Mast Cell Mediated Cardiac Effects of Particulate Matter

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Hypothesis:

Particulate matter mediated activation of cardiac mast cells results in matrix metalloproteinase (MMP) activation and accelerated myocardial remodeling, thereby further impairing cardiac function and leading to an increased incidence of adverse cardiovascular events.
Mast Cell Mediated Myocardial Remodeling

- Cardiac mast cell-mediated activation of gelatinase and alteration of ventricular diastolic function.
  

- Cause and effect relationship between myocardial mast cell number and matrix metalloproteinase activity.
  
Link Between Mast Cells, Particulate Matter Exposure and Cardiovascular Disease

Canines as sentinel species for assessing chronic exposures to air pollutants: part 2. Cardiac pathology.


- Cardiac Mast Cell Degranulation Noted
Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers.


- Histamine Release and Increase in Mast Cell Number
Particulate Matter Mediated Increase in Endothelin

Elevation of Serum Endothelins and Cardiotoxicity Induced by Particulate Matter (PM(2.5)) in Rats with Acute Myocardial Infarction.


- Total serum endothelin concentrations were significantly elevated in both myocardial infarct and sham-operated control rats following PM exposure.
Endothelin-1 Mediated MMP Activation

LV Matrix Metalloproteinase Activity (% Relative to Control)

Control  Isolated Normal Heart + ET-1  Normal Tissue Extract + ET-1

Collagen Volume Fraction

Control  0.99% ± 0.04  ET-1 Treated  0.69% ± 0.09*


* p < 0.01 vs. Control
Particulate Matter: Mast Cell - MMP Hypothesis

- Particulate Matter Exposure
- Mast Cell Recruitment
- Mast Cell Degranulation
- Collagenase Activation
- Collagen Degradation
- ET-1
- Ventricular Dilatation

Proteases:
- Trypsin
- Stromelysin
- Chymase
- Cathepsin G

Cytokines:
- TNF-α

Chemokines:
- ET-1

MMPs:
Specific Aims

To determine:

• 1) the causal relationship between acute diesel PM exposure, mast cell activation, and exacerbation of CHF with a resultant increase in morbidity and mortality

• 2) the mechanisms by which subchronic diesel PM exposure accelerates cardiac remodeling and the development of CHF.
Infrarenal A-V Fistula

Aortocaval Fistula
Opened Between
Aorta and Vena Cava Using an 18 Gauge Needle
Cardiac Remodeling Post-Fistula

Particulate Matter Exposure

Nebulization

• SRM 2975 DEP (NIST)
  - 4.5 mg / 20 ml 0.9% Saline
  - Nebulized delivery at 3.0-3.5 l/min O2
  - One 30 min exposure per day

Diesel Exhaust Emissions

• Lovelace Respiratory Research Institute
PM Mediated Depression in Cardiac Function of Normal Hearts
PM Mediated Mast Cell Response

LV Mast Cell Density (mm$^{-2}$)

- Control
- 2 Day PM
- 3 Day PM

Comparison of LV mast cell density between control and days 2 and 3 of PM exposure.
PM Mediated MMP Activation

LV Matrix Metalloproteinase Activity (% Increase Above Control)

Control | Days of PM Nebulization

1 | 2 | 3
Ongoing Collaborations

Auburn University
- Jason Gardner
- Joseph Janicki

Lovelace Respiratory Research Institute
- Matt Campen
- Joe Mauderly
- Jake McDonald

University of Arkansas for Medical Sciences
- Martin Hauer-Jensen

University of Alabama - Birmingham
- Lou Dell’Italia
- Susan Oparil

University of South Carolina
- Tom Borg
- Wayne Carver