Mast Cells in the Immune Response Against Bacteria

Soman N Abraham, PhD
Duke University
Duke-National University of Singapore
Mast Cells (MCs)

Paul Ehrlich 1878 doctoral thesis
Diseases associated with Mast Cells

- Allergic diseases
- Asthma
- Rheumatoid arthritis
- Bullous pemphigoid
- Multiple sclerosis

However, what is the true physiological function of these cells?
Four of top ten causes of death are infectious diseases
Critical balance between microbial challenge and the immune system

Rapid and appropriate immune responses = Health
Slow and inappropriate immune responses = Disease
Raison d'être for mast cells

Immune surveillance against pathogens through modulation of Immune cell trafficking
MC-bacteria interactions during infection and immunity

- Unique properties of mast cells that favor immune surveillance
- Modulation of innate and adaptive Immunity to pathogens
- Boosting mast cell activity to enhance immunity.
- Contraction of inflammatory responses and initiation of wound repair.
- Mast cell Suppression by pathogenic bacteria
Unique properties of MCs that favor immune surveillance

• Location, Location, Location...........

Skin, Mucosal surface, Circulatory system
Location at the periphery

- **Location:** Preponderance at host environment interface

Skin

10,000 per mm$^3$

Bronchial epithelium

3,000 per mm$^3$
Location near blood and lymphatic vessels

- Location near vasculature

Abraham and St. John Nat. Rev Immune, 2010
St. John and Abraham, J. Immune, 2013
Ability to dynamically sample blood vessels

Cheng LE, Hartmann K, Roers A, Krummel MF, Locksley RM.

Capacity to detect broad repertoire of incoming pathogens

Direct

Cell surface receptors: e.g. TLR2 and TLR4
Intracellular receptors e.g. RIG I

Indirect

Complement or IgG coated bacteria

Danger” signals or Alarmins: Defensins,
IL-33, ATP

Abraham and St. John Nat. Rev Immun, 2010
St. John and Abraham, J. Immunol, 2013
Two phase mediator response

Two phase response for rapid and sustained mobilization of immune cells

opsonized *E. coli*  
*Vibrio cholera* toxin

Denovo synthesis & secretion

Degranulation

15min  
3hrs

Sustained mediator response: Degranulation → Regranulation

Abraham and St. John Nat. Rev Immun, 2010  
St. John and Abraham, J. Immunol, 2013
Mediators released by mast cells

**Preformed mediators (from the granules):**

- serine proteases, such as tryptase
- histamine (2-5 pg/cell)
- serotonin
- proteoglycans, mainly heparin (active as anticoagulant)

**Newly formed (produced after activation):**

- thromboxane
- prostaglandin D2
- leukotriene C4
- platelet-activating factor

- cytokines
Mobilization of Immune cells

Vascular leakage

Activation of Endothelial Cells
- Upregulation of adhesion molecules
- Breakdown of tight junctions
- Exocytosis of Weibel-Palade bodies
- Inflammatory mediator production/secretion

Activation of Smooth Muscle Cells
- Vasodilation

Increased Blood Flow

Systemic Spread of Mast Cell Mediators

Extravasation of Leukocytes
- Neutrophils, DCs, NK cells, etc.

Leakage of Plasma Proteins
- (IgG, complement, etc.)

Mediator Release
- Cellular Recruitment
- Vascular Leakage
- Clot Prevention

Studies employing wild type and mast cell deficient mice:
Mobilization of Immune cells to sites of infection in the skin and mucosal sites

Wild type  
MC deficient  
MC deficient + MC

+ Pathogen  (Skin, gut, lungs, bladder, peritoneal cavity)

Microbial clearance  >> mouse mortality
Mast cell mediated mobilization of Innate Immunity: Recruitment of key immune cells to sites of infection through TNF.

Neutrophil mediated clearance of bacterial pathogens in the lung and peritoneal cavities

Mast cell mediated recruitment of neutrophils

Second wave counter
Attack (adaptive immune response):
Mobilization of
dendritic cells
and lymphocytes

Injected E.coli

Coordinate trafficking of
dendritic cells and lymphocytes (24hrs)
Mast cells recruit dendritic cells to the site of infection (limited DCs seen in MC deficient mice).

Mast cells also modulate trafficking of DCs from sites of infection to draining lymph nodes.

Mast cell promote sequestration of T cells from the circulation resulting in Lymph node hypertrophy.

How can mast cells mediate immune cell trafficking in distal lymph nodes?

- Dilution effect
- Degradation potential on mast cell cytokines


Draining node

Infection
MC degranulation results in release of stable particles
Mast cells release cytokine loaded granules as highly stable drug delivery devices.
Mast cell granules retain TNF even after extracellular release (slow drug release vehicle)

TNF-GFP expressing RBL-2H3 cells
Mobilization of Immune cells to Distal Sites

- Mast cells are in close proximity with lymphatic system

Mast cell granule trafficking along lymphatic vessel
Trafficking of mast cell granules in lymphatic system

Trafficking of isolated mast cell granules into draining lymph nodes of mast cell deficient mice


Isolated granule induced lymph node hypertrophy

Can we co-opt the immune enhancing properties of MCs?
A major limitation in the vaccine industry is the lack of effective adjuvants.

Vaccine = Protective antigen(s) + adjuvant
(typically not immunogenic)

*Bottleneck in the vaccine industry*
Nasal site: A convenient for vaccination…..
Very small amounts of antigen required
Convenient for vaccine delivery
Needle free
Proximal to the NALT (nasal-associated lymphoid tissue)
- an immunological inductive and sampling site
Mucosal in addition to systemic immunity

Cross section of the mouse snout
Immune cell mobilization in vivo by triggering mast cell activation with small molecule activators

Small molecule mast cell activator as adjuvant

**Compounds**: 48/80

- Fold change in dendritic cell numbers
  - Wild-type
  - W/W^v
  - W/W^v + Mast Cells

- Lymph node weights (% of control)
  - WT
  - W/W^v

-McLachlan et al. Nature Med. 2008-
Enhancing immune responses to anthrax vaccine by adding MC activator as adjuvant
Immune responses at mucosal sites in mice to PA of *Bacillus anthracis* following nasal instillation

Protection against lethal vaccinia virus infection using B5R antigen (nasal immunization)

MCs are always not protective during bacterial infections

Dilemma faced by the immune system: For tissue repair to commence inflammation must cease

- Infection
- Microbial clearance
- Tissue repair
- Immune Response
- Tissue destruction
Bladder: Need for Temporal Contraction of immune responses

- Mast cells initiate inflammation in the bladder following infection. However, after several hours, they also initiate contraction of immune reactions to facilitate repair of epithelium.

Superficial bladder epithelium (above) is shed to reduce bacterial burden. Mast cells contract inflammation through IL-10 production.

*Chan et al. Immunity, 2013*
Exfoliation of Bladder Epithelial cells following infection

Saline Control

6 h infection

12 h infection
Selective upregulation of immunosuppressive IL-10 6 hours after infection

Chan et al. Immunity, 2013
Downsides for the early inactivation of the adaptive immune system

- Lack of IgG antibodies after bladder infection
- Recurrent bladder infections

Mast cell suppression by Salmonella

Highly evolved gut pathogen that rapidly spreads in the host

Salmonella inject SptP, a tyrosine phosphatase into MCs blocking MC degranulation

Rapid Salmonella spread is attributable to suppression of gut MCs allowing for bacterial trafficking to mesenteric lymph nodes.

It appears Salmonella has recognized the importance of MCs and have evolved ways to neutralize these cells.

Mast Cell Communicate with multiple Host Cells
In order to be effective the immune responses needs to be precisely coordinated and synchronized.

Conductor of the orchestrated immune response?

Orchestra can still play without the conductor……..
Research colleagues

Ashley St. John, PhD
Haewoong Choi
Cheryl Chan, PhD
Christian Kunder, MD, PhD
Guojie Li, Ph.D
James B. McLachlan, Ph.D
Justin P. Hart, Ph.D, MD

Faculty:
Herman F. Staats, Ph.D
M. Dee Gunn, MD
Salvatore Pizzo, MD, Ph.D
Brent Berwin, PhD
Kam Leong, Ph.D
Salvatore Pizzo, MD, Ph.D