Diet, Intestinal Microbiota, and Cardio-Renal Disease Risk

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Learning Objectives

• To describe the contribution of intestinal microbiota and its interactions with dietary intake in the development and progression of cardio-renal diseases.

• To discuss the evolving mechanistic insights of dietary induced, microbiota-mediated metabolic pathways and their clinical implications.

• To highlight the promise of novel strategies that target intestinal microbiome to modulate cardio-renal disease risk.
Introducing the Human Gut Microbiota …

Microbial cells may out-number human cells 10 to 1

Total mass >1.2 kg, (>80% in gut)

70% of our immune cells reside in GI tract

The gut produces 3/4 of the body’s neurotransmitters

Cerf-Bensussan et al, Nat Rev Immunol 2010
Intestinal Microbiome in Health & Diseases

- Heart attack
- Heart failure
- Atherosclerosis
- Arrhythmia

- Psoriasis
- Atopy

- Autism
- Stroke
- Neurocognitive functional decline

- Asthma
- Atopy

- Thrombosis
- Platelet hyperresponsiveness
- HTN

- Chronic kidney disease
- Uremic toxins

- Diabetes

- Rheumatoid arthritis

- Marrow/Lymphoid
  - Immunity
  - Inflammation

- Insulin resistance
- Adiposity
- Obesity

- IBD

- Lungs
- Pancreas
- GI tract
Intestinal Microbiota, Metabolites & Immunity

“Food Metabolome”

- All metabolites that derive from digestion and metabolism from food components.

- The biggest environment exposure is represented by what we ingest as food and filtered by gut microbiota.

Colonic Fermentation from Dietary Intake

Scott et al, Pharmacol Res 2012;
David et al, Nature 2014
Short-Chain Fatty Acid (SCFA): Renal Sensory Nerve Activation via GPR41-Olfr78

Gut Microbiota-dependent Choline/Carnitine Metabolism Leads to TMA/TMAO Production

Selection Criteria (2000+ analytes):
Case-control 2-sided $t$-test $P<0.05$
Dose-response (analyte vs phenotype)
  Cochran-Armitage $P<0.05$
Minimal signal-to-noise ratio of 5:1
LC/MS in positive MS1 mode

Gut Microbiota Play Obligatory Role in TMAO Generation from Dietary PC in Mice

Involvement of Gut Microbiota

Involvement of Foam Cells

Transmission of Atherosclerotic Susceptibility: “Koch’s Postulate”

Cecal Transplantation

Microbial Transplantation


Romano et al, *MBio* 2015
Gut Flora-dependent Phosphatidylcholine Metabolism in Humans by d9-PC

Human: Impact of Antibiotics

Two hard-boiled eggs
Each 250 mg choline

Isotope-labelled PC
d9(trimethyl)-dipalmitoyl-PC or d9-DPPC 250 mg

Increased TMAO Levels Portend Higher Risk of MACE and Atherosclerotic Burden

Human: Major Adverse Cardiac Events


Human: SYNTAX Score

Senthong et al., *JACC* 2016
Gut Microbiota-Dependent TMAO Production from L-Carnitine in Humans

Humans: Impact of antibiotics

Koeth et al, Nat Med 2013
TMAO Enhances Platelet Hyperreactivity and Thrombotic Risk

Mice: In Vivo Thrombosis

Humans: Impact of oral choline & aspirin

Zhu et al, Cell 2015; Zhu et al, Circulation 2017
Prognostic Value of Plasma TMAO Levels in Heart Failure

Chronic Heart Failure

Tang et al, *J Am Coll Cardiol* 2014

Acute Heart Failure

Increased Susceptibility of Adverse Remodeling with Dietary TMAO/Choline

C57BL/6J mice

Withdrawing of dietary TMAO (0.12%) at 6 weeks

Organ et al, *Circ Heart Fail* 2016

Organ et al, *AHA* 2016 (abstract)
Elevated TMAO Levels in CKD Patients is Associated with Adverse Outcomes

Stubbs et al, *JASN* 2015
Dietary Choline/TMAO Exposure Contributes to Progressive Renal Fibrosis

** p<0.01

Summary: TMAO Metaorganismal Pathway

Zhu et al, Cell 2016
Strategies to Target Intestinal Microbiome

Adherence to Mediterranean Diet Lowers Urinary TMAO Levels

De Filippis et al, *Gut* 2015
Probiotics and TMAO with High-Fat Diet

Boutagy et al, *Obesity* 2016
TMA-Lyase Inhibitor: 3,3-dimethyl-1-butanol (DMB) as prototype

Brown & Hazen, J Biol Chem 2017
Wang et al, Cell 2015
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Tang, Kitai & Hazen, Circ Res 2017
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