Give a NOD to diabetes: NOD proteins link immunity and metabolism

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Diabetes is an eating disorder

Why does obesity cause diabetes?

- We eat more fat
- We eat more

USDA
Immunity: Obesity and diabetes

Obesity is the main cause of diabetes

Immuno-compromised

Under-nutrition

“Tipping the scales”

Immuno-activated

Over-nutrition

Pathogen and nutrient sensing systems are linked (evolutionarily conserved)

Augmented inflammation is a key component of diet-induced insulin resistance
Insulin Resistance: Precedes T2D

- Diabetes death every 7 seconds
  - Comparable with all cancers combined

Glucose → Insulin

- X

Production → Blood Glucose

- X

Glucose → Insulin → Blood Glucose

- Pancreas
- Blood Glucose

- Liver
- Muscle and Fat

Major contributor
Don’t forget about the gut

Flora: Weighs ~5 Kg

Microbiome has ~3M genes compared to < 30K human genes

>10X more bacterial cells than human cells in/on “you”

Linked to obesity and many inflammatory diseases

What factors from the microbiota are linked to metabolism?
Innate immune system

• Detection of conserved molecular danger motifs (bacteria, virus, metabolites)
• Germ-line encoded Pattern Recognition Molecules (PRMs)
• Neutrophils
• Macrophages

• In principle - all tissues
  • Adipose Tissue: many immune cells
  • Liver: Kupffer cells
  • PRMs are present in metabolic cells
• Promote inflammation (to defend the host)
  • Cytokines, stress kinases, chemicals (NO)
What bacterial components cause insulin resistance?

NODs detect bacterial cell wall PGN

Does this alter metabolism?

NOD1 and NOD2 detect specific PGN motifs

- MDP containing PGN: **NOD2**
- mesoDAP PGN: **NOD1**
- **LPS: TLR4**
Hypothesis

NOD proteins propagate inflammatory signals causing insulin resistance

Objectives

• Do NODs link inflammation and insulin resistance during obesity?

• Does direct NOD-mediated sensing of PGN cause insulin resistance?

• Which NODs are important for insulin resistance? (NOD1 v NOD2)
Do NODs link inflammation and insulin resistance during obesity?

Give a NOD to insulin resistance

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Genetic mouse models:
High Fat Diet (~50% kJ fat)
Diet-induced obesity: NOD1 and NOD2

**High Fat diet:**
NOD1/2^{-/-} Double KO mice

Reduced
- Hepatic Inflammation
- Fatty Liver

Reduced
- Adipose Inflammation
- Adipocyte Size
- Immune cells
NODs link inflammation and insulin resistance during obesity

Does PGN cause insulin resistance?
PGN and NODs *in vivo*: “CLAMPS”

Whole Body

Muscle & Fat

Liver

Hyperinsulinemic euglycemic clamp 6 hours post ligand injection:

NOD1 activation = more pronounced insulin resistance involving the liver

NOD2 activation = decrease in glucose disposal
PGN = insulin resistance via NODs
PGN/NOD1 = profound IR

What cells mediate PGN/NOD-induced insulin resistance?
PGN/Insulin resistance: NOD1 v. NOD2

Direct muscle effects

**Muscle Cells**

NOD1 = no effect on glucose uptake

NOD2 = Decreased insulin stimulated glucose uptake
PGN/Insulin resistance: NOD1 v. NOD2

Direct muscle effects

NOD1:
Hepatocytes?
Adipocytes?

In vivo injection of NOD ligands - clamp

In vivo injection of NOD ligands
PGN:NOD1 = IR directly in primary hepatocytes
PGN:NOD1 = IR directly in adipocytes

**In vivo: Adipose Tissue**

**In vitro: Adipocytes**

**In vitro: Adipocytes**

PGN: NOD1 → Insulin → Glucose Uptake

NOD1 ligands cause inflammation and insulin resistance directly in adipocytes
Discovered that:

Bacterial PGN can cause insulin resistance

NOD1 sensing of PGN causes liver and fat insulin resistance

Metabolic cells sense PGN and respond with insulin resistance

NOD1 or NOD2 a target for obesity related therapeutics?
Moving forward

• Do chronic changes in NOD ligands occur during high fat feeding or obesity?

• Are bacteria responsible for NOD1⁻/⁻ and NOD2⁻/⁻ phenotypes?
  – Germ-free mice

• Can NOD activation/signalling or NOD ligands be targeted to alleviate metabolic disease?
  – Probiotics, Exercise
  – Can cancer drugs treat obesity? (EGFRi = potent Rip2i)

• How do bacteria regulate food intake and energy expenditure
  – in addition to gut absorbance

• Common “obesity or diabetes” drugs that activate/inhibit immune responses
  – statins, glyburide, aspirin
Thank you

Amira Klip
Dana Philpott
Adria Giacca
Greg Steinberg
Waliul Khan
Phil Bilan
Akhilesh Tamrakar
Emmanuel Denou
Morgan Fullerton

SickKids
University of Toronto
McMaster University

Degroote Academic Fellowship

NSERC CRSG
HEART & STROKE FOUNDATION
Canadian Diabetes Association
Canadian Institutes of Health Research