Adjuvant Effects of Mast Cell Granules

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Pathogen-Immune System Tussle

Health

Microbial attack

Disease

Slow and inappropriate Immune response

Rapid and appropriate Immune response

Microbial attack
There growing evidence that mast cells play critical and previously unappreciated roles in modulating major immune responses.
Sequential Primary Immune Responses to Pathogens

1. Exfoliation of epithelial cells
   (Innate immune response)

2. Recruitment of immune cells
   (Innate immune response)

3. Trafficking of antigen-presenting cells to draining nodes
   (Adaptive immune response)
Mast cells possess several unique traits that promote their contribution to immune defense.

Mast cells function primarily through orchestration of immune cell trafficking.
Secretory Properties of mast cells
(able to achieve rapid and sustained signaling to a wide variety of cells)

Two phase response to insult:

Large repertoire of Inflammatory mediators

Degranulation

15min

3hrs

Denovo synthesis & secretion

Proinflammatory responses followed by antiinflammatory responses

Can undergo multiple bouts of degranulation and regranulation
Location at the interface of the host–environment (immediately able to perceive insult)

Skin

Bronchial epithelium

10,000 per mm³

3,000 per mm³
Located proximal to blood and lymphatic vessels
(able to disperse signals rapidly and widely in the body)

Mouse ears
Broad spectrum Recognition of Pathogens

Virus

Antibody mediated recognition
(IgE, IgG, etc)

Bacteria

Parasite

Direct recognition
(TLR3, TLR4, etc)
Adaptive Immune Responses to Pathogens

Coordinate Trafficking of antigen presenting cells and naïve T cells to draining nodes

How does TNF derived from peripheral mast cells reach draining lymph nodes without degradation of dilution? Could they be trafficking within nanosized particles?
Do mast cells release stable, insoluble heparin/protein complexes?
Close proximity between mast cells and lymphatic system

Mast cell granule trafficking along lymphatic vessel

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


Isolated granule induced lymph node hypertrophy
Isolated mast cell granule—highly stable can remain intact in excess of 70 days at room temperature.
Our studies reveal that during infections, mast cells orchestrate the trafficking of key immune cells to infection sites or to draining lymph nodes through the release of cytokine loaded nanoparticles.

There is currently a dearth in available adjuvants for vaccines........

Can we boost immune responses to vaccines by co-administering cytokine loaded synthetic particles inspired by mast cell granules?

Synthesis of TNF bearing mast cell inspired nanoparticles

Natural granules:
- polyanion: heparin proteoglycans, MW ~750 kDa in great excess
- polycation: Proteases, MW ~ 25-35 kDa

Synthetic granules:
- polyanion: commercial heparin, MW 15-30 kDa
- polycation: Chitosan (Poly-(1-4)-2-Amino-2-deoxy-β-D-Glucan) MW 70-160 kDa in approximately equal quantities
Synthetic particles can rapidly traffic from the periphery to the draining lymph nodes (15min)
TNF is highly potent when packed into synthetic particles

Natural granules          Synthetic granules

Particulate TNF as an adjuvant promotes germinal-center production.

Particulate TNF is an effective adjuvant

Particulate TNF is an effective adjuvant that protects against a lethal flu challenge.
TNF-bearing nanoparticles enhance immune responses to current Flu vaccine

Serum IgG Endpoint Titer (2-fold over naive)

- Saline
- Fluzone alone
- pTNF
- sTNF

The graph shows that pTNF enhances immune responses significantly compared to saline, Fluzone alone, and sTNF.
Relevance of particle distribution and concentration gradient of released mediators in activating cells
Conclusions

Mast cells play a key immune surveillance and regulatory role against infectious diseases.

Mast cells modulate local and distal immune cell trafficking by releasing multiple mediator loaded particles.

It is possible to coopt some of their functions to enhance current vaccines or in the development of new vaccines.
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