UMEÅ UNIVERSITET

Impact of a Western-style diet on small-intestinal mucosal barrier function

Fabiola Puértolas Balint

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Stora Hörsalen, KBC-huset byggnad KBE303, Plan 3
Fredag 14th Juni 2024, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Prof. Charles L. Bevins
Department of Medical Microbiology and Immunology, UC Davis, California, USA.

Department of Molecular Biology

Organization
Umeå University
Department of
Molecular Biology

Document type
Doctoral thesis

Date of publication
24 May 2024

Author
Fabiola Puértolas Balint

Title
Impact of a Western-style diet on small-intestinal mucosal barrier function

Abstract
Specialized defense mechanisms at mucosal barriers along the gastrointestinal tract constantly protect us against the trillions of microorganisms living inside the human body. These mechanisms include a mucus layer as a physical barrier that prevents bacteria from reaching the epithelium and the production of antimicrobial peptides (AMPs) as a chemical barrier that helps neutralize or lyse these bacteria. On the other hand, many intestinal bacteria benefit human health by providing colonization resistance against pathogenic bacteria, helping produce vitamins, aiding in the digestion of complex carbohydrates, and producing anti-inflammatory short-chain fatty acids. Therefore, the intestinal mucosal barrier has the challenging task of maintaining a homeostatic interaction between the host and the intestinal microbiota.

Alterations in the integrity of the mucus barrier and the expression of AMPs have been associated with inflammatory bowel disease and obesity. This thesis investigates how the intake of a high-fat and low-fiber Western-style diet (WSD) as an exogenous factor can affect the protective function of the mucus barrier and intestinal AMPs in mice with or without modulation of the microbiota.

In paper 1 **"Intestinal α-Defensins Play a Minor Role in Modulating the Small Intestinal Microbiota Composition as Compared to Diet"** we fed wild-type and *Mmp7*$^{-/-}$ mice, which lack active a-defensins, the major family of AMPs in the small intestine, a control or a WSD. We found that diet had a stronger impact on modulating small intestinal microbiota composition, while defensins only modulated the abundance of specific bacteria. In addition, defensins protected against metabolic dysfunction induced by the intake of a WSD.
In paper 2 **"Investigating the link between antimicrobial defense, gut microbiota and metabolic dysfunction at the small intestinal mucosal barrier"** we investigated the effect of obesogenic diets (Western diet or a high fat diet), obesity itself and other variables, including microbiota composition and sex, on small intestinal AMP expression. We observed that prolonged intake of a WSD had a stronger impact on AMP expression than genetic obesity, and determined that experimental set-up defined by mouse vendor and diet type, may have a larger influence than the specific dietary disturbances.
In paper 3 **"Muc2-dependent microbial colonization of the jejunal mucus layer is diet sensitive and confers local resistance to enteric pathogen infection"** we determined that the mucus layer of the jejunum formed aggregates and became more penetrable to bacteria-sized beads following the intake of a WSD. Both *Muc2*$^{-/-}$ and WSD-fed mice had an altered microbiota composition and increased susceptibility to enteric infection with *Citrobacter rodentium* in the jejunum, highlighting the role of the mucus layer as a microbiota- supporting niche that mediates colonization resistance against infection.

In summary, our work investigates the mechanisms by which a WSD changes the small intestinal microbiota composition at different intestinal sites while simultaneously disrupting mucus and AMP function. Our findings can aid the development of potential therapeutic avenues for addressing obesity and inflammatory bowel diseases through targeted modulation of mucus function, AMP expression or microbial composition.

Keywords
Western-style diet, High-fat diet, small intestine, microbiota, antimicrobial peptides, mucus layer, mucosal defense

Language
English

ISBN
print: 978-91-8070-423-6
PDF: 978-91-8070-424-3

ISSN
0346-6612

Number of pages
42 + 3 papers/manuscript