

HIGH-VALUE NUTRITION Ko Ngā Kai Whai Painga

The HVN Immune Health Platform: Innovating for the Future of the New Zealand Food & Beverage Industry

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Challenge Host



Challenge Collaborating Parties



How to achieve innovation in nutritional immunology?

Biggest obstacle:

-> limited understanding of how food is being 'sensed' by (and can therefore influence) the immune system



The immune system

- <u>Well understood</u>: sensing of threats to homeostasis:
 - microbial or cancerous,
 - damage-associated, or
 - <u>metabolic</u>
- **Poorly understood**: sensing of prohomeostatic signals from the:
 - <u>diet</u>
 - environment



Dietary sensing



Dietary sensing

- Sensing through antigen- / metabolite-specific:
 - 1. transcription factors (intracellular), or
 - 2. cell surface receptors





Dietary sensing

- Sensing through:
 - 1. the Arylhydrocarbon receptor (AhR)









• Why?

- mediates toxicity of environmental pollutants which impact the HVN target population (China)

- integrates environmental, dietary, microbial (including probiotic products) and metabolic signals

- impacts a very large number of physiological processes (developmental, metabolic, immune, gastrointestinal, ...)

- Food-bioactives: (poly)phenolic compounds



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1. AhR

• How?

- *in vitro* screening of dietary compounds with AhR reporter cell lines

- *in vitro* assessments of immunological impact using primary human blood cells (GI trafficking)

- Indigo naturalis dose escalation study (NZ-INDES study)

- analysis of clinical samples from HVN-funded studies

AGRICULTURAL AND FOOD CHEMISTRY

pubs.acs.org/JAFC

Practical Approach To Explore the Effects of Polyphenols on Aryl Hydrocarbon Receptor Regulated Immune Function

Perspective

Jeffry S. Tang,* Alissa Cait, Yanyan Li, Helena Abolins-Thompson, Katie Gell, Patries M. Herst, David O'Sullivan, and Olivier Gasser*



Figure 1. Classes of dietary compounds and environmental pollutants that are described to affect AhR signaling.



inhibition

activation

		Benzoic acid	1.1	1.2	1.2	1.1
	1	2-Hydroxybenzoic acid	1.0	1.1	1.0	0.9
Benzoic acid	3-Hydroxybenzoic acid		1.0	1.3	1.3	1.1
derivatives	1	4-Hydroxybenzoic acid	1.1	1.1	1.1	0.9
	3,4-Dihydroxybenzoic acid		1.0	1.1	1.2	1.1
	3,4-Dihydroxybenzoic acid-3-O-glucuronide		1.0	0.9	1.1	1.0
	3,4-Dihy	ydroxybenzoic acid-3-O-sulfate	1.1	1.2	1.3	1.1
		2,5-Dihydroxybenzoic acid	1.1	1.0	1.1	1.1
2,3-Dihydroxybenzoic acid 2,4-Dihydroxybenzoic acid 3,5-Dihydroxybenzoic acid		2,3-Dihydroxybenzoic acid	1.1	1.1	1.1	1.2
		2,4-Dihydroxybenzoic acid	1.0	1.0	1.0	0.8
		3,5-Dihydroxybenzoic acid	1.1	1.1	1.2	1.3
r	2,6-Dihydroxybenzoic acid		1.0	1.0	0.9	1.0
Chlorogenic acid derivatives	3-O-Catteoylquinic acid		0.8	0.9	0.8	1.0
	3-O-(E)-Feruloylquinic acid		0.8	0.8	0.9	0.9
	5-O-Caffeoylquinic acid		0.9	1.0	1.0	0.9
	5-O-(E)-Feruloylquinic acid		0.9	0.8	0.9	0.9
	4-C+Cateoyiquinic acid		1.0	0.9	0.9	1.1
	Collab and		0.8	0.9	1.0	0.9
	Caffeic acid 3-O-B-D-Glucuronide		0.9	1.0	1.1	1.0
	Caffeic acid 4-O-B-D-Glucuronide		0.9	0.9	1.0	0.9
	Dihydrocaffeic acid		0.8	0.8	0.8	0.8
	Dihydrocaffeic acid-3-O-sulfate		0.9	1.0	1.0	1.0
	Ferulic acid		0.8	0.0	0.9	0.9
	Ferulic acid 4-O-β-D-Glucuronide		1.0	1.0	0.9	1.0
	Ferulic acid-4-O-sulfate		1.0	0.0	1.0	0.9
Cinnamic acid derivatives	Dihydrofe	rulic acid 4-O-B-D-Glucuronide	11	1.0	10	1.0
	Dihydroferulic acid 4-O-sulfate Isoferulic acid-3-O-B-O-Glucuronide Isoferulic acid-3-O-gulfate Isoferulic acid-3-O-gulfate Dihydroisoferulic acid 3-O-B-O-Glucuronide Dihydroisoferulic acid 3-O-S-Sulfate		0.9	0.9	10	0.8
			0.9	1.0	10	1.0
			0.9	0.9	11	1.0
			0.8	0.8	0.9	0.9
			0.8	10	10	11
			0.8	11	1.0	1.0
l			0.9	0.9	1.0	1.4
		Daidzein	1.0	1.1	1.1	1.1
	Daidzein 4'-O-B-D-glucuronide Daidzein 4'-O-Sulfate		1.0	1.0	0.9	1.1
			1.0	1.0	1.1	1.0
	line parage	Daidzein 7-0-β-D-Glucuronide	1.0	0.9	0.9	1.0
	Daidzein 7	7-O-β-D-Glucuronide 4'-Sulfate	1.0	1.0	1.0	0.8
soflavone		Genistein	1.0	1.0	0.9	0.9
netabolites	G	Genistein 4'-O-β-D-Glucuronide	1.1	1.2	1.1	1.0
	Genistein 7-O-β-D-Glucuronide		0.9	1.0	1.1	1.2
		Genistein 7-O-Sulfate	0.8	1.0	1.0	0.9
	Our let	Genistein-diglucuronide	0.9	1.0	0.8	1.0
	Genistein-	/-sunate-4-O-β-D-glucuronide	1.0	1.0	1.0	1.0
Elavan 2 ol	Genistein 7-β-D-Glucuronide-4'-O-Sulfate		0.9	1.0	1.0	1.1
metabolites (4R)-5-(3',4'-1		4/n-5-(3,4-DIOHPhenyl)-Y-VL	0.8	1.0	1.0	0.9
		Cionir netiyi)-y-vL-4-O-sulfate	0.8	0.9	0.9	0.9
Flavonol	metabolites	Quercetin-2- Quercetin	1.0	1.3	1.0	0.9
		Quercetin-3-O-glucurohide	0.9	0.8	0.8	0.9
	-	Cvanidin-3-O-nkicoeide	1.0	1.0	1.0	1.1
Anthocyanins* (0.1, 1, 10, 100 nM)		Cvanidin-3-O-galactoside	1.0	0.0	0.0	1.0
		Cyanidin-3-O-rutinoside	0.9	0.9	0.9	0.9
		Cvanidin-3-Q-arabinoside	0.0	0.9	0.9	1.0
		Delphinidin-3-O-glucoside	0.8	1.0	0.9	0.9
		Delphinidin-3-O-rutinoside	11	0.9	0.9	10
		Malvidin-3-O-glucoside	0.9	11	1.0	0.9
		Malvidin-3-O-galactoside	0.9	0.9	10	0.9
		Pelargonidin-3-O-glucoside	0.8	0.8	1.0	1.0
		Peonidin-3-O-glucoside	0.9	0.9	10	0.9
		Peonidin-3-O-galactoside	0.9	0.8	0.9	0.9
		Petunidin-3-O-glucoside	1.0	0.9	1.1	0.9
		Hippuric acid	1.1	1.1	1.1	1.1
Hippuric a	1CIG	α-Hydroxyhippuric acid	0.8	1.0	1.2	0.9
metabolit	es"	2-Hydroxyhippuric acid	1.0	1.0	1.2	3.2
(0.1, 1, 10,	, 100 µM)	3-Hydroxyhippuric acid	1.1	1.2	1.0	1.1
		L 4-Hydroxyhippuric acid	1.0	1.1	1.0	1.0
Glucosinolate		C 3,3'-Diindoyimethane	1.2	1.3	1.6	2.6
indole metabolites		Indole-3-carboxaldehyde	0.9	1.1	1.6	3.1
	20000000000000	Indole-3-carboxylic acid	0.9	1.0	1.2	2.0
-		Ellagic acid	0.9	0.8	0.8	0.7
		Urolithin A	0.9	0.9	0.9	0.8
	in metabolites	Urolithin B	1.0	0.8	0.6	0.7
Ellagitann		Urolithin B glucuronide	0.8	0.9	0.8	0.8
Ellagitann			10	1.0	0.8	0.9
Ellagitann		L Urolithin D	1.0			
Ellagitann		0.1% DMSO	1.0	1.0	1.0	1.0
Ellagitann		0.1% DMSO Untreated	1.0 1.0	1.0 1,0	1.0 1.0	1.0

Tang et al. submitted



1. AhR

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How does the acute ingestion of a known AhR agonist Influence the peripheral immune system?

Dose-dependent AhR activity





Dietary sensing

- Sensing through:
 - 2. MHC-class 1 related molecule (MR1)







• Why?

- overlap between dietary metabolites binding AhR and MR1

- MR1 restricts the largest T cell subset in humans (mucosal associated invariant T – MAIT cells)

- MR1 immunobiology linked to gastrointestinal, metabolic, pulmonary, skin, liver health as well as antibacterial and antitumoral immunity.

- Food-bioactives: (poly)phenolic compounds (quinones, flavones, isoflavones) and likely others





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ORIGINAL ARTICLE

MR1-dependent immune surveillance of the skin contributes to pathogenesis and is a photobiological target of UV light therapy in a mouse model of atopic dermatitis

Karmella Naidoo¹ | Katherine Woods¹ | Christophe Pellefigues¹ | Alissa Cait¹ | David O'Sullivan^{1,2} | Katie Gell¹ | Andrew J. Marshall³ | Regan J. Anderson³ | Yanyan Li^{1,2} | Alfonso Schmidt¹ | Kef Prasit¹ | Johannes U. Mayer¹ | Aurelie Gestin¹ | Ian F. Hermans¹ | Gavin Painter³ | Elizabeth A. Jacobsen⁴ | Olivier Gasser^{1,2}



Allergy. 2021;00:1-16.

Allergy WILEY



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frontiers Frontiers in Immunology

MR1-dependence of unmetabolized folic acid side-effects

Jeffry S. Tang^{1,2}, Alissa Cait¹, Reuben M. White³, Homayon J. Arabshahi³, David O'Sullivan^{1,2} and Olivier Gasser^{1,2*}

> TYPE Hypothesis and Theory PUBLISHED 09 August 2022 DOI 10.3389/fimmu.2022.946713





• How?

- *in vitro* screening of dietary compounds with MAIT cell competition assay



National SCIENCE

Challenges

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• How?

- *in vitro* screening of dietary compounds with MAIT cell competition assay



John Arabshahi, UoA



O'Sullivan et al. unpublished

Aligned project: CD1d

• Why?

- CD1d is, like MR1, a non-classical MHC

molecule, but binds lipids

- CD1d is known to bind dietary lipids and

thereby influence the immunological activity of **NKT** cells







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Goat Milk–Derived Lipids Restrain NK T Cell–Dependent Eosinophilic Inflammation in a Murine Model of Atopic Dermatitis

Journal of Investigative Dermatology (2022) ■, ■-■; doi:10.1016/j.jid.2022.03.006





^{JID}Open

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Dietary sensing



• Why?

- has rapidly become an essential part of immunology but never applied to nutrition

- obvious relevance for immunophenotyping of dietary intervention samples

- impacts virtually every aspect of immune function

- Food bioactives: probably most ...

Immunometabolism: Cellular Metabolism Turns Immune Regulator^{*}

Published, JBC Papers in Press, November 3, 2015, DOI 10.1074/jbc.R115.693903 Róisín M. Loftus[‡] and David K. Finlay^{‡§1}



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• Why?

Basic concept: if the ingestion of a food can induce a metabolic shift in a cell, it can change immune function.



• How?

- metabolic flow cytometry

MCT1: Monocarboxylate transporter moves lactate across Glucose cell membrane CD25 PKM: Pyruvate kinase is a key ATP producing step in alycolysis Growth-factor & Metabolic mTORC1 nutrient sensing remodelina GLS1: Glutaminase is required for alutamine utilisation in the TCA cycle PFP pS6 p4EBP1 PKM MCT1 LDHA Lactate -CD98: transporter of branched chain Pyruyate and aromatic amino acids PDHB Ac¹CoA Amino CD98 Citrate synthase: rate limiting enzyme acids of the tricarboxylic (TCA) cycle GLS1 p4EBP1& pS6: phosphorylation of 4EBP1^(thr37/46) - Glutamine O'Sullivan et al. or S6^(Ser235/236) induces increased translation TCA NZASI 2022 poster PDHB: pyruvate dehydrogenase converts pyruvate to acetyl-CoA to link glycolysis and the TCA cycle **HIGH-VALUE** Ko Ngā Kai Whai Painga NUTRITION CD25: IL-2RA receptor upregulation following T cell activation is associated with metabolic remodeling

Phenotypic & Metabolic Targets

Ahl et al. *Commun Biol.*Hartmann et al. *Nat Biotechnol.*Levine et al. *Immunity*Artyomov et al. *Cell Metab.*

• How?

- metabolic flow cytometry: acute changes upon ingestion of equicaloric foods with different glycemic index (preliminary data; Metabolic Health PRP sample)



Glucose transporter

Amino acid transporter



O'Sullivan et al. unpublished HIGH-VALUE

National SCIENCE

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- Diet is fundamentally linked to human health via immune sensing. The underlying mechanisms are poorly understood
- The characterization of novel and specific interactions between immune receptors and dietary ligands can lead to innovation and is commercially valuable
- Compositional analyses of (your) products is very important (NZ-origin can be leveraged)
- Immune-phenotyping approaches are, and always will be, customized to the clinical outcome and the interventional product
- Il Receptors are not necessarily conserved across species (implications for preclinical models of disease)



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Dr David O'Sullivan

Dr Jeffry Tang



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