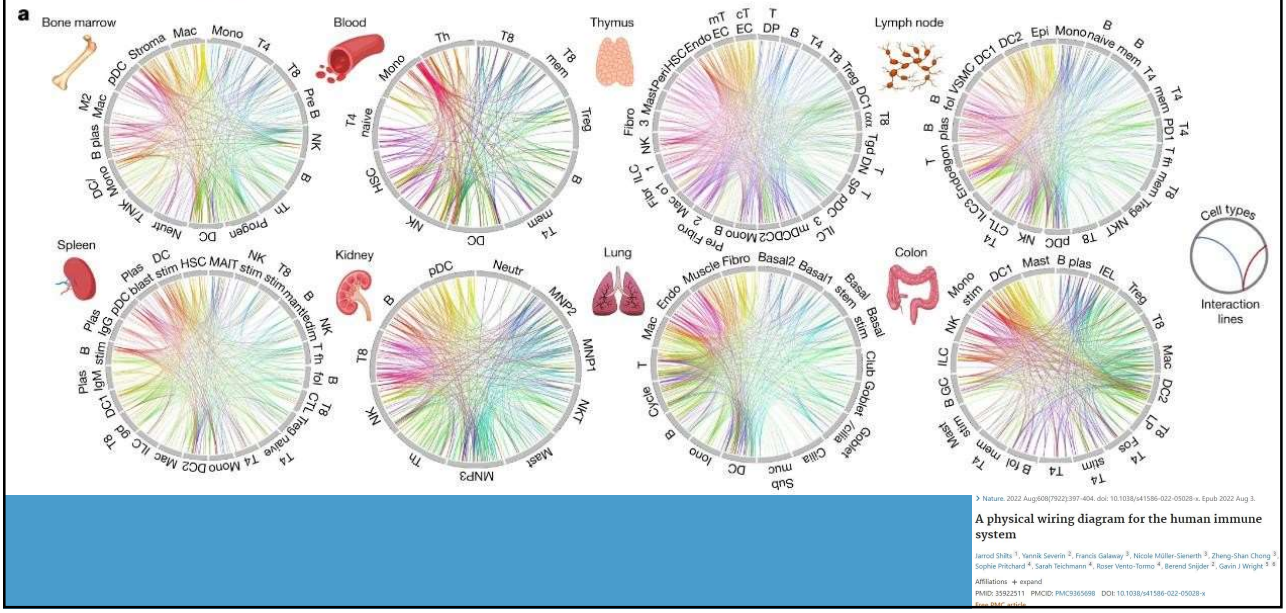
Fig. 3: An interactive atlas of immune cell connections across the human body.

From: A physical wiring diagram for the human immune system



Nature. 2022 Aug;608(7922):397-404. doi: 10.1038/s41586-022-05028-x. Epub 2022 Aug 3.

A physical wiring diagram for the human immune system

Jarrod Shilts [1], Yannik Severin [2], Francis Galaway [3], Nicole Müller-Sienerth [3], Zheng-Shan Chong [3], Sophie Pritchard [4], Sarah Teichmann [4], Roser Vento-Tormo [4], Berend Snijder [2], Gavin J Wright [3]

Affiliations + expand

PMID: 35922511 PMCID: PMC9365698 DOI: 10.1038/s41586-022-05028-x

Free PMC article

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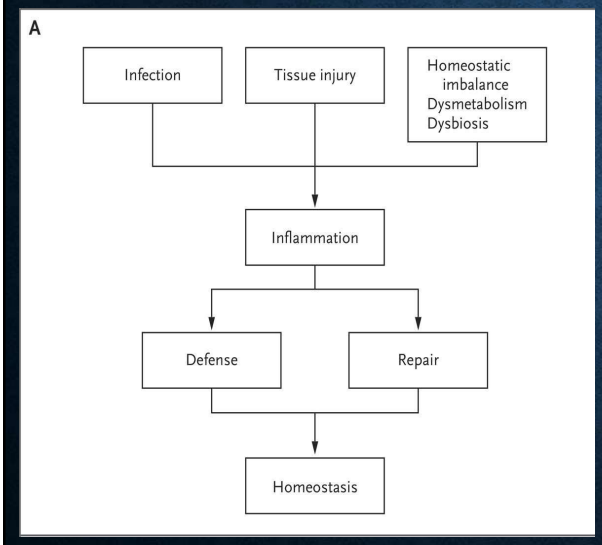
Basic Immune System Function



A Mantovani, C Garlanda. N Engl J Med 2023;388:439-452.

NON-IMMEDIATE:

-ANTIGEN-PRESENTING CELLS

-PRESENT FOREIGN ANTIGEN TO HOST T LYMPHOCYTES, WHICH ARE SUBSEQUENTLY ACTIVATED

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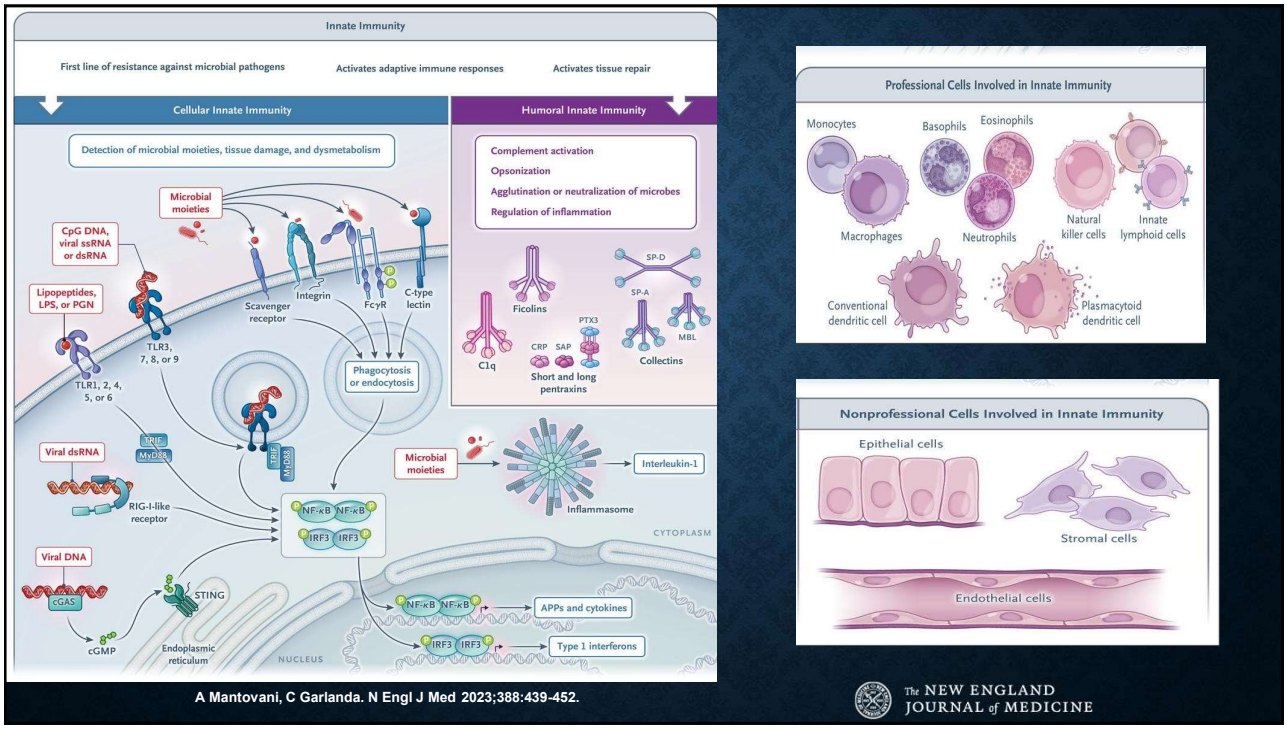
Innate Immunity
First line of resistance against microbial pathogens
Activates adaptive immune responses
Activates tissue repair
Cellular Innate Immunity
Humoral Innate Immunity
Detection of microbial moieties, tissue damage, and dysmetabolism
Complement activation
Opsonization
Agglutination or neutralization of microbes
Regulation of inflammation
Microbial moieties
CpG DNA, viral ssRNA or dsRNA
Lipopeptides, LPS, or PGN
Scavenger receptor
Integrin
FcγR
C-type lectin
TLR3, 7, 8, or 9
TLR1, 2, 4, 5, or 6
Phagocytosis or endocytosis
Ficolins
SP-D
SP-A
PTX3
CRP
SAP
C1q
MBL
Short and long pentraxins
Collectins
Viral dsRNA
TRIF
MYD88
RIG-I-like receptor
NF-κB
IRF3
Microbial moieties
Interleukin-1
Inflammasome
CYTOPLASM
Viral DNA
cGAS
STING
cGMP
Endoplasmic reticulum
NUCLEUS
APPs and cytokines
Type 1 interferons
Professional Cells Involved in Innate Immunity
Monocytes
Basophils
Eosinophils
Macrophages
Neutrophils
Natural killer cells
Innate lymphoid cells
Conventional dendritic cell
Plasmacytoid dendritic cell
Nonprofessional Cells Involved in Innate Immunity
Epithelial cells
Stromal cells
Endothelial cells
A Mantovani, C Garlanda. N Engl J Med 2023;388:439-452.
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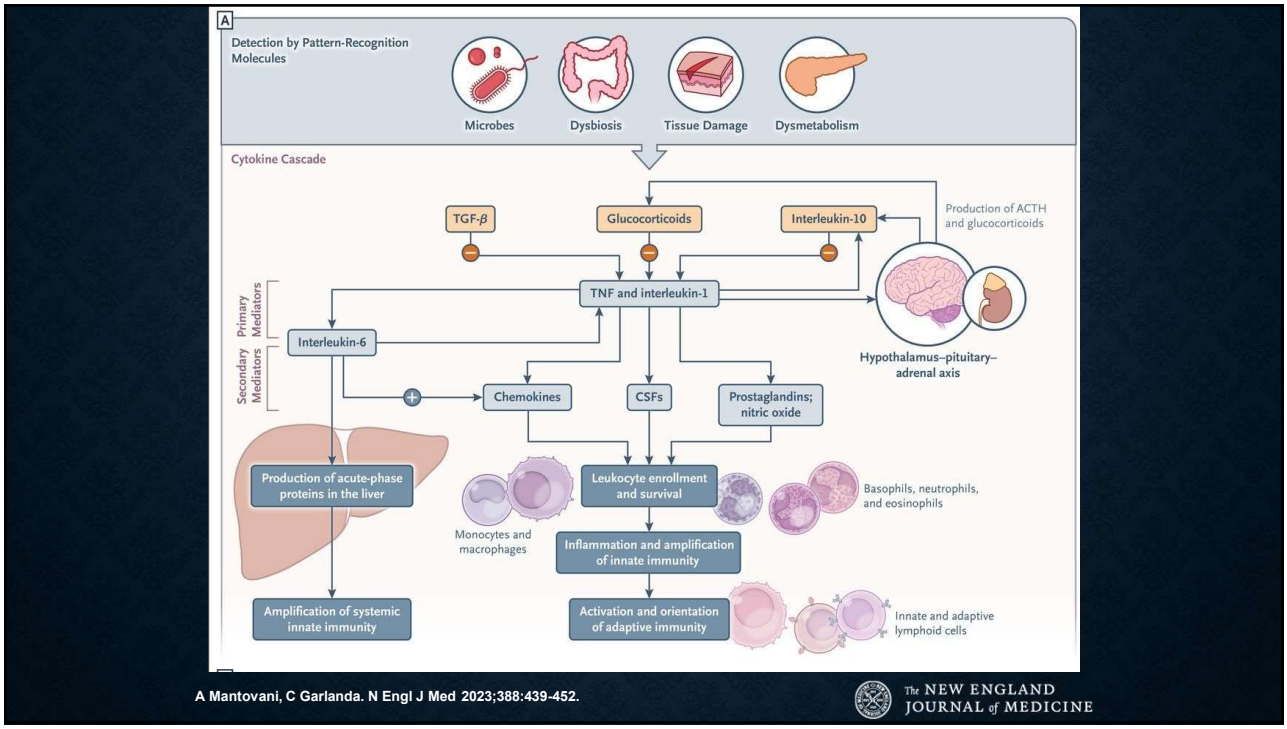
A
Detection by Pattern-Recognition Molecules
Microbes
Dysbiosis
Tissue Damage
Dysmetabolism
Cytokine Cascade
TGF-β
Glucocorticoids
Interleukin-10
Production of ACTH and glucocorticoids
TNF and interleukin-1
Primary Mediators
Secondary Mediators
Interleukin-6
Hypothalamus–pituitary–adrenal axis
Chemokines
CSFs
Prostaglandins; nitric oxide
Production of acute-phase proteins in the liver
Leukocyte enrollment and survival
Basophils, neutrophils, and eosinophils
Monocytes and macrophages
Inflammation and amplification of innate immunity
Amplification of systemic innate immunity
Activation and orientation of adaptive immunity
Innate and adaptive lymphoid cells
A Mantovani, C Garlanda. N Engl J Med 2023;388:439-452.
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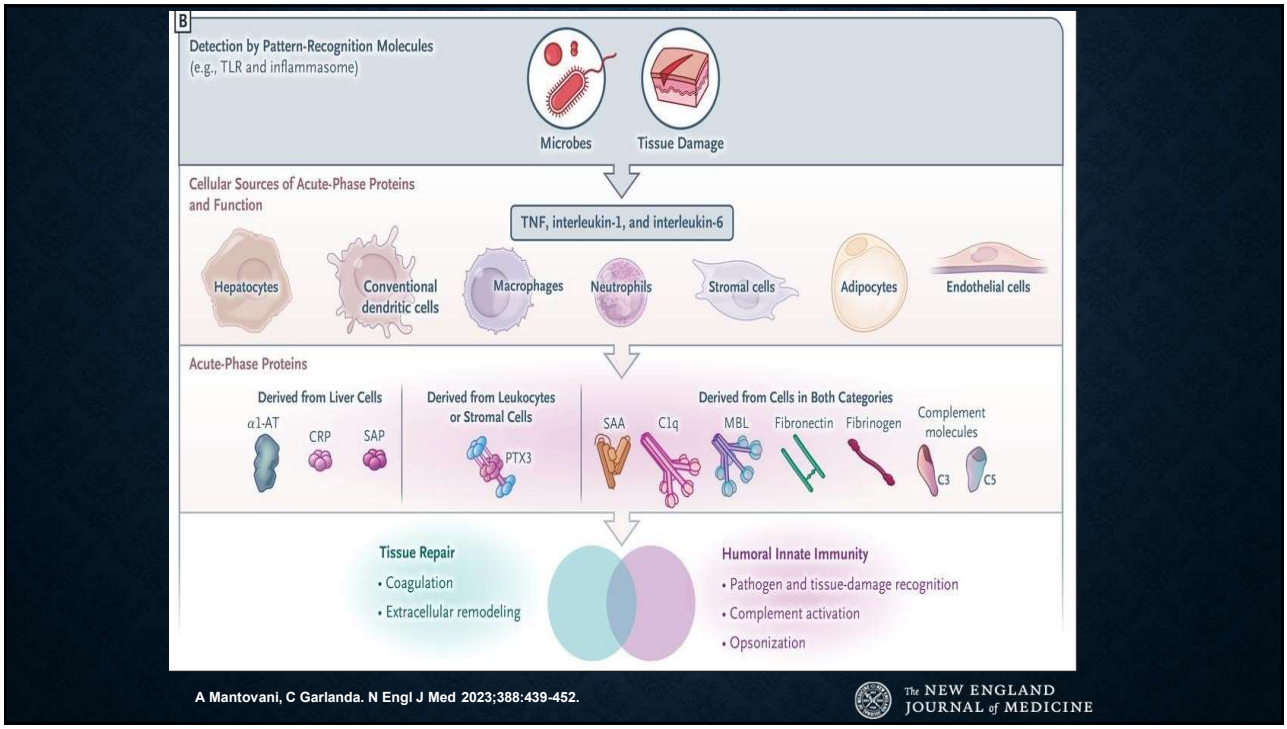
B
Detection by Pattern-Recognition Molecules
(e.g., TLR and inflammasome)
Microbes
Tissue Damage
Cellular Sources of Acute-Phase Proteins and Function
TNF, interleukin-1, and interleukin-6
Hepatocytes
Conventional dendritic cells
Macrophages
Neutrophils
Stromal cells
Adipocytes
Endothelial cells
Acute-Phase Proteins
Derived from Liver Cells
α1-AT
CRP
SAP
Derived from Leukocytes or Stromal Cells
PTX3
Derived from Cells in Both Categories
SAA
C1q
MBL
Fibronectin
Fibrinogen
Complement molecules
C3
C5
Tissue Repair
• Coagulation
• Extracellular remodeling
Humoral Innate Immunity
• Pathogen and tissue-damage recognition
• Complement activation
• Opsonization
A Mantovani, C Garlanda. N Engl J Med 2023;388:439-452.
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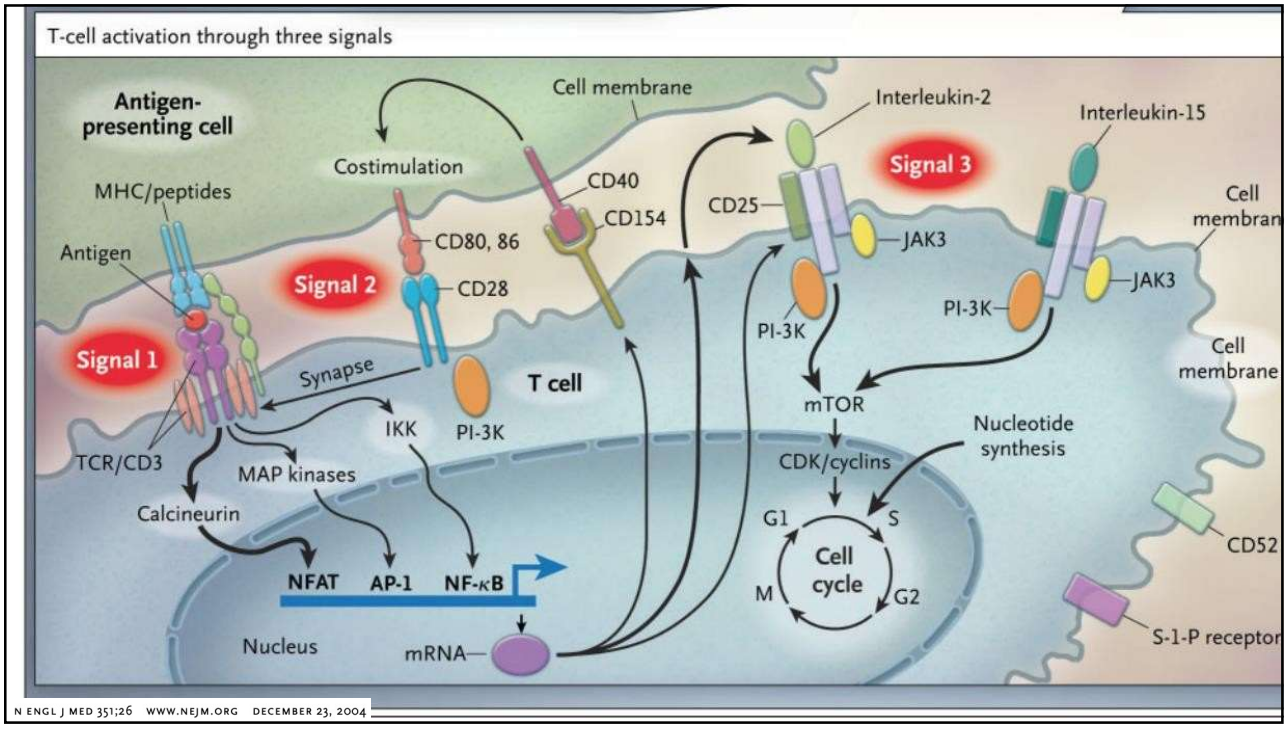
T-cell activation through three signals
Antigen-presenting cell
Cell membrane
Costimulation
MHC/peptides
Antigen
CD40
CD154
CD80, 86
CD28
Signal 1
Signal 2
Signal 3
Synapse
T cell
TCR/CD3
IKK
PI-3K
MAP kinases
Calcineurin
NFAT
AP-1
NF-κB
Nucleus
mRNA
Interleukin-2
Interleukin-15
CD25
JAK3
PI-3K
mTOR
CDK/cyclins
Nucleotide synthesis
G1
S
M
G2
Cell cycle
CD52
S-1-P receptor
N ENGL J MED 351;26 WWW.NEJM.ORG DECEMBER 23, 2004

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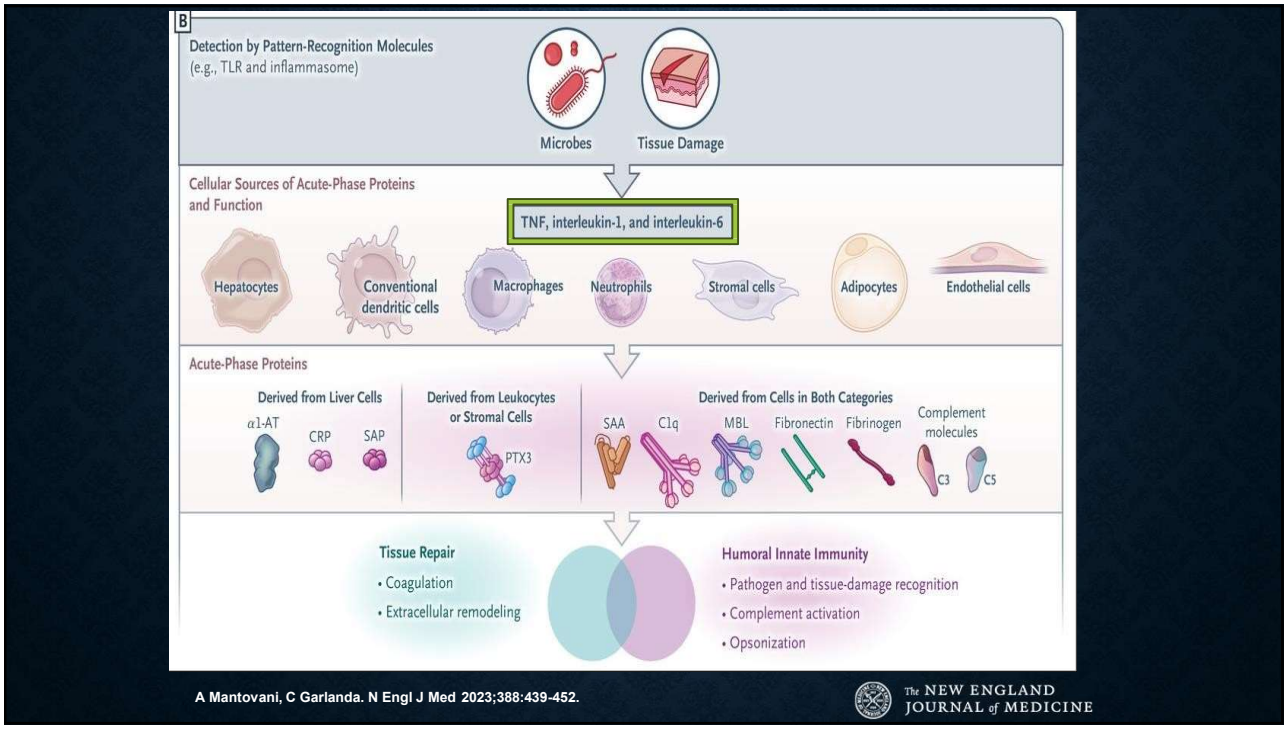
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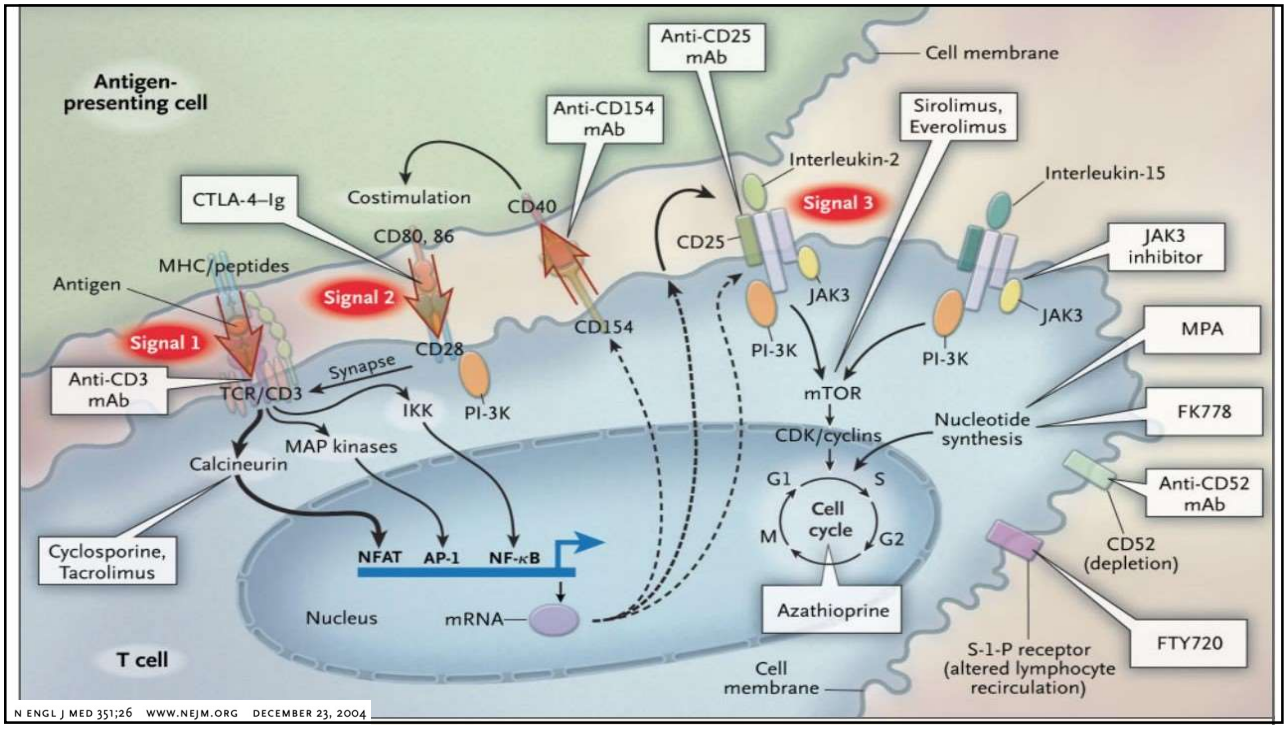
Antigen-presenting cell
Anti-CD25 mAb
Cell membrane
Anti-CD154 mAb
Sirolimus, Everolimus
Interleukin-2
Interleukin-15
CTLA-4–Ig
Costimulation
CD40
Signal 3
CD25
JAK3 inhibitor
CD80, 86
MHC/peptides
Antigen
Signal 2
JAK3
JAK3
MPA
CD154
Signal 1
CD28
PI-3K
PI-3K
Anti-CD3 mAb
Synapse
TCR/CD3
IKK
PI-3K
mTOR
FK778
Nucleotide synthesis
MAP kinases
CDK/cyclins
Calcineurin
G1
S
Cell cycle
M
G2
Anti-CD52 mAb
CD52 (depletion)
Cyclosporine, Tacrolimus
NFAT
AP-1
NF-κB
Azathioprine
Nucleus
mRNA
FTY720
T cell
Cell membrane
S-1-P receptor (altered lymphocyte recirculation)
N ENGL J MED 351;26 WWW.NEJM.ORG DECEMBER 23, 2004

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A BASIC FRAMEWORK OF MECHANISMS TO SUPPRESS THE IMMUNE SYSTEM

- Cytokine blockade (IL-1, TNF, IL-6)
- Blockade of T cell coactivation
- Blockade of post-activation cascade

NEJM 2004;351:2715-29.

Additional options:

- Depletion of lymphocytes
  - Polyclonal antibodies
  - Targeted monoclonal antibodies against cell surface markers

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DEPLETING LYMPHOCYTES: MONOCLONAL ANTIBODIES TARGETING CELL SURFACE RECEPTORS

Rituximab

-Chimeric mouse/human MAB against CD20 (pre-B and mature B lymphocytes)

Anti-CD25 (IL2r) antibodies (**daclizumab, basiliximab**)

- Bind to and block activates IL2r (activated T cells)

Alemtuzumab

- AntiCD52
- Recombinant humanized MAB against T&B lymphocytes, monocytes, macrophages

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FRAMEWORK: TRANSPLANTS VS IMMUNE-MEDIATED INFLAMMATORY DISEASES

- **Solid organ transplants**
  - Transplant = foreign (recognized through APCs, activating multiple mechanisms to rid the body of the transplant)
  - Require broad immunosuppression (e.g., glucocorticoids, tacrolimus, mycophenolate)
  - With these therapies comes increased risk of serious infections and cancers

- **Immune-mediated inflammatory diseases**
  - Complex; multiple subtle inherited defects in immune regulatory pathways + environmental triggers lead to gradual autoreactivity
  - Chronic inflammatory state
  - Effective therapy can often be quite targeted and specific
  - Targeted therapy can often allow for minimal increased infection risk

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NEJM 2004;351:2715-29.

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A FEW QUESTIONS TO PONDER

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22

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IMMUNOSUPPRESSANTS—BROAD EFFECTS

Drug	Effect	Other Considerations
Glucocorticoids	Genomic effects on immune and inflammatory pathways	Bone, BP, glycemia, eye, mood, HPA axis supression
Azathioprine	Antiproliferative	Bone marrow suppression, drug interactions
Mycophenolate	Antiproliferative, pronounced effect on lymphocyte purine biosynthesis	Bone marrow suppression, abdominal discomfort
Cyclophosphamide	Alkylating agent, antiproliferative	Fertility, hemorrhagic cystitis
Tacrolimus, Sirolimus, and Cyclosporine	Calcineurin inhibitors (lymphocyte signaling)	Renal toxicity, monitoring

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IMMUNOMODULATORS—SPECIFIC EFFECTS

Drug	Effect	Other Considerations
TNF Inhibitors (etanercept, infliximab, adalimumab, certolizumab, golimumab)	Specific cytokine blockade	Tuberculosis
IL-6 receptor (tocilizumab, sarilumab)	Specific cytokine blockade	Lipids, GI perforation
B cell depletion/inhibition (rituximab, belimumab, Obinutuzumab, anifrolumab)	Varying depletion of B cell count or activity	Hypogammaglobulinemia, hepatitis B reactivation, PML
Abatacept	T cell costimulation blockade	
IL-1 blockade (anakinra, canakinumab, rilonacept)	Specific cytokine blockade	

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IMMUNOMODULATORS—SPECIFIC EFFECTS

Drug	Effect	Other Considerations
IL-17 inhibition (secukinumab, ixekizumab, bimekizumab)	Specific cytokine blockade	IBD
IL-12, 23 inhibition (ustekinumab, guselkumab, risankinzumab)	Specific cytokine blockade	
Methotrexate	Folate antagonist	GI effects, bone marrow suppression, teratogen
Leflunomide	Inhibits pyrimidine synthesis	Teratogen, hepatic recirculation
Hydroxychloroquine	Increases pH in lysosomes	Visual field, skin discoloration
JAK inhibition (tofacitinib, baricitinib, upadacitinib	JAK-STAT pathway blockade	Lipids, MACE events, malignancies

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TAKE HOME POINT

- **Immunosuppressants** have broad effects
  - Therefore broad side effects, most importantly increased infection risk
- **Immunomodulators** have targeted, specific effects
  - Therefore specific side effects for which to watch out

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JUSTICE, DIVERSITY, EQUITY, AND INCLUSION

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QUESTIONS?

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