Impact of Age and Fat Content on Toxicities Due to Pro-inflammatory Cytokine Storm Induced During Immunotherapy

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MOLECULAR BASIS OF THE AGING PROCESS IN THE IMMUNE SYSTEM

ALTERED TRANSCRIPTION FACTORS

Hormonal changes
ROS

THYMIC INVOLUTION

↓ Thymic Output
↓ Naive T cells
↑ Memory T Cells

Bone marrow microenvironment
↓ Functional HSC

REACTIVE OXYGEN SPECIES

- Dysfunctional Proteasome
- Chaperone overload
- Altered Autophagy / Proteostasis

ALTERED DNA REPAIR / CHROMATIN REMODELING; TELOMERASE ATTRITION

Altered Gene Regulation

Loss of cell surface Costimulators (CD28+ Cells)

ALTERED FUNCTION
T Cells, B Cells, APC

Increased Constitutive NFκB

‘INFLAMM-AGING’ / ‘OXI-INFLAMM-AGING

Altered Niche

ALTERED IMMUNE REGULATION “IMMUNE SENESCEENCE”

Ponnappan, S et al. Aging and Immune Function: Molecular Mechanisms to Interventions. 2011
GIVEN THE AVERAGE AGE OF A CANCER PATIENT, WHAT IS THE IMPACT OF AGE ON IMMUNOTHERAPY?
AGED MICE RAPIDLY SUCCUMB TO MULTI-ORGAN PATHOLOGY FOLLOWING IMMUNOTHERAPY
INCREASED PRO-INFLAMMATORY CYTOKINES FOLLOWING IMMUNOTHERAPY IN AGED MICE

**TNF-α**
- Serum TNF-α (pg/ml)
- Young: Ctrl, IT
- Aged: Ctrl, IT

**IL-6**
- Serum IL-6 (pg/ml)
- Young: Ctrl, IT
- Aged: Ctrl, IT

**IFN-γ**
- Serum IFN-γ (pg/ml)
- Young: Ctrl, IT
- Aged: Ctrl, IT

***Significant difference***
DIFFERENCES IN BODY FAT CONTENT WITH AGE AND CALORIC RESTRICTION

WS
FS
Young Middle Aged
Ad Libitum

Calorie Restricted

<table>
<thead>
<tr>
<th></th>
<th>Body Weight (g)</th>
<th>Visceral fat (g)</th>
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<tbody>
<tr>
<td>AL:young</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>AL:aged</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>Aged:young</td>
<td>30</td>
<td>1.5</td>
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<tr>
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*** indicates statistical significance.
ROLE OF FAT IN INFLAMMATORY PROCESSES

Obesity Associated With:
- Infiltration of CD8s, MOs
- Decreased T regs
- TNFα mediated induction of insulin resistance (IR) by activating SOCS proteins that bind to insulin receptor
- IL-6 promotes IR by activating SOCS-3, STAT 3-5
- FFAs lead to ER stress activating NFkB and recruitment of immune cells
CALORIC RESTRICTION RESCUES AGED MICE FROM EXACERBATED CYTOKINE STORM AND ACUTE TOXICITY
YOUNG OBESE MICE EXPRESS HEIGHTENED LEVELS OF PROINFLAMMATORY CYTOKINES SIMILAR TO AGED
MACROPHAGE DEPLETION PROTECTS AGED MICE FROM ACUTE TOXICITY AND DIMINISHES CYTOKINE STORM
TNF-BLOCKADE RESCUES AGED MICE FROM ACUTE TOXICITY FOLLOWING IMMUNOTHERAPY

6A

![Graph showing percent survival over days post start of treatment for different groups.]

- **Aged: rIgG/PBS**
- **Aged: Low IT/hIgG**
- **Aged: Low IT/Enbrel**

![Bar chart showing ALT (U/L) for different groups.]

- **rIgG/PBS**
- **Low IT/hIgG**
- **Low IT/Enbrel**

**Aged**
CONCURRENT TNF-BLOCKADE WITH IMMUNOTHERAPY ALLOWS FOR ANTITUMOR EFFECTS IN AGED MICE
CONCLUSIONS

• FOLLOWING IT, AGED MICE EXHIBIT:
  – CYTOKINE STORM: ELEVATED TNFa, IL-6, and IFNg
  – MULTIORGAN FAILURE, RAPID DEATH
  – MACROPHAGE DEPENDENT
  – TNFa CRUCIAL MEDIATOR

• BODY FAT PLAYS ROLE IN EXACERBATED CYTOKINE PRODUCTION

• AGE and BODY FAT MAY PLAY SIGNIFICANT ROLES IN CLINICAL CANCER THERAPY OUTCOMES
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