The Effects of Obesity on Innate Immune Response

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Obesity Trends Among U.S. Adults
(BMI ≥30, or about 30 lbs. overweight for 5’4” person)

1990

1999

2009

No Data  <10%  10%–14%  15%–19%  20%–24%  25%–29%  ≥30%

Source: Behavioral Risk Factor Surveillance System, CDC.
Obesity as an inflammatory disease

• A chronic inflammatory state manifest by:
  – Elevated levels of inflammatory cytokines
  – Blood neutrophilia

• Many of the medical complications of obesity are believed to be related to this inflammatory state
Pathogenesis of critical illness

- Underpinning of most critical illness is a systemic inflammatory state (SIRS)
- Cytokine-driven influx of activated neutrophils to the lung and other organs
- Mortality from critical illness has been shown to correlate with levels of both:
  - Proinflammatory cytokines
  - Blood and tissue neutrophilia
Obesity reduces mortality in critical illness

60 day mortality from the multicenter international ICU nutrition practices survey (n=8838).

Martino, et al, in review
Inflammatory cytokines levels in critical illness are lower in the obese.

*Plotted data are unadjusted. p-values: <0.05 (IL-6), <0.001 (IL-8) from multivariable linear regression adjusting for APACHE 3 score, gender, ALI risk factor, tidal volume group assignment, and comorbid diabetes.

Stapleton, et al CHEST 2010
Our focus: Obesity and the innate immune response

• Clinical consequences: Paradoxical
  – Improved outcomes in severe inflammatory illness
  – Impaired response to infection

• Translational research: Iterative process from clinical samples to laboratory modeling & back

• Collaborations:
  – Clinical trials networks in critical illness & nutrition
  – NIH, Canada, Belgium, Netherlands
Our focus: Obesity and the innate immune response

• We find that obesity is associated with:
  – Abnormal cytokine response
  – Defects in neutrophil function

• Elements of metabolic syndrome:
  – Dyslipidemia
  – Leptin resistance
  – Insulin resistance
Interdisciplinary opportunities

• Non-critical illness
  – E.g. effects of obesity on cancer immune surveillance

• Public health/epidemiology
  – E.g. infectious complications of obesity

• Nutrition
  – E.g. nutritional effects on innate immunity
College of Medicine Obesity Research Group

- Effects of weight loss in overweight patients with heart disease in the cardiac rehabilitation setting – Ades
- Clearance of brain natriuretic peptide in obesity and the expression of the natriuretic peptide clearance receptor in adipose tissue – Annis
- Mechanisms through which Natural Killer T cells become activated by oxidized LDLs in disease – Boyson
- Impact of resistance training added to a weight loss intervention (Vtrim) for overweight breast cancer survivors – Dittus
- Obesity and asthma – Dixon
- Effects of obesity on tumor progression – Heintz
- Lung-chest wall mechanics of the obese and asthma phenotype – Irvin
- Effect of high fat diet on proteolysis-mediated remodeling within the brain regions regulating feeding behavior and energy expenditure – Jaworski
- Pancreatic β-cell mass compensation to insulin resistance – Jetton
- Transcription factors and the insulin and glucose signaling pathways in the regulation of pancreatic β-cell growth and function – Peshavaria
- Critical care nutrition and outcomes of obese critically ill patients – Stapleton