Gut Microbiota and Atherothrombotic Heart Disease

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Drugs for Bugs
Drugging the Microbiome
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- Dr. Hazen is named as a co-inventor on pending and issued patents held by the Cleveland Clinic relating to cardiovascular diagnostics and/or therapeutics.

- Dr. Hazen reports having been paid as a consultant for the following companies: Esperion, and Procter & Gamble.

- Dr. Hazen reports receiving research funds or support from Abbott, Astra Zeneca, Pfizer, Procter & Gamble, Roche, and Takeda.

- Dr. Hazen reports having the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics and/or therapeutics from Cleveland Heart Laboratory, Esperion, Frantz Biomarkers, LLC and Siemens.

- Dr. Hazen was the scientific founder of Cleveland Heart Laboratory, and reports having equity in that company.
The microbiome can be considered as our largest endocrine organ.

The microbiome is a drugable target.

The microbiome is a filter of our largest environmental exposure – what we eat.

The human body is an integrated circuit between our gut microbes and our human genes.

Some take home concepts:

- The human body is an integrated circuit between our gut microbes and our human genes.
- The microbiome is a filter of our largest environmental exposure – what we eat.
- The microbiome can be considered as our largest endocrine organ.
- The microbiome is a "drugable" target.
Diet and Intestinal Microbes are Mechanistically Linked to Atherosclerotic Heart Disease

Meta-organismal pathway:
(i) gut microbe
(ii) host hepatic FMOs

Trimethylamine (TMA)
RA Koeth (2013) *Nature Medicine*
B Bennett (2013) *Cell Metab*
Z Wang (2014) *Eur Heart J*
WHW Tang (2014) *JACC*
RA Koeth (2014) *Cell Metab*
M Warrier (2015) *Cell Reports*
C Organ (2016) *Circ Heart Fail*
W Zhu (2016) *Cell*
TMAO alters macrophage phenotype, EC activation and sterol metabolism in multiple compartments

Adapted from:
The gut microbial TMAO pathway contributes to the development of “The Vulnerable Patient”

Atherosclerosis
- Mφ scavenger receptors
- Mφ foam cell formation
- Reverse cholesterol transport

Platelet hyperactivity
- Enhanced thrombosis

Vulnerable Plaque
- EC activation

Vulnerable Patient
- EC activation
- Intracoronary thrombosis
- Adverse ventricular remodeling
- Heart failure

Adverse Cardiovascular Event
- Stroke
- Heart attack

Intracoronary thrombosis

EC activation

The gut microbial TMAO pathway contributes to the development of “The Vulnerable Patient”

Elevated plasma levels of TMAO predict incident risk for thrombotic events (myocardial infarction and stroke)

Adjusted for traditional risk factors include age, gender, systolic blood pressure, meds, BMI, LDLc, HDLc, smoking, DM, TG, eGFR, CVD

Zhu et al, Cell (2016)
Brief exposure to TMAO enhances human platelet responsiveness to multiple agonists

Weifei Zhu, PhD

Zhu et al, Cell (2016)
TMAO enhances stimulus dependent Ca^{2+} release in platelets

Zhu et al, Cell (2016)
Carotid artery injury in vivo thrombosis model

- Internal carotid artery cut down
- Vital microscopy imaging of fluorescent labeled platelets

Dietary choline enhances thrombosis susceptibility in vivo

Zhu et al, Cell (2016)
Plasma levels of TMAO show a strong correlation with \textit{in vivo} thrombosis rates

\begin{equation}
\begin{aligned}
r &= -0.60 \\
p &< 0.001
\end{aligned}
\end{equation}

\textbf{Zhu et al, Cell (2016)}
“Let food be thy medicine and medicine be thy food.”
Hippocrates, Father of Western Medicine
431 B.C.
What are Dietary Sources of Choline/Phosphatidylcholine?

Lekithos (Greek) = Egg yolk
Chole (Greek) = Bile

Sources: National Academies of Science; U.S. Department of Agriculture
Chronic Dietary Choices Impact TMAO Levels

De Filippis et al, Gut 2015
Development of inhibitors (and activators) of microbial TMA lyases

![Graph showing inhibition of TMA-d9 formation with various compounds]

Sources of DMB
Olives/Cold-pressed extra virgin olive oil

Grape seed oil

Guinness Lager
Stout
DMB is a non-lethal microbial TMA lyase inhibitor in multiple human commensals

New concept: Non-lethal microbial enzyme targeting as a therapeutic

Small molecule inhibition of microbial choline TMA-lyase activity

Wang et al, Cell (2015)
Microbial TMA-lyase inhibition reduces TMAO levels in vivo

C57Blk/6J, apoE-/- mice

Wang et al, Cell (2015)
Microbial TMAO lyase inhibition attenuates dietary choline enhanced atherosclerosis

C57BL/6J ApoE-/- mice

Wang et al., Cell (2015)
Drugging the Microbiome - It's in Our Future for CVD Therapeutics

Z Wang et al, Cell, Dec 17, 2015
Thank you

Hazen Lab

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