**Immunology for the Non-Immunologist**

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**Session Summary**

MS is believed to be an immune-mediated disease and over the past 25 years much has been learned about the inflammatory and degenerative processes responsible for the CNS damage seen in the disease. While much has been learned and applied to disease modifying treatment strategies, additional immunopathological mechanisms continue to be elucidated and will have implications on future directions of treatment. This program will review normal immune response, our basic understanding of the immunopathology in MS and the mechanisms of action of our current DMT’s. This will be followed a deeper look into more recently discovered inflammatory and degenerative mechanisms that are involved with the inflammatory as well as degenerative processes seen in relapsing and progressive forms of MS.
Agenda Part I:
Basic Immunology for the Non-Immunologist
1:15 PM - 2:45 PM

1:15 – 1:45 PM  How does the normal immune system work?
                 Kathleen Costello

1:45 – 2:15 PM  What causes CNS inflammation in MS?
                 Anne Gocke, PhD

2:15 – 2:45 PM  How do the current DMT’s affect the altered immune response in MS?
                 Scott Newsome, DO

2:45 - 3:00 PM  Questions?

Agenda: Part 2
Advanced Immunology for the Non-Immunologist
3:00 PM – 4:30 PM

3:00 pm – 3:45 PM  Inflammation; Is it all bad? New insights in MS immunopathology
                   Suhayl Dhib-Jalbut, MD

3:45 – 4:15 PM  How does progressive MS differ from relapsing MS?
                 Anne Gocke, PhD

4:15 – 4:30 PM  Questions?
Objectives

Following this session, participants will:

1. Differentiate between innate and adaptive immunity.
2. Describe antigen presentation and lymphocyte activation.
3. Contrast the normal immune response to that seen in multiple sclerosis.
4. Compare the MoA’s of the current FDA approved DMT’s for MS.
5. Describe how inflammation in MS may be beneficial.
6. Explain immunological differences between RRMS and progressive MS.

PART 1: BASIC IMMUNOLOGY FOR THE NON-IMMUNOLOGIST
The Normal Immune Response

Kathleen Costello, MS, ANP-BC, MSCN, MSCS
National Multiple Sclerosis Society
Purpose of the Immune System

• Prevent infections
• Eliminate established infections

Important Properties of the Immune System

• Specificity
• Diversity
• Memory
• Ability to distinguish self from non-self
  – Inability to recognize self
    • innate immunity
  – Ability to self-regulate and eliminate auto-reactive cells
    • adaptive immunity
Innate and Adaptive Immunity

• **Innate**
  – Rapid response system
  – No memory
  – Reacts to cells and substances: identifiers of different microbes
  – Can stimulate adaptive immunity

• **Adaptive**
  – Slower to respond
  – Has memory
  – Humoral
    • Recognizes pathogens outside of cells
  – Cell mediated
    • Recognizes pathogens inside of cells

Who’s who in the Immune System?

**Cells**
- Neutrophils
- Monocytes
  - Macrophage
  - Dendritic cells
- NK cells
- T-cells
  - T-helper cells: CD4
  - Cytotoxic T cells: CD8
  - T-regulatory cells
- B-cells

**Molecules**
- MHC I and II
- Costimulatory molecules
- Adhesion molecules

**Proteins and messengers**
- Chemokines
- Cytokines
- Interleukins
- Interferons
- Complement
How does the Immune System Prevent Infection?

- Innate Immune activity
  - First defense:
    - Stop entry of pathogens into the body by creating barriers to pathogen entry:
      - Respiratory
      - Skin
      - GI tract
  - Activation of cells that destroy the pathogen
  - Involved in inflammation and eradication of infected cells

Injury

Splinter, causing local bacterial infection

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Macrophages: Sentries of Innate Immunity
Innate Immunity: First Responders
Neutrophils and Monocytes

NK cells
**Innate Immunity**

1. Neutrophils #1
   - Short lived
   - After about 24 hrs

2. Monocytes #2
   - Differentiate into macrophages
     - Powerful phagocytes
     - Stimulate repair mechanisms
     - Produce IL-1, TNF, ROS (H2O2) when activated
     - APC for lymphocyte function in adaptive immunity
     - Become further stimulated by adaptive immune mechanisms

**Innate Immunity**

3. NK cells – destroy viral infected cells
   - Cytotoxic lymphocytes that are Killing machines
   - Recognize and destroy infected cells without presentation
     - injects infected cells with suicide proteins
   - Induce secretion of interferon gamma which activates macrophages

4. Complement activation
   - Complement proteins recognizes chemical groups on the surface of an invader and signal other proteins.
   - Complement can tag an invader so other cells know it needs to be destroyed. Also complement can bore a hole in an invading cells which will destroy it.
Neutrophils and Monocytes

- Both neutrophils and monocytes can directly recognize the characteristic features of microbes
  - Detect features on the cell surface
    - Virus, bacteria, parasite
  - Phagocytosis follows recognition
- But, some microbes that cause human disease are able to resist phagocytosis – can be engulfed but not destroyed
- The innate immune system responders create the “game plan” for the activation and response of the adaptive immune system.

Adaptive Immunity
Adaptive Immunity

- When the actions of the innate immune system are not sufficient to eliminate the pathogens, the adaptive immune system is activated
  - Cell-mediated
    - T-cells
      - Th-1, Th-2, Th-17
  - Humoral
    - B-cells
    - T-cells
    - Antibodies
    - Complement

Activation of Adaptive Immunity

- B-cells recognize pathogens that are in circulation and outside of the cell
  - Able to recognize and make antibodies –
    - An initial and weaker response
  - They are also stimulated to become active by T cells
    - This takes longer, but provides a more robust Ab response
- T-cells recognize pathogens that are presented to them by antigen presenting cells
  - APC's process a virus and display part of it on the APC cell surface and only in this way can the T-cell recognize the antigen
T-cell Activation

- Antigen presenting cells encounter antigens, engulf them and process them.
- A particle of the antigen is then presented on the APC cell surface on a specific type of surface cell called MHC (major histocompatibility complex).
- CD-4 cells (Th-1, Th-2, Th-17) recognize antigen presented by MHC class II.
- CD-8 cells (Cytotoxic T cells) recognize antigen presented by MHC class I.

Adaptive Immunity: T-cell activation
**T-cell activation**

- *The differentiation into Th-1, Th-2 or Th-17 cells is not a random process*
- It is regulated by the stimuli the naïve T-cell receives with antigen presentation
  - **Th-1** differentiation occurs with stimulation by IL-12 and IFN-γ which are produced by macrophages, dendritic cells. NK cells produce IFN-γ
  - **Th-2** differentiation occurs with stimulation by IL-4
    - As with parasitic infections
  - **Th-17** differentiation occurs with stimulation by IL-6, and IL-1 and IL-23 produced by macrophages and dendritic cells

**Adaptive Immunity:**
**B-cell activation**

- Pathogen in circulation is recognized by B cell surface receptor
- B cell processes some of the pathogen and displays on MHC for T helper recognition.
- Comstimulation from the T cell is necessary for activation
- T cell then helps to activate the B-cell to become an effector B-cell or plasma cell, an Ab secreting cell.
B-cell activation

Different antibodies for different jobs (infections)

- IgM – first Ab made, activates complement, opsonizes pathogen
- IgA – abundant in mucosal surfaces, and protects those surfaces. Resistant to digestive acidity. Coats pathogens so they cannot attach to mucosal wall
- IgG – opsonizes pathogen (binds) and optimizes phagocytosis
- IgE – mast cells bind to IgE causing a signal for the mast cell to degranulate – releasing histamine and other chemicals.
T-Regulatory Cells

Turning off the Immune Activation

- T regulatory cells
  - A subpopulation of T cells
  - Modulate the immune system
    - Shut down the immune responses after they have successfully eliminated invading organisms
  - Maintain tolerance to self antigens
    - To help prevent auto-immunity
Summary

• The immune system is a highly complex system that protects us from pathogens and eliminated those that have caused infection
• The normal functioning immune system has three important features:
  – Specificity
  – Diversity
  – Memory
• And it has the ability to differentiate self from non-self, and leave self alone
• However, if the immune system malfunctions and loses the ability to distinguish self/non-self an autoimmune response may occur

References

Part 2: Advanced Immunology for the non-immunologist

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