Obesity - from clinical practice to research (aka Cluster 4).

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October 11th 2013
Outline of talk

A few facts

Obesity and the immune system

Gastrointestinal hormones and immunity
1. We don’t recognise obesity..

BMI 40

BMI 52
1. We don’t recognise obesity..

BMI 40
Guess 32

BMI 52
Guess 41

Body mass index estimation and measurement by healthcare professionals
Tomás Ahern, Kirsten Doherty, Daniel Kapeluto, Maeve Davis, Una Mulholland, Edwina Rossiter, Irene Gilroy, Astrid Billfalk-Kelly, Patricia FitzPatrick, Leslie Daly, Cecily Kelleher, Donal O’Shea
Open Journal Preventive Medicine August 2012
2. Morbidly obese individuals have altered decision making capacity

*J Psychosom Res.* 2011 Feb;70(2):189-96.

**Impaired decision making among morbidly obese adults.**

Brogan A, Hevey D, O'Callaghan G, Yoder R, O'Shea D.
TOXIC ENVIRONMENT
How much insulin would you advise?
They tell you what they do.
Nutrition in pregnancy vital
3. Einstein was bright

Albert Einstein (1879 - 1955)

I fear the day when the technology overlaps with our humanity.
3. Einstein was bright

**Albert Einstein** (1879 - 1955)

I fear the day when the technology overlaps with our humanity. The world will only have a generation of idiots.
4. Sedentary Time Kills

Now 4\textsuperscript{th} leading preventable cause of death

“Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it.”
Times and play have changed….
4. Sedentary Time Kills

Now 4\textsuperscript{th} leading preventable cause of death

“Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it.” - Plato
5. Obesity drives inflammation

Anti-inflammatory cytokines: IL-10, IL-4, IL-13

Pro-inflammatory cytokines and chemokines: IL-1β, TNF-α, IL-6, CCL2, CCL3, CXCL8

LEAN INSULIN SENSITIVE

OBESE INSULIN RESISTANT

Treg
CD4+ (Th1)
CD8+

Anti-inflammatory M2-like
Pro-inflammatory M1-like
Mixed M1/M2
Necrotic adipocyte "crown-like" structure
Blood vessel
6. Weight loss especially gastric bypass improves inflammation

• Asthma

• Psoriasis

• Arthritis

• Cancer

• Multiple Sclerosis
Outline of talk

A few facts

Obesity and the immune system

Gastrointestinal hormones and immunity
Obesity causes and worsens outcome in...

- Diabetes
- Cancer
- Dementia
- Sleep Apnoea
- Asthma
- Everything

- Suggests a common mechanistic fault
- Focussed our research on the circulating immune system
Circulating Immune System

• 10 mls of blood drawn from each patient day 1
• Contains 20 million “white cells”
• Analysed number and function of cell subtypes
Various cell types – with different surface markers
Studied five cell types to date

- Natural Killer Cells, invariant Natural Killer cells, Dendritic cells, MAIT cells and Macrophages

- Each cell subtype defined by surface markers on flow cytometry
Various cell types – with different surface markers
Flow cytometry
Flow cytometry
Natural Killer Cell  
- foot soldier of the immune system

- Key cell in attacking viruses and cancer cells

- Involved in a range of autoimmune conditions
Decrease in circulating natural killer cells in obesity

$n = 110, p = 0.006$

Natural Killer Cells in Obesity: Impaired Function and Increased Susceptibility to the Effects of Cigarette Smoke

Donal O’Shea¹, Tom J. Cawood², Cliona O’Farrelly³, Lydia Lynch⁴,⁵*

¹Department of Endocrinology, St. Vincent’s University Hospital, Dublin, Ireland, ²Department of Endocrinology, Christchurch Hospital, Christchurch, New Zealand, ³School of Biochemistry and Immunology and School of Medicine, Trinity College Dublin, Dublin, Ireland, ⁴Oncology and Hematology, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, Massachusetts, United States of America, ⁵Obesity and Immunology, Education and Research Centre, St. Vincent’s University Hospital, Dublin, Ireland
Smoking machine
Invariant Natural Killer Cell
– Swiss army knife of immune system

A key cell in the innate immune system

Represents 0.2% - 1.2% of circulating T cells

Interacts with other immune cells to determine the downstream immune response:

- Pro-inflammatory
- Anti-inflammatory
- Cytotoxic

Diagram Showing Interactions:
Invariant Natural Killer Cell

• Established role in pathogenesis of

  Cancer

  Psoriasis

  Asthma
iNKT cells in obesity

The invariant natural killer T cell is significantly depleted in severe obesity

Lynch et al, Immunity 2012
Gastric Bypass restores iNKT cell population in humans

Longitudinal

![Graph showing the relationship between Body Mass Index (BMI) and NKT cells (% T cells) pre-op and post-op. The graph indicates a significant increase in NKT cell population post-op.]
What happens if you get rid of iNKT cells in mice?

- Mouse model

- 0-12 weeks High Fat Diet (60% of kcals from fat) in wild type or iNKT knockout mouse

- Look at weight, metabolic status and inflammation
iNKT cell KO mice get fatter & more severe metabolic disease on HFD

**Weight (g)**

- WT
- Ja18KO

**Fat pads**

- WT
- Ja18KO

**Liver**

- WT HFD
- Ja18KO HFD

**Adipocyte diameter (µm)**

- WT
- Ja18KO

**HOMA-IR**

- WT
- Ja18KO
Adoptive transfer of iNKT cells but not T cells improves metabolism & weight

IL-4 & IL-10 dependent mechanism
Also re polarization of ATM
Reduction in serum inflammation

Please cite this article in press as: Lynch et al., Adipose Tissue Invariant NKT Cells Protect against Diet-Induced Obesity and Metabolic Disorder through Regulatory Cytokine Production. Immunity (2012), http://dx.doi.org/10.1016/j.immuni.2012.06.016

Adipose Tissue Invariant NKT Cells Protect against Diet-Induced Obesity and Metabolic Disorder through Regulatory Cytokine Production
IL-4 & IL 10 drive macrophages to switch on thermogenesis (UCP-1)

- Factors that affect IL-4 & IL-10 production will impact on thermogenesis and weight
Looked at thyroid hormone and cigarette smoke
Looked at cortisol and antipsychotic medication
Conclusion

• Weight effects the immune system

• The immune system effects weight
## Paediatric Cohort

<table>
<thead>
<tr>
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<th>Lean</th>
<th>Obese</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>12.6 yrs old</td>
<td>11.9 yrs old</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>52kgs</td>
<td>90kgs</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>4.9</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td></td>
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# Childrens Baseline Data

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<td>149</td>
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Reduction in iNKT cells number and function already present in obese children.
iNKT cells in breast fed versus bottle fed children

![Graph showing iNKT cell number in Breast vs. Formula feeding](image)
Percentage increase in BMI categories since 1986

Sturm and Hattori, Int J Obes 2012
Mucosal Associated Invariant T Cells

- Subset of innate T cells which represent 4% of circulating T cells

- MAIT cell population described by Lantz et al in 2003

- MAIT cells are absent in germ free mice and are defined by the gut microflora
MAIT cells in obesity

• No studies to date

• Gut Microflora significantly altered in obesity
  – Germ free mice don’t have MAIT cells

• Other innate populations altered in obesity – iNKT cell

Adipose Tissue Invariant NKT Cells Protect against Diet-Induced Obesity and Metabolic Disorder through Regulatory Cytokine Production
MAIT cells are depleted in adult obesity.
Obese MAIT cells show increased IL-17 production suggesting alternative activation.
MAIT cells are expanded in pediatric obesity.

The diagram shows a comparison of Va7.2+CD161+ T cells in non-obese and obese individuals. The scatter plot on the left indicates a significant increase in the number of these cells in the obese group compared to the non-obese group, as indicated by the *** symbol.
MAIT cells are expanded in pediatric obesity

![Graph showing the expansion of MAIT cells in pediatric obesity]
MAIT cells are expanded in pediatric obesity

- **Correlation with BMI:**
  - $r = 0.39$
  - $p = 0.01$

- **Correlation with Age:**
  - $r = -0.5$
  - $p = 0.02$

**Graphs:**
- **MAIT Cell Frequency vs. BMI:**
  - Non-Obese: Low
  - Obese: High

- **CD161 vs. Vα7.2 TCR:**
  - Non-Obese: Sparsely scattered points
  - Obese: Denser cluster of points

- **Legend:**
  - Non-Obese
  - Obese

---

$Vα7.2^+CD161^+T$ cells

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**Statistical Significance:**
- *** for high significance
MAIT cells in breast fed versus bottle fed children

MAIT Cell Frequency in Breast vs. Formula Fed

*n p=0.01

MAIT Cells % Lymphocytes

n=11

Breast Fed

n=26

Formula Fed
Outline of talk

A few facts

Obesity and the immune system

Gastrointestinal hormones and immunity
GI hormones after obesity surgery

Increase in GLP-1, PYY, Adiponectin

Decrease in leptin, Ghrelin, resistin
GLP-1 and the incretin effect

McIntyre et al. Lancet. 1964
Gave GLP-1 to a diabetes patient with psoriasis

• Itch went within days and slept through for first time in 46 years
Gave GLP-1 to a diabetes patient with psoriasis

- Itch went within days and slept through for first time in 46 years

- iNKT cell crucial to psoriasis
Gave GLP-1 to a diabetes patient with psoriasis

• Itch went within days and slept through for first time in 46 years

• iNKT cell crucial to psoriasis

• Could GLP-1 be regulating iNKT cell?
Glucagon-like peptide-1 (GLP-1) and the regulation of human invariant natural killer T cells: lessons from obesity, diabetes and psoriasis

A. E. Hogan · A. M. Tobin · T. Ahern · M. A. Corrigan · G. Gaoatswe · R. Jackson · V. O’Reilly · L. Lynch · D. G. Doherty · P. N. Moynagh · B. Kirby · J. O’Connell · D. O’Shea
Was it a consistent effect?

PASI reduced by average of 38% (p = 0.008)

DLQI reduced by average of 46% (p = 0.014)

Ahern et al, n=10 JEADV 2012
GLP-1 as a immunomodulator

• Looked at 12 T2DM starting GLP-1:

  Circulating cytokines

  Soluble CD163 (shed by macrophages)

  iNKT levels
GLP-1 therapy and soluble CD163
GLP-1 therapy restores depleted circulating iNKT cell populations in patients with T2DM
UCP-1 expression is restored by GLP-1 therapy

A. UCP-1 expression intensity

B. Fold expression of UCP1 mRNA

C. UCP-1 expression intensity

UCP-1 expression is restored by GLP-1 therapy
GLP-1 in mice increases thymic proliferation of iNKT cells
GLP-1 summary

• Anti-inflammatory

• Restores innate immune population and function

• Immune effects at least part independent of weight and glycaemic actions
PYY receptor expression and intracellular signalling in iNKT cells

![Diagram of experiment results with bar graph and Western blots](image)

**a.** Fold expression relative to HDEC expression

- HDEC
- iNKT cells
- CD3 T cells

**b.** IB: p-IκBα

**c.** IB: pCREB

**b.** IB: IκBα

**c.** IB: CREB

**b.** IB: β-Actin

**c.** IB: β-Actin

PYY (time) iNKT cells

<table>
<thead>
<tr>
<th>Time</th>
<th>0'</th>
<th>30'</th>
<th>90'</th>
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<tbody>
<tr>
<td>PYY</td>
<td>+</td>
<td>+</td>
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PYY (time) iNKT cells

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<td>+</td>
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</table>
PYY: restores killing capacity of NK from obese individuals
Y59 – Tumour growth and tumour killing by iNKT cells

c. Y-59

<table>
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<tr>
<th>Condition</th>
<th>Tumor Cell Growth</th>
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<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Colonies</th>
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<td>Control</td>
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PYY summary

• System-wide regulation of innate immunity

• Different effects to GLP-1

• Looks more anti-tumour potential than anti-inflammatory
Outline of talk

Background

Obesity and the immune system

Gastrointestinal hormones and immunity
### Differential side effects of anti-inflammatories

<table>
<thead>
<tr>
<th>Steroids</th>
<th>GLP-1</th>
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<tr>
<td>Weight gain</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Lower blood pressure</td>
</tr>
<tr>
<td>High glucose</td>
<td>Lower glucose</td>
</tr>
<tr>
<td>Immune suppression</td>
<td>Immune “restorative”</td>
</tr>
<tr>
<td>?Cancer</td>
<td>?Cancer/Pancreatitis</td>
</tr>
</tbody>
</table>
Conclusion

• Weight regulates innate immune system

• Innate Immune system regulates weight

• iNKT cells and MAIT cells emerging as key

• Gut hormones differentially regulate both and impact on inflammation and cancer biology