The effects of dietary eicosapentaenoic acid and arachidonic acid on gene expression changes in a mouse model of human inflammatory bowel diseases

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ABSTRACT

Nutrigenomics studies the genome-wide influence of nutrients to understand the association between nutrition and human health. Studies in animal models and humans have demonstrated that dietary n-3 polyunsaturated fatty acids (PUFA) from fish oil may be beneficial in inflammatory bowel diseases (IBD).

This thesis aimed to test the hypothesis that dietary n-3 PUFA eicosapentaenoic acid (EPA) reduced and n-6 PUFA arachidonic acid (AA) increased colitis in the interleukin-10 gene-deficient (*Il10*$^{-/-}$) mouse model of IBD, and that these PUFA altered the intestinal bacteria community during colitis development using genome-wide expression and bacterial profiling.

Using a combined transcriptomic and proteomic approach, the time-course study defined the onset and progression of colitis in *Il10*$^{-/-}$ mice. Histopathology, transcript and protein changes before and after colitis onset involved in innate and adaptive immune responses suggested delayed remodelling processes in colitic *Il10*$^{-/-}$ mice and 11 weeks of age as suitable time point to study the effects of dietary PUFA on colitis development. Comparing the transcriptome and proteome profiles associated with colon inflammation of mice fed with the AIN-76A or oleic acid (OA) diet showed that OA was an appropriate control for unsaturated fatty acids in multi-omic studies. The PUFA intervention study indicated that dietary EPA-induced lipid oxidation might have a potential anti-inflammatory effect on inflamed colon tissue partially mediated through activation of peroxisome proliferator-activated receptor alpha (PPARα). Unexpectedly, dietary AA decreased the expression of inflammatory and stress colonic genes in *Il10*$^{-/-}$ mice. Altered intestinal bacteria community observed in *Il10*$^{-/-}$ mice before and after colitis onset was associated with the lack of IL10 protein led to changes in intestinal metabolic and signalling processes. Interestingly, dietary EPA and AA seemed to change intestinal bacteria profiles during colitis development. The role of PPARα in the colon was further examined in a concluding study which identified vanin1 as a likely new PPARα-target gene which may also be involved in lipid metabolism.

These findings using a state-of-the-art approach combining transcriptomics, proteomics and physiology provide a basis for future research on molecular mechanisms underlying

the effects of dietary PUFA, and might contribute to the development of fortified foods that improve intestinal health and wellness.

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LIST OF ABBREVIATIONS

AA	arachidonic acid
ABC	ATP-binding cassette
ACSL	long chain acyl-CoA synthase
ALA	α-linolenic acid
ALDH	aldehyde dehydrogenase
APC	antigen presenting cells
APOA1	apolipoprotein (apo) AI
B. vulgatus	*Bacteroides vulgatus*
CARD15	caspase activation recruitment domain family member15
CD	Crohn's disease
cDNA	complementary DNA
CES	carboxylesterase
cfu	colony forming units
CLA	conjugated linoleic acid
C. perfringens	*Clostridium perfringens*
CoA	CoenzymeA
COX2	cyclooxygenase2
CYP	cytochrome P450
DGGE	denaturing gradient gel electrophoresis
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
DNBS	dinitrobenzene sulfonic acid
DSS	dextran sulfate sodium
GC-clamp	GC-rich sequence
EDTA	ethylenediamine tetraacetic acid
EPA	eicosapentaenoic acid
E. coli	*Escherichia coli*
E. faecalis	*Enterococcus faecalis*
ER	endoplasmic reticulum
FABP	fatty acid binding protein
FATP	fatty acid transport protein
FC	fold change
FDR	false discovery rate
FXR	farnesoid X receptor
GO	gene ontology
H. pullorum	*Helicobacter pullorum*
H&E	haematoxylin and eosin
HDL	high-density lipoprotein
HNF4	hepatocyte nuclear factor 4
IBD	inflammatory bowel disease
ICAM	intercellular adhesion molecule
IFNγ	interferon gamma
IκB	inhibitor of κB
IL	interleukin
IL1ß	interleukin1 beta
Il10$^{-/-}$	interleukin-10 gene-deficient
IPA	Ingenuity Pathway Analaysis
JAK1	Janus kinase1
LA	linoleic acid
L. reuteri	*Lactobacillus reuteri*
limma	linear models for microarray data
LOX	lipoxygenase

lsd	least significant difference
LPS	lipopolysaccharide
LT	leukotriene
LX	lipoxin
LXR	liver X receptor
MAPK	mitogen-activated proteine kinase
MHC	major histocompatibility class
MMP	matrix metallopeptidase
mRNA	messenger RNA
MUFA	monounsaturated fatty acid
NCBI	National Centre for Biotechnology Information
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NOD2	nucleotide-binding oligomerisation domain containing2
OA	oleic acid
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PG	prostaglandin
PPARα, β/δ, γ	peroxisome proliferator-activated receptor alpha, beta/delta or gamma
PPRE	PPAR response element
PUFA	polyunsaturated fatty acids
qRT-PCR	quantitative real-time reverse transcription PCR
Rho GDIβ	Rho GDP dissociation inhibitor (GDI) beta
RNA	ribonucleic acid
rRNA	ribosomal RNA
ROS	reactive oxygen species
RXR	retinoid X receptor
SAA	serum amyloid A
SEM	standard error of mean
SCID	severe combined immune deficiency
SNP	single nucleotide polymorphism
SOCS	suppressor of cytokine signalling
spp.	species
SREBP	sterol regulatory element binding protein
STAT	signal transducer and activator of transcription
SULT	sulfotransferase
TAE, TBE	tris-acetate-EDTA, Tris-borate-EDTA buffer
TG	triglyceride
Th	T helper
TLR	toll-like receptor
TNBS	trinitrobenzene sulfonic acid
TNFα	tumour necrosis factor alpha
TSS	transcription start site
TX	thromboxane
UC	ulcerative colitis
VNN1	vanin1