Pattern recognition and immune regulation in health and disease

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Team approach to modeling. The figure illustrates the various technical, data-gathering, and biological components of an integrated research approach to computational systems biology with a focus on fine-grained, dynamic modeling and simulation of processes such as cell signaling. Abbreviations: CMB, cell and molecular biology; HTS, high-throughput screening.
Immunity?

The body's ability to resist or eliminate potentially harmful foreign materials or abnormal cells

Consists of the following activities:

- Defense against invading pathogens (viruses & bacteria)
- Removal of 'worn-out' cells (e.g. old RBCs) & tissue debris (e.g. from injury or disease)
- Identification & destruction of abnormal or mutant cells (primary defense against cancer)
- Rejection of 'foreign' cells (e.g. organ transplant)
- Inappropriate responses:
  - Allergies - response to normally harmless substances
  - Autoimmune diseases
A delicate equilibrium

Challenges

• Discrimination between *self* and *non-self*
  – bacteria
  – fungi
  – vira
  – parasites
  – (transplants)

• Evolution

• Dealing with non-pathogenic factors
Lethality from pathogenic factors

**Bacteria** - induce tissue damage & produce disease largely by releasing enzymes or toxins that physically injure or functionally disrupt affected cells & organs.

**Viruses** - can only reproduce in host cells & cause cellular damage or death by:
- depleting essential cellular components
- causing cellular production of substances toxic to cells
- transforming normal cells into cancer cells
- inducing destruction of cells because infected cells is no longer recognized as 'normal-self' cell
Collaboration between various immune cell subsets

**Structural pattern-based response**
(non clonal)

**Peptide sequence-based response**
(clonal)
Dendritic cells and their functions

Linking innate and adaptive immune compartments
Sensing of danger

Different environmental triggers:

- Lipopolysaccharide (TLR2 Ligand)
- Lipoteichoic Acid (TLR2 Ligand)
- Bacterial DNA (TLR3 Ligand)
- Lipopolysaccharide (TLR4 Ligand)
- Peptidoglycan (TLR2 Ligand)
- Flagellin (TLR5 Ligand)

[Diagram showing various triggers and their interactions with the immune system]

References:
The impact of the molecular signature of DC on IR
The ‘sweet’ deal – sugar induced signalling

Nature Reviews Immunology 11, 275-288 (2011)
Dendritic cell activation
Gearing of Th cell functionality based on DC signature

**Cell mediated immunity**
- CD8+ activation
- Macrophage activation (Th1)
- Neutrophil activation (Th17)
- Immunopathology: Autoimmune diseases

**Humoral immunity**
- B cell activation
- Immunopathology: Atopic diseases

**Tolerance**
- Tolerance to harmless antigens
- Immunopathology: Hyporesponsiveness?
Discrimination between “self” and “non-self”

Every immune response depends on regulation at the single-cell level.
Meeting places (DC – T)

- Adenoids
- Tonsil
- Thoracic duct
- Left subclavian vein
- Lymph nodes
- Right lymphatic duct
- Thymus
- Spleen
- Peyer’s patches
- Large intestine
- Appendix
- Bone marrow
- Tissue lymphatics

Antigen recognition in lymphoid organs

- CD4+ T cells
- CD8+ T cells
- CD8+ effector T cells (Tc1 cells)
- CD8+ T cells (CTLs)

T cell proliferation and differentiation

- Naive T cell
- Effector T cell
- Memory T cell

Migration of effector T cells to site of antigen

- Infected cell with microbes in cytoplasm
- CD8+ T cells (CTLs)

MACROPHAGE ACTIVATION, KILLING OF INGESTED MICROBES

INFLAMMATION

KILLING OF INFECTED CELLS

© Elsevier, Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com
Infectious agents
Allergens
Foods

Mediastinal LN, BALT from lung;
PP, mesenteric LN from gut

“2nd hit” upon entry
Attention-specific functions induced?

Blood

Efferent lymphatics

Migration of effector, naive, and memory T cells
into bloodstream to lymphoid and nonlymphoid tissues

An inter-collaborative network
Molecular signature induced in PBMCs by influenza vaccination

Nature Immunology (2011); DOI: doi:10.1038/ni.2067
Explicit transcriptional profile in distinct immune cell subsets: The importance of single cell type targeting

Nature Immunology (2011); DOI: doi:10.1038/ni.2067
Why is the molecular signature of DC relevant?

DC regulates the adaptive immune response by means of its functional phenotype.

Specific on/off switching of regulatory pathways in DC may be one place to focus in order to switch on/off the host response – depending on the situation.

Yet, we lack explicit knowledge into the signalling events that drives the response in the proper direction.

- But combinatorial efforts will do the job...
Conserved innate and adaptive immune effector modules in the gut

Adverse immune reactivity in lung tissue

**IMMUNE PATHOGENESIS IN ASTHMA**

- TLR2,3,8,9
- γδ T
- TSLP
- IL-33
- IL-25
- Eotaxin
- IL-8
- TNF-α
- IL-1β
- DC
- NKT
- Mφ, M2
- Eosinophils
- Neutrophils
- CCL17
- CCL22
- OX40L
- IL-4
- IL-13
- No IFN-γ
- IgE
- IgG1
- B cell
- IL-4
- IL-5
- TH2
- Asthma

Muscles spasm, Narrowed bronchioles, Mucus
Intelligent design of future therapies

**Computer modeling/simulation**
- Creation of software tools for constructing and simulating complex multiscale biological processes

**Genomics**
- Collection and analysis of data on gene expression, miRNA, epigenetic modifications, discovery of gene regulatory networks; in connection with CMB, experiments to connect signaling to gene expression prior to and in follow-up to modeling such connections

**Cell/molecular biology**
- HTS: high-throughput screening, and interactions) in modular networks; testing of predictions from models using RNAi and related technologies

**Proteomics**
- Protein modifications, number of molecules, \( k_a / k_d / k_{cat} \ldots \) for parameterizing models

**Bioinformatics**
- Development and application of statistical tools for extracting new data, construction of statistical inference network models

**Immunology**
- Wet lab experiments at the cell and organism levels to explore immune behavior and feed data into as well as test emerging models of immune function and host/pathogen interactions

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