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The role of the small intestine in modulating metabolism and inflammation in atherosclerosis and cancer

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Abstract

Purpose of review—To discuss recent findings on the importance of the small intestine in modulating metabolism and inflammation in atherosclerosis and cancer.

Recent findings—Integrin $\beta7^{+}$ natural gut intraepithelial T cells modulated metabolism and accelerated atherosclerosis in mice. Reducing the generation of lysophospholipids in the small intestine mimicked bariatric surgery and improved diabetes. Enterocyte-specific knockdown of stearoyl-CoA desaturase-1 significantly improved dyslipidemia in LDL receptor null ($Ldlr^{-/-}$) mice fed a Western diet. Adding a concentrate of tomatoes transgenic for the apolipoprotein A-I mimetic peptide 6F to the chow of wild-type mice altered lipid metabolism in the small intestine, preserved Notch signaling and reduced tumor burden in mouse models. The phospholipid-remodeling enzyme Lpcat3 regulated intestinal stem cells and progenitor cells by stimulating cholesterol biosynthesis; increasing cholesterol in the diet or through genetic manipulation promoted tumorigenesis in Apc^{min+} mice.

Summary—The small intestine is important for regulating metabolism and inflammation in animal models of both atherosclerosis and cancer.

Keywords

atherosclerosis; cancer; inflammation; metabolism; small intestine

INTRODUCTION

The small intestine is often thought of as the portion of the gastrointestinal tract that is responsible for the absorption of dietary bulk lipids (e.g., triglycerides, phospholipids, cholesterol) and is responsible for the reabsorption of bile acids. While this is true, the small intestine has also emerged as a site where local lipid metabolism modulates inflammation that is important to the development of both atherosclerosis and cancer.

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Conflicts of interest

A.M.F. is a principal and officer in Bruin Pharma. P.M. and A.C. have no conflicts to declare.

Surprisingly, the content of unsaturated lysophosphatidic acid (LPA) species (but not saturated LPA species) in the tissue of the small intestine predicted the extent of aortic atherosclerosis in *Ldlr*$^{-/-}$ mice [1]. Subsequently, it was found that adding unsaturated LPA to a chow diet mimicked many of the changes observed after feeding Western diet to *Ldlr*$^{-/-}$ mice [2]. Adding freeze-dried powder derived from tomatoes transgenic for the apolipoprotein A-I (apoA-I) mimetic peptide, 6F, largely prevented the systemic inflammation and dyslipidemia induced by feeding chow supplemented with unsaturated LPA or feeding Western diet to *Ldlr*$^{-/-}$ mice [2]. A concentrate of the transgenic 6F tomatoes (Tg6F) was effective in mouse models of dyslipidemia and cancer when added to Western diet or chow, respectively, at only 0.06% by weight [3]. A major source of unsaturated LPA was found to be unsaturated lysophosphatidylcholine (LysoPC), which was acted upon by phospholipase D (autotaxin) [4]. Western diet was found to contain very little unsaturated LysoPC; the saturated LysoPC in Western diet was converted to unsaturated species in the enterocytes [5]. Adding Tg6F to chow supplemented with unsaturated LysoPC or added to Western diet ameliorated the increase in oxidized phospholipids and inflammatory cells that occurred upon feeding these diets to *Ldlr*$^{-/-}$ mice [5]. An extraordinary affinity of the proximal small intestine for apoA-I mimetic peptides was found using 4F, a peptide closely related to 6F [6]. After intravenous injection of 4F into the tail vein of mice, more peptide was found in the duodenum and jejunum than in the liver, and the transport of the peptide into the lumen of the small intestine was associated with an increase in transintestinal cholesterol efflux [6]. These studies and the more recent studies described below provide evidence that the small intestine is important for regulating metabolism and inflammation in animal models of both atherosclerosis and cancer.

ROLE OF SMALL INTESTINE INTEGRIN β7^{+} INTRAEPITHELIAL T CELLS

Retention of effector and memory lymphocytes in the gut epithelial layer is facilitated by αE β7 integrin via interactions with E-cadherin [7]. He *et al.* [8■■] found that mice lacking β7 integrin (β7$^{-/-}$) gained weight on a chow diet similar to control wild-type mice but ate more food despite being equally active. The β7$^{-/-}$ mice expended more energy and expended more heat although their respiratory exchange was similar to wild-type mice. By PET/computed tomography, the β7$^{-/-}$ mice accrued more glucose in brown fat compared with wild-type mice. The β7$^{-/-}$ mice had higher plasma insulin levels and tolerated glucose better than wild-type mice even at thermoneutrality. The β7$^{-/-}$ mice had lower fasting triglyceride levels with better fat tolerance and no differences in hepatic secretion of triglycerides compared with wild-type mice, and no change in fat absorption or gut permeability. On a high-fat, high-sugar and high-sodium diet, the β7$^{-/-}$ mice remained relatively lean compared with wild-type mice. Inguinal white adipose tissue and perigonadal white adipose tissue were heavier in the β7$^{-/-}$ mice compared with wild-type mice, and there were less Ly-6C^{high} monocytes, neutrophils, and macrophages in these tissues in the β7$^{-/-}$ mice. On this diet wild-type mice developed hypertension, but the β7$^{-/-}$ mice did not. The β7$^{-/-}$ mice were also more glucose tolerant to this dietary challenge than wild-type mice. *Ldlr*$^{-/-}$ mice transplanted with bone marrow from β7$^{-/-}$ mice had lower plasma cholesterol levels, improved glucose tolerance, and less aortic atherosclerosis on a diet high in cholesterol compared with *Ldlr*$^{-/-}$ mice transplanted with bone marrow from wild-type mice. On

generating $\beta7^{-/-}/Ldlr^{-/-}$ mice, and comparing them with $Ldlr^{-/-}$ mice, similar results were found to those in the bone marrow transplanted mice. Injecting antiintegrin β7 antibodies into $Ldlr^{-/-}$ mice resulted in improved glucose tolerance and attenuated aortic atherosclerosis. Thus, three different experimental models confirmed that β7 deficiency protects against atherosclerosis.

Intraepithelial lymphocytes that reside in the small intestine had the highest integrin β7 expression, which is consistent with prior studies demonstrating that integrin β7 is important for lymphocyte homing to mucosal sites [9,10]. In contrast to the blood, and other tissues where the proportion of $\beta7^{-/-}$ and wild-type cells was similar, in the gut, and particularly in the small intestine intraepithelium, there were many fewer $\beta7^{-/-}$ cells compared with wild-type cells. The leukocytes relying on integrin β7 for homing to the gut were αβ and γδ T cells, B cells, and myeloid cells. Experiments to determine which of these cells were responsible for the improved glucose tolerance revealed that the specific absence of integrin β7 on either αβ or γδ T cells improved glucose tolerance.

Enteroendocrine L cells in the gut produce the incretin hormone glucagon-like peptide-1 (GLP-1), which stimulates postprandial pancreatic insulin secretion [11,12]. $\beta7^{-/-}/Ldlr^{-/-}$ mice fed a high-cholesterol diet had higher levels of fasting GLP-1 in plasma and higher levels of mRNA for glucagon in the gut. Natural αβ and γδ T cells in the gut of wild-type mice had robust GLP-1 receptor expression. In contrast, the guts of $\beta7^{-/-}$ mice were relatively deficient in the expression of the GLP-1 receptor. The authors concluded that in wild-type mice, intraepithelial lymphocytes with high expression of the GLP-1 receptor limited the bioavailability of GLP-1, which decreased glucose tolerance, and on a high-fat, high-cholesterol, high-caloric, and high-sodium diet, led to obesity, diabetes and increased atherosclerosis. Conversely, the authors concluded that in $\beta7^{-/-}$ mice with a relative deficiency of natural αβ and γδ T cells in the gut and diminished GLP-1 receptor expression, GLP-1 bioavailability was increased, glucose tolerance was improved, diabetes and atherosclerosis were decreased. In addition, the $\beta7^{-/-}$ mice had more enteroendocrine L cells in the gut which led to increased production of GLP-1. The authors speculated that while intraepithelial lymphocytes may be advantageous when food is scarce, when there is an overabundance of diets high in fat and sugar, this metabolic checkpoint may be detrimental to health.

ROLE OF GROUP 1B PHOSPHOLIPASE A_2

Cash *et al.* [13■■] demonstrated that lowering the lysophospholipid content in the duodenum and jejunum of the small intestine by any of three different means gave similar positive results in mice. Reducing the activity of group 1B phospholipase A_2 (PLA2G1B) by inactivation of its gene ($Pla2g1b^{-/-}$) or by pharmacologic inhibition or by bariatric surgery, all resulted in similar changes in gut micro-biota, a reduction in hyperlipidemia and trimethylamine oxide levels, decreased adiposity, and improvement in diet-induced diabetes. PLA2G1B is produced by the acinar cells of the pancreas where inactive enzyme with a propeptide is found within zymogen granules together with other digestive enzymes [14■]. After a meal is ingested the zymogen granules release their contents into pancreatic fluid that flows through the pancreatic duct to the duodenum. In the lumen of the small intestine

the propeptide is removed to activate the PLA2G1B enzyme. The phospholipase A_2 activity of the enzyme generates lysophospholipids derived from dietary phospholipids by selectively removing the fatty acid (FA) moiety from the *sn*-2 position of the phospholipid [14■]. Mice lacking the gene for PLA2G1B (*Pla2g1b*$^{-/-}$) when bred with *Ldlr*$^{-/-}$ mice were protected against diet-induced hyperlipidemia and atherosclerosis [15,16]. The metabolic differences between fat-fed wild-type mice and fat-fed *Pla2g1b*$^{-/-}$ mice could not be due to differences in lipid absorption because similar amounts of fat were absorbed [17]. Indeed, the fat-fed *Pla2g1b*$^{-/-}$ mice absorbed more fat than chow-fed wild-type mice, yet their weight gains were similar [17]. Hui [14■] concluded that PLA2G1B must have a direct contributory role in diet-induced cardiometabolic diseases via a mechanism that is independent of fat absorption.

ROLE OF STEAROYL-CoA DESATURASE-1

Mukherjee *et al.* [18■] crossed floxed stearoyl-CoA desaturase-1 (*Scdl*$^{fl/fl}$) mice with *Ldlr*$^{-/-}$ mice and then with Villin Cre (*VilCre*) mice to produce mice with enterocyte-specific knockdown of *Scd1* (*Scd*$^{fl/fl}$/*Ldlr*$^{-/-}$/*VilCre*) mice. On Western diet the mice with enterocyte knockdown of *Scd1* gained less weight than control mice. Levels of LysoPC 18 : 1 and LPA 18 : 1 in jejunum were significantly less in the mice with enterocyte knockdown of *Scd1*. This occurred despite a marked abundance of C18 : 1 FA (oleic acid) in Western diet. Based on the work of Miyazaki *et al.* [19] and Man *et al.* [20] the authors hypothesized that the enzymes in enterocytes that convert LysoPC to phosphatidylcholine in the Lands Cycle [21,22] preferentially utilize endogenously synthesized oleic acid over oleic acid derived from the diet. On Western diet, the mice with enterocyte knockdown of *Scd1* had lower levels in enterocytes and plasma of lipopolysaccharide-binding protein (LBP), cluster of differentiation 14 (CD14), Toll-like receptor 4 (TLR4), and myeloid differentiation factor-88 (MyD88). These mice also had less dyslipidemia and systemic inflammation. Adding Tg6F to Western diet resulted in reduced enterocyte protein levels of LBP, CD14, TLR4, and MyD88 in mice with normal levels of Scd1 in their enterocytes, and was similar to the levels achieved without Tg6F, but with knockdown of enterocyte *Scd1*. It was also found that adding LysoPC 18 : 1 (but not the saturated LysoPC 18 : 0) to chow induced *Scd1* expression in jejunum and increased dyslipidemia and plasma serum amyloid A and IL-6 levels in the control mice, but not in the mice with enterocyte knockdown of *Scd1*. The authors concluded that enterocyte *Scd1* is partially responsible for LysoPC 18 : 1 and Western diet-induced dyslipidemia and inflammation in *Ldlr*$^{-/-}$ mice.

ROLE OF THE SMALL INTESTINE IN MODELS OF METASTATIC LUNG CANCER

As Tg6F is not absorbed into the blood [1], Chattopadhyay *et al.* [23■] sought to understand how adding Tg6F to the chow of wild-type mice the day after they had received tail vein injections of colon cancer cells that metastasize to the lungs resulted in a dramatic decrease in lung tumor burden [3]. Gene expression array analysis identified upregulation of Notch pathway genes in both jejunum and lung, and down regulation of *Spp1* (osteopontin) in both jejunum and lung in wild-type mice fed chow containing Tg6F starting the day after the

mice received tail vein injections of colon cancer cells. In jejunum, adding Tg6F to chow increased protein levels for Notch1, Notch2, Dll1, and Dll4. In lung, adding Tg6F to chow increased protein levels for Notch1 and Dll4 and decreased levels of Spp1. Adding T6F to chow also reduced levels in the jejunum of oxidized phospholipids, and reduced 25-hydroxycholesterol (25-OHC) levels, which are known to inhibit Notch1 and induce Spp1, respectively. Notch pathway is known to promote antitumorigenic patrolling monocytes, and Spp1 is known to facilitate the formation of protumorigenic myeloid suppressor cells (MDSCs). Tg6F-fed mice had higher numbers of patrolling monocytes in both jejunum and lung, lower plasma levels of Spp1 with reduced numbers of MDSCs in both jejunum and lung. The authors concluded that Tg6F altered levels of specific oxidized lipids and 25-OHC to modulate Notch pathways and Spp1, which altered small intestine immune cells, leading to similar changes in lung that reduced tumor burden.

ROLE OF THE LANDS CYCLE AND CHOLESTEROL IN THE SMALL INTESTINE

Wang *et al.* [24■] found that inhibition of the phospholipid-remodeling enzyme Lpcat3, which plays an important role in the Lands Cycle in the small intestine [25■] increased membrane saturation and stimulated cholesterol biosynthesis, which in turn stimulated intestinal stem-cell proliferation. Inhibiting cholesterol synthesis normalized intestinal crypt hyperproliferation in Lpcat3-deficient organoids and mice. Conversely, increasing cellular cholesterol content stimulated crypt organoid growth. Providing excess dietary cholesterol or stimulating endogenous cholesterol synthesis through expression of sterol regulatory element binding protein-2 promoted intestinal stem-cell proliferation *in vivo*. In $Apc^{min/+}$ mice, disruption of Lpcat3-dependent phospholipid and cholesterol homeostasis dramatically enhanced tumor formation. These studies provide evidence for a critical dietary-responsive phospholipid–cholesterol axis that regulates intestinal stem cell proliferation and tumorigenesis.

CONCLUSION

Recent research shows that the small intestine is a very complicated organ. The small intestine must breakdown and transport nutrients into the body, while keeping out billions of bacteria and viruses. The small intestine must maintain an army of immune cells to deal with those bacteria and viruses that are able to penetrate its defenses. These immune cells can have profound metabolic effects such as is the case of the β7 expressing αβ and γδ T cells, which regulate the production (i.e., the number of enteroendocrine L cells, which secrete the incretin hormone GLP-1), and regulate the bioavailability of GLP-1. Dietary phospholipids are converted to lysophospholipids in the small intestine to promote absorption. In the process, the phospholipids are remodeled through the Lands Cycle, which results in the conversion of saturated phospholipids to unsaturated phospholipids, which then can be a substrate for the formation of unsaturated lysophospholipids such as LysoPC 18 : 1 and LPA 18 : 1. These unsaturated lysophospholipids have dramatically different biologic activities compared with their saturated counterparts (e.g., LysoPC 18 : 0 and LPA 18 : 0). Local lipid metabolism in the small intestine affects the complement of immune cells, and their state of

activation in the small intestine, which in turn can result in major changes in distant organs such as the lungs. As a result of these processes, the small intestine plays an important role in atherosclerosis and cancer that goes well beyond the bulk transport of dietary nutrients needed for energy.

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KEY POINTS

- β7 expressing αβ and γδ T cells in the small intestine profoundly affect GLP-1 levels, obesity, glucose tolerance, and atherosclerosis in mice.
- Lowering the lysophospholipid content in the small intestine improves obesity and glucose tolerance similar to the improvement with bariatric surgery in mice.
- Stearoyl-CoA desaturase-1 in the enterocytes of the small intestine strongly influences the response of *Ldlr*$^{-/-}$ mice to a Western diet.
- Adding a concentrate of tomatoes transgenic for the apolipoprotein A-I mimetic peptide 6F to the chow of wild-type mice the day after tail vein injection of colon cancer cells that metastasize to the lungs, results in similar changes in immune cells in the small intestine and lungs, and a dramatic reduction in tumor burden in the lungs.
- Lpcat3 plays an important role in phospholipid remodeling in the Lands Cycle of the small intestine regulating the production of stem cells via the modulation of enterocyte cholesterol biosynthesis, and influencing tumorigenesis.