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FACULDADE DE CIÊNCIAS FARMACÊUTICAS

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LARISSA SBAGLIA CELIBERTO

INTESTINAL HOMEOSTASIS AND HOST DEFENSE AS PROMOTED BY COMMENSAL BACTERIA AND THE COLONIC MUCUS LAYER

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Orientador no exterior: *Prof. Dr. Bruce A. Vallance*
Co-orientador: *Dr. Luis Caetano Martha Antunes*

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Abstract

The intestinal tract harbours the largest population of microbes in the human body where they play an important role in promoting the health of their host. If the composition of these microbes is altered, this may lead to dysbiosis that triggers or exacerbates intestinal and extra-intestinal diseases. Probiotics have been investigated as a complementary therapy in dysbiosis-related diseases. However, their effectiveness in treating severe conditions such as Inflammatory Bowel Disease (IBD) is quite variable and have shown controversial results. To address the importance of a personalized probiotic approach to treat intestinal inflammation, we first examined the effect of personalized bacteria using a model of chemical induced colitis. The animals that received commensals isolated from their own feces were more protected against inflammation as they showed reduced signs of colitis, less histological damage and lower levels of inflammatory markers as compared to mice given a commercial probiotic strain. Next, the role of the intestinal mucin Muc2 and the Core-1 enzyme that glycosylates it were explored using the *Citrobacter rodentium* model of infectious colitis. The intestinal mucus layer is the first line of defense in the intestine and is largely composed of the secreted mucin Muc2. Since almost all enteric bacteria must cross the overlying mucus layer to infect the host, the mucus-enteric bacterial interactions provide fundamental knowledge about infectious diseases as well as inflammatory conditions linked to dysbiosis (e.g. IBD). Specifically, we compared *C. rodentium* susceptibility by infecting WT, *Muc2* $^{-/-}$, core 3 (*C3GnT)* $^{-/-}$, core -1 (*C1galt1)* $^{-/-}$, and *C1galt1* $^{f/f}$ mice. While *C3GnT* $^{-/-}$ mice showed a very similar phenotype to WT mice with only mild inflammation, complete absence of Muc2 or just core 1 derived O-glycans resulted in significantly higher histological damage, barrier disruption, and increased pathogen burdens. Interestingly, the supplementation of tributyrin protected mice against infection resulting in less histological damage and lower *C. rodentium* colonization as compared to control groups. These studies highlight a novel personalized therapy that may be considered relevant to diseases affected by dysbiosis as well as the key role of Muc2 and its core 1 glycosylation in host defense against enteric infections.

Keywords: IBD; colitis, microbiota; microbiota biobank, personalized probiotic, mucus layer

Lay Summary

The human gut harbors several types of bacteria that play an important role in the well-being of their host. The intestinal mucus layer is also important for intestinal health, since it acts as a physical barrier that prevents bacteria and food products from escaping the gut and causing inflammation. Using an animal model of intestinal inflammation, I discovered that beneficial bacteria isolated from the host are more effective in protecting mice against intestinal damage as compared to probiotic bacteria available on the market. Further, using an animal model of a gut bacterial infection, I tested the impact of the mucus layer on protection against intestinal inflammation. I found that the mucin Muc2 and one of its sugar compounds protect mice against intestinal damage caused by enteric bacteria. These findings have implications for both Inflammatory Bowel Disease and people with gut infections– and could help develop new and effective complementary treatments.

Preface

Chapter 2

I designed and conducted the majority of the studies reported in this chapter, analyzed the data, prepared all of the figures and wrote the manuscript under the supervision of Dr. Daniela C.U. Cavallini and Dr. Bruce A. Vallance. Dr. Elizeu A. Rossi provided input to the study design. Ms. Roseli A. Pinto assisted in microbiological tests and performed the antibiotic susceptibility test leading to Supplemental Figure A1.

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Ethics approval was required for this research and was obtained from the Sao Paulo State University Animal Care Committee certificate number 34/2014 and the University of British Columbia Animal Care Committee certificate number A15-0206.

Chapter 3

I conducted the majority of the studies reported in this chapter, analyzed the data, prepared all of the figures and wrote the manuscript under the supervision of Dr. Bruce A. Vallance and Dr. Daniela CU Cavallini. Dr. HT Law, Dr. Genelle Healey, Mr. Justin HY Chan and Ms. Qiaochu Liang assisted with study design, animal experimentation, histopathological scores and provided useful insights regarding the results discussion. Dr. Kiran Bhullar performed experiments with *C3GnT -/-* mice leading to figure 3.4 IEC *C1galt1 -/-* and *C3GnT -/-* mice were generated and kindly provided by Dr. Lijun Xia, University of Oklahoma. A version of this chapter will be submitted for publication.

Ethics approval was required for this research and was obtained from the University of British Columbia Animal Care Committee certificate number A15-0206.

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List of symbols and abbreviations

α	alpha
β	beta
γ	gamma
κ	kappa
µ	micro
°	degree
C	Celsius
<	less than
≤	less than or equal to
>	greater than
+	positive
±	plus or minus
-/-	deficient
5-HT	5-hyroxytyrtamine (serotonin)
ADP	adenosine diphosphate
A/E	attaching and effacing
AMP	antimicrobial peptide
ATP	adenosine triphosphate
CFU	colony forming units
CTRL	control
DAI	disease activity index

DAPI	4',6-diamidino-2-phenylindole
DC	dendritic cell
DNA	deoxyribose nucleic acid
DNBS	2,4-dinitrobenzenesulfonic acid
DSS	dextran sodium sulfate
EHEC	Enterohemorrhagic *Escherichia coli*
e.g.	*exempli gratia* (for example)
ER	endoplasmic reticulum
EPEC	Enteropathogenic *Escherichia coli*
F/B	*Firmicutes/Bacteroidetes*
FITC	fluorescein isothiocyanate
FOS	fructooligosaccharide
g	gram
GI	Gastrointestinal tract
GF	germ free
GL	glycerol
GOS	galactooligosaccharide
GPR	G protein coupled receptor
HIV	Human Immunodeficiency virus
HMP	Human Microbiome Project
IAP	intestinal alkaline phosphatase
IBD	Inflammatory Bowel Disease
IBS	irritable bowel syndrome

i.e.	*id est* (that is)
IEC	intestinal epithelial cell
IEC-C1galt1-/-	IEC specific deletion of core 1-derived O-glycans
IEL	intraepithelial lymphocyte
IFN	interferon
Ig	immunoglobulin
IL	interleukin
ITS	internal transcribed spacer
L	litre
LEE	locus of enterocyte effacement
LGG	*Lactobacillus rhamnosus* GG
LI	large intestine
LPS	lipopolysaccharide
m	meters
M cells	microfold cells
MAPK	mitogen activated protein kinase
MDA	malonaldehyde
MetaHIT	Metagenomics of the Human Intestinal Tract.
MLN	mesenteric lymph nodes
MPO	myeloperoxidase
Muc2	mucin 2
NGS	next generation sequence
NIH	National Institute of Health

NOD	nucleotide-binding oligomerization domain
NF-κB	Nuclear factor kappa-B
pi	post infection
PP	personalized probiotics
PTS	Proline- threonine -serine
qPCR	quantitative PCR
Reg III γ	regenerating islet-derived protein 3 gamma
Relmβ	resistin like molecule beta
RNA	ribonucleic acid
rRNA	ribosomal RNA
ROS	reactive oxygen species
SCFA	short chain fatty acid
SD	standard deviation
SEM	standard error mean
SI	small intestine
S. Typhimurium	*Salmonella* enterica serovar Typhimurium
T3SS	type 3 secretion system
TB	tributyrin
TCR	T cell receptor
TFF3	trefoil like factor 3
TGF β	transforming growth factor beta
Th	T helper
Tir	translocated intimin receptor

TJ	tight junction
TLR	toll like receptor
TNBS	2,4,6-trinitrobenzene sulphonic acid
TNF	tumor necrosis factor
Treg	T regulatory
Wnt	Wingless/Integrated
WT	wildtype
ZO	zonula occludens

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