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The gut wall's potential as a partner for precision oncology in immune checkpoint treatment

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ABSTRACT

The gut wall is the largest immune organ and forms a barrier through which gut microbiota interact with the immune system in the rest of the body. Gut microbiota composition plays a role in the strength and timing of the anticancer immune response on immune checkpoint inhibitors (ICI). Surprisingly, the effects of gut wall characteristics, such as physical barrier integrity, permeability, and activity and composition of the intestinal immune system, on response to ICI has received little attention. Here, we provide an overview of markers to characterize the gut wall and interventions that can modulate these gut wall characteristics. Finally, we present a future perspective on how these gut wall markers and interventions might be utilized and studied to improve ICI treatment strategies.

Introduction

Tumor cells escape destruction by the immune system by exploiting mechanisms that suppress an anticancer immune response. [1] An important mechanism is the activation of immune checkpoints, which are the 'brakes' in the immune system that prevent inappropriate cytotoxic T-cell activation. Immune checkpoint inhibitors (ICI) can release these immune brakes and thus trigger a durable anticancer immune response. These medicines have dramatically improved patient outcomes across numerous tumor types. [2] Unfortunately, most patients with cancer still do not benefit from ICI as they fail to obtain a durable response. [3]

A complex set of tumor and patient characteristics is emerging that govern the anticancer immune response's strength and timing. [2,4] Together, these characteristics determine the 'cancer-immune set point', the threshold that must be surpassed in a patient to trigger an anticancer immune response to ICI. [2] The gut microbiota and microbial metabolites can influence the cancer-immune set point. [5–7] Pilot studies showed that transplantation of fecal microbial samples obtained from patients responding to ICI into patients not responding to ICI can lead to tumor response in initially non-responding patients after reintroduction of ICI. [8] This has sparked a series of clinical trials currently investigating whether modulation of gut microbiota through fecal microbial transplantation (FMT), probiotics, and specific diets can enhance tumor response to ICI. [8,9]

The gut microbiota interacts with the immune system in the rest of the body through the gut wall, which encompasses the intestinal mucosa and submucosa, in which immune cells are located which reflect the physical gut barrier. The gut is the primary site of interaction between the host and the outside world and harbors over 70% of the body's immune cells. [10] Surprisingly, the relationship between ICI response, integrity, and permeability of the physical gut barrier and the activity of the intestinal immune system has been largely overlooked. So far, we know that the intestinal immune system becomes activated during ICI treatment, and adequate baseline intestinal epithelial cell function, reflected by high plasma citrulline levels ($\geq$20 μM), is associated with a favorable anticancer immune response to ICI. [11–13] Interventions that could modulate the integrity, permeability, and immune activity of the gut wall into a more favorable state for response to ICI have the potential to improve disease outcomes in patients. To develop such interventions, we need to understand how gut wall characteristics can impact the strength and timing of the anticancer immune response to ICI. Furthermore, this understanding might also provide us with tools to better predict response to ICI.

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Here, we provide an overview of markers that can be used to characterize the integrity, permeability, and immune activity of the gut wall. We also review interventions that can modulate these gut wall characteristics. Finally, we present a future perspective on how these gut wall characterization markers and interventions might improve ICI treatment strategies.

Search strategy and selection criteria

We retrieved articles from PubMed published up to February 2022 reporting results for relevant markers and interventions. Search terms are provided in Suppl. Table 1. Only articles published in English, Q1, and Q2 journals, with full-text availability, and concerning human subjects were considered eligible. Next, titles, abstracts, and full text were sequentially assessed to remove non-relevant articles. Articles reporting gastrointestinal malignancy markers or disease-specific markers, conference abstracts, commentaries, editorial correspondence, or pre-clinical studies were excluded. If multiple studies address the same marker, we selected the article(s) that reported results with the highest level of evidence as defined by the Oxford 2011 Levels of Evidence, v2.1. To identify articles missed by our search strategy, we screened the references of the remaining articles for additional relevant studies. The final selection of references included for each marker and intervention are provided in Suppl. Tables 2–5.

Characterizing gut wall integrity, permeability, and immune activity

The gut, formed by the small and large intestine, is selectively permeable. While protection from potentially noxious luminal contents by the gut wall is essential, low-grade exposure of the body to the gut's contents builds and maintains an adequate immune defense. [14] Two components of the gut wall are vital to preserving intestinal homeostasis: the physical gut barrier and the intestinal immune system.

We identified markers that characterize the integrity and permeability of the physical gut barrier (n = 11, Table 1) and the activity of the intestinal immune system (n = 10, Table 2).

Characterizing the integrity and permeability of the physical gut barrier

Physical gut barrier integrity and permeability can be measured non-invasively using sugar absorption tests, the most common of which is the lactulose-to-mannitol (L:M) ratio. Under physiological conditions, an intact physical gut barrier preferentially facilitates absorption of mannitol over lactulose, resulting in a low L:M urinary ratio. When the physical gut barrier becomes disrupted and more permeable, absorption of lactulose increases, resulting in an increased L:M ratio. Differences in methodologies across laboratories hamper the standardization and comparison of studies using L:M ratios. [15,36,37]

Blood-based alternatives such as intestinal fatty acid-binding protein (i-FABP) and citrulline can also be used to characterize physical gut barrier integrity and permeability. i-FABP is a water-soluble cytosolic protein expressed by mature enterocytes. When intestinal mucosal damage occurs, i-FABP is released into the circulation. [16,38,39] Citrulline is an amino acid produced by small bowel enterocytes from glutamine and derived amino acids Decreased plasma citrulline reflects reduced enterocyte mass and function. [17,40]

Ex-vivo assessment of physical gut barrier integrity and permeability is possible through immunohistochemical staining of tight junctions and zonula adherens components. [18] Physical gut barrier integrity can also be assessed ex-vivo by measuring transepithelial electrical resistance with Ussing chambers. [19]

In-vivo physical gut barrier integrity assessment is possible using probe- or endoscope-based confocal laser endomicroscopy. Confocal laser endomicroscopy can visualize leakage of lanthanum nitrate into the paracellular space. This leakage is, which is associated with tight junction and zonula adherens loss. [18] Confocal laser endomicroscopy, combined with intravenous fluorescein administration, allows grading of physical barrier integrity and permeability using the Confocal Leak Score. The Confocal Leak Score measures fluorescein leakage from the submucosa into the gut lumen through epithelial breaks. The Confocal Leak Score has been validated and is predictive for diarrhea motions per day in inflammatory bowel disease (IBD). [20] In-vivo and ex-vivo tissue analyses may be cumbersome for patients. Still, in the case of in-vivo analysis, they offer a level of real-time diagnostic accuracy that is not obtainable otherwise.

Table 1
Physical gut wall markers.

Marker	Specimen	Cut-off	Sens/Spec (%)	Context	LoE	Ref.
Lactulose: Mannitol	Urine	> 0.03	NR	Asymptomatic first-degree relatives of individuals with Crohn's disease	2	[15]
i-FABP	Plasma & Serum	382 pg/mL	80/87	Celiac disease vs normal	2	[16]
Citrulline	Plasma & Serum	20 μmol/L	80/84	Enteropathies* vs normal	2	[17]
TJ proteins	Biopsy	NR	NR	Intestinal ischemia–reperfusion	3	[18]
Transepithelial electrical resistance	Biopsy	NR	NR	Functional dyspepsia vs normal	3	[19]
TJ and ZA function with lanthanum nitrate electron microscopy	Biopsy	NR	NR	Intestinal ischemia–reperfusion	3	[18]
Confocal leak score	eCLE ileal images	Confocal leak score >13	95/98	Symptomatic IBD vs asymptomatic IBD vs normal	2	[20]
Epithelial gap density	pCLE duodenal images	> 15 gaps / 1000 cells	79/88	Functional dyspepsia vs normal	2	[19]
^{51}Cr-EDTA	Urine	NR	NR	IBS vs normal	3	[21]
D-lactate	Plasma & Urine	NR	NR	Comparison of patients with acute gastrointestinal injury grade I-IV	3	[22]
Carotenoids	Serum	NR	NR	Children with no, mild, moderate, or severe malnutrition	3	[23]

*Celiac disease, tropical enteropathy, Crohn's disease, mucositis, acute rejection in intestinal transplantation.
^{51}Cr-EDTA, Chromium-51 ethylenediaminetetraacetic acid; D-lactate, D-lactate dehydrogenase; eCLE, endoscope-based confocal laser endomicroscopy; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; i-FABP, intestinal fatty acid-binding protein; LoE, Level of Evidence (as defined by Oxford 2011 Levels of Evidence, v2.1.); NR, not reported; pCLE, probe-based confocal laser endomicroscopy; Sens, sensitivity; Spec, specificity; TJ, tight junction; ZA, zonula adherens.

Table 2
Source articles of intestinal immune system markers.

Marker	Specimen	Cut-off	Sens/ Spec (%)	Context	LoE	Ref.
Lactoferrin	Feces	>7.25 μg/g	82/79	IBD vs controls (IBS and normal)	1	[24]
Calprotectin	Feces	>50 μg/g	88/73	IBD vs controls (IBS and normal)	1	[24]
S100A12	Feces	>0.8 μg/g	100/ 81	Crohn's disease vs normal	2	[25]
			100/ 91	Ulcerative colitis vs normal		
			86/96	IBS vs normal		
Lipocalin-2	Feces	0.81 μg/g	95// 96	IBD vs controls (IEC, IBS or normal)	2	[26]
CHI3L1	Feces	>13.7 ng/g	85/89	IBD vs normal	2	[27]
Immune cells	Biopsy	NR	NR			
IE CD3 + T cells, LP CD45 + cells and eosinophils		NR	NR	Celiac disease vs NCGWS vs non-NCGWS	3	[28]
Macrophages		NR	NR	IBD vs normal	3	[29]
MAIT cells		NR	NR	Ulcerative colitis vs normal	3	[30]
CD4 + CD25+ FoxP3 + cells				Ulcerative colitis vs normal	3	[31]
PMN-elastase	Feces	>19 ng/g	84/87	IBD vs IBS	2	[32]
DPP4	Feces	NR	NR	IBD	2	[33]
HMGB1	Feces	NR	NR	IBD vs normal	3	[34]
UMH	Urine	NR	NR	IBD vs normal	3	[35]

CHI3L1, Chitinase 3-like-1; DPP4, Dipeptidyl Peptidase-4; HMGB1, high mobility group box 1; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IE, intra-epithelial; IEC, Infectious enterocolitis; LoE, Level of Evidence (evidence as defined by the Oxford 2011 Levels of Evidence, v2.1.); LP, lamina propria; MAIT, mucosal-associated invariant T cells; NCGWS; non-coeliac gluten/wheat sensitivity; NR, not reported; PMN, polymorphonuclear neutrophil; S100A12, S100 calcium-binding protein A12; Sens, sensitivity; Spec, specificity; UMH, urinary excretion of n-methylhistamine.

Characterizing the activity of the intestinal immune system

Calprotectin and lactoferrin are the most commonly used markers of intestinal immune activation. Calprotectin is the predominant cytosolic protein in neutrophils, while lactoferrin is a protein in neutrophil secondary granules. Their elevation in feces can reflect microscopic and macroscopic intestinal inflammation. Calprotectin can serve to predict and monitor IBD flare-ups and distinguish IBD from non-inflammatory intestinal conditions. [24,41,42] Variations in calprotectin and lactoferrin levels across age groups have been reported, therefore age-adjusted cut-off values for both markers have been proposed. [43]

Fecal markers S100 calcium-binding protein A12 (S100A12), lipocalin-2, and Chitinase 3-like-1 (CHI3L) are not yet clinically validated alternatives to detect bowel inflammation. S100A12, like calprotectin, is a cytoplasmic neutrophil-derived protein released upon neutrophil activation. [25] Lipocalin-2 is a glycoprotein with immunomodulatory and antimicrobial effects secreted into the gut lumen primarily by enterocytes but also by macrophages, monocytes, and granulocytes in response to proinflammatory stimuli. Lipocalin-2 can detect low-grade inflammation and is equivalent to fecal calprotectin in IBD. [26,41] Glycoprotein CHI3L is highly expressed in colon epithelial cells and lamina propria macrophages at sites of mucosal inflammation. Fecal CHI3L levels correlate with clinical and endoscopic IBD activity. [27]

Detailed characterization of immune cell infiltrates is possible through ex-vivo assessment of biopsies using immunohistochemical stainings, flow cytometry, or quantitative real-time polymerase chain reaction. Thus, immune cell populations can be quantified and characterized, and their infiltration patterns analyzed [21–31,41–43]. Biopsies are considered the gold standard to diagnose and monitor intestinal inflammation. However, biopsies they face the limitation that they represent a small tissue area and therefore may not be representative.

Interventions modulating the integrity, permeability, and immune activity of the gut wall

Modulation of the integrity, permeability, and immune activity of the gut wall is possible through pharmaceutical intervention, diet and supplements, pre- and pro-biotics, and FMT. We identified 11 pharmaceutical interventions, one dietary intervention, and three microbiota-directed interventions (Table 3).

Pharmaceutical interventions

Clinically approved treatments that non-selectively promote gut mucosal healing through immunomodulation are Janus kinase (JAK) inhibitors, tumor necrosis factor-α (TNF-α) inhibitors, corticosteroids, cyclosporine, ustekinumab, and thiopurines. In addition, selective modulation of the intestinal immune system is possible with 5-aminosalicylic acid and vedolizumab. [44–52,61–65]

Next to these clinically used gut wall modulators, larazotide acetate and propionyl-L-carnitine increase physical gut wall integrity and decrease intestinal permeability, colonic-release low-molecular-weight heparin promotes mucosal healing and reduces inflammation, and dersalazine sodium modulates intestinal immune system activity. [53–56]

Dietary interventions

Improvement of integrity, permeability, and immune activity of the gut wall with diets has been explored in a broad range of gastrointestinal conditions. While consensus on dietary interventions targeting gut wall function remains to be reached, certain dietary patterns are considered to be noxious or protective. High consumption of sugar, animal protein, and saturated fats is associated with gut microbiota dysbiosis, intestinal inflammation, and increased risk for IBD. High fiber consumption has been associated with more favorable and varied gut microbiota composition and increased short-chain fatty acid (SCFA) production, thus promoting gut wall homeostasis. [66–68]

We identified one dietary intervention directed at the gut wall: oral glutamine supplementation. Glutamine is a major energy source for enterocytes. Without glutamine, enterocytes decay, causing physical gut barrier disruption and increased permeability. Oral supplementation of glutamine normalizes intestinal permeability in patients with post-infectious diarrhea-predominant IBS. [57]

Interventions with prebiotics, probiotics, and gut microbiota

The use of pre- and probiotics to reinstate gut wall homeostasis shows promising results in experimental settings. Prebiotics are non-digestible compounds that are metabolized by gut microbiota. Prebiotics promote favorable gut microbiota composition and/or activity, resulting in beneficial physiological effects on the host. [58] Suppletion with prebiotic inulin-type-*6* fructans suppletion is beneficial for some

Table 3
Source articles of gut wall directed interventions.

Intervention	Mechanism of action	Gut-selective?	Effect	Context	LoE	Ref.
Corticosteroids	Interact with glucocorticoid receptors in cell nuclei Promote tolerogenic over immunogenic phenotype, neutralize proinflammatory cytokines	No	Anti-inflammatory and mucosal healing	IBD	1	[44]
Integrin inhibitor	Not fully understood Vedolizumab blocks α4β7 integrin on T and B cells	Yes	Anti-inflammatory and mucosal healing	IBD	1	[45]
Thiopurines	Inhibit nucleotide and purine synthesis, reducing the proliferation of rapidly dividing cells Block gene activation of effector T cells, downregulate their cytotoxic activity and reduce B cell infiltration in the gut mucosa	No	Anti-inflammatory, mucosal healing	Crohn's disease	1	[46]
Cyclosporine	Calcineurin inhibitor	No	Anti-inflammatory and mucosal healing	Ulcerative colitis	1	[47]
JAK-inhibitors	Selectively inhibit JAK-1 and JAK-2, thus downmodulating signaling of pro-inflammatory cytokines of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21	No	Anti-inflammatory and mucosal healing	IBD	1	[48]
5-ASA	Not fully understood Metabolized by IECs, local effect	Yes	Anti-inflammatory and mucosal healing	IBD	2	[49]
Ustekinumab	Inhibits the T-helper 1 and 17 pathways by blocking the p40 subunit of IL-12 & IL-23	No	Anti-inflammatory and mucosal healing	Crohn's disease	2	[50]
TNF-α inhibitors	Inhibit the proinflammatory activity of the cytokine TNF-α	No	Anti-inflammatory, mucosal healing	Ulcerative colitis	2	[51]
			Improve physical gut barrier function and decrease permeability	Crohn's disease	2	[52]
Dersalazine sodium	Decreases expression of inflammatory genes and proinflammatory cytokines in colonic tissue through anti-platelet activating factor activity	Yes	Anti-inflammatory and mucosal healing	Ulcerative colitis.	2	[52,53]
Propionyl-L-carnitine	Source of l-carnitine and propionyl-coenzyme-A for colonocytes, proposed to in this way facilitate energy release	Yes	Mucosal healing	Ulcerative colitis, as co-treatment	2	[54]
Lazarotide acetate	Peptide derived from zonula occludens toxin, modulator of tight-junctions and inhibitor of paracellular permeability	Yes	Increases physical gut barrier integrity and decreases intestinal permeability	Coeliac's disease	2	[55]
LMWH	Not fully understood Thought to modulate complement pathways and proinflammatory cytokines	No	Anti-inflammatory	Ulcerative colitis	2	[56]
Oral glutamine	Not fully understood Glutamine is a major source of energy for enterocytes	No	Decreases intestinal permeability	Post-infectious IBS-D	3	[57]
Prebiotics	Not fully understood	No	Anti-inflammatory, functional changes gut microbiota	IBD	1	[58]
Probiotics	Not fully understood	No	Mucosal healing, improve physical gut barrier integrity, decrease intestinal permeability, anti-inflammatory	IBD, IBS, *C. difficile,* SIBO	1	[59]
FMT	Not fully understood	No	Mucosal healing, anti-inflammatory, eubiosis?	Ulcerative colitis	1	[60]

5-ASAs, mesalamine or 5-aminosalicylic acid; FMT, fecal microbial transplant; IBD, inflammatory bowel disease; IBS-D, diarrhea-predominant irritable bowel syndrome; IL, interleukin; JAK, Janus kinase; LMWH, low-molecular weight heparin; LoE, Level of Evidence (evidence as defined by the Oxford 2011 Levels of Evidence, v2.1.); SIBO, small intestinal bacterial overgrowth; TNF-**α**, tumor necrosis factor alpha.

patients with ulcerative colitis. It reduces inflammation, promotes mucosal healing, and induces functional and compositional microbiota changes. [59] Probiotics are live microorganisms that can be beneficial to the host's health. Probiotics exert their effects by promoting a favorable gut microbiota composition and functionality, improving physical gut barrier function, immunomodulation and modulating physiological processes on the host. [69] In diarrhea-predominant IBS, lactic acid bacteria supplementation improves mucosal barrier function. [70] When added to the conventional treatment of patients with mild to moderate ulcerative colitis, probiotic mix VSL#3 can boost mucosal healing and increase endoscopic remission rates. [71] While studies suggest that use of prebiotic and probiotics may be beneficial in certain clinical settings like IBD, the variation in formulations and dosages used, as well as the limited data available from controlled trials, preclude deriving firm conclusions on their effects and efficacy. [58] Importantly, data suggest that probiotic supplementation may also enhance the therapeutic effects of ICI therapy. Supplementation with CMBM588, a probiotic containing *Clostridium butyricum* which produces the SCFA butyrate appears to improve progression-free survival in patients with metastatic renal cell cancer receiving dual ICI therapy. Patients receiving CBM588 showed changes in gut microbiota functionality, like upregulated rhamnose synthesis and an increase of the SCFA propionate production. [72] Manipulation of the gut microbiota through FMT has been explored in the context of severe reduction in microbial diversity caused by pathogens like *C. difficile* and as an experimental treatment in IBD. In patients with *C. difficile,* FMT induced remission and symptomatic relief. [73] In patients with ulcerative colitis, FMT increased diversity, induced remission, and mucosal healing. FMT did not lead to objective changes in inflammatory markers like calprotectin. [60,74] The exact effects of FMT are unknown. It is hypothesized that FMT promotes recolonization of bacteria with properties beneficial for health, and thus an optimal balance of microbiota in the gastrointestinal tract. While the short-term effects of FMT are promising, several aspects remain unclear. Ongoing studies will provide more data on the effect of FMT on objective endpoints such as mucosal healing or disease extent. Further research is required to address the impact of bowel preparation on FMT effectiveness, to determine the best administration route and dosage of FMT as well as to define the long-term effects of FMT on the recipient. [60,73]

Gut wall integrity, permeability, and immune activity in the context of ICI treatment

To date, efforts have focused on the relationship between gut lumen microbiota composition and the strength of the anticancer immune response induced by ICI. In addition, an association between gut mucosa microbial composition and response to ICI and to gastrointestinal immune-related adverse events was recently shown. [75] In initial ICI non-responders, FMT, and re-introduction of ICI can lead to tumor response. [8] However, there is no consensus on which bacterial species are favorable. [8,76] Promising data suggest that supplementation with probiotics may improve clinical outcomes of patients receiving dual ICI therapy. [72]

It is becoming increasingly evident that microbial functionality may be equally relevant or even more relevant than gut microbiota composition itself. Shotgun metagenomic sequencing was performed on pre-ICI-treatment stool samples collected in 5 observational cohorts recruiting ICI-naive patients with advanced cutaneous melanoma (n = 165). It showed that the gut microbiome has a relevant but cohort-dependent association with response to ICI. [77] We are currently generating metabolomics data and will measure markers discussed in this review to characterize the gut wall in the abovementioned cohorts of ICI-naïve patients.

SCFAs have been associated with response to ICI. SCFAs are microbial metabolites produced by microbial fermentation of dietary fibers. SCFAs interact with the gut wall, contribute to intestinal immune homeostasis and intestinal epithelial barrier integrity. Patients with non-small cell lung cancer (NSCLC) responding to programmed cell death protein 1 (PD-1) antibody therapy had a higher baseline fecal SCFAs concentration. [78] In line with this, in patients with a wide range of malignancies treated with PD-1 antibodies, high baseline fecal concentrations of SCFAs propionic, butyric, valeric, and acetic acid and high plasma levels of isovaleric acid were associated with longer progression-free survival. [79] Furthermore, in patients with NSCLC, SCFAs were shown to be the main metabolites produced by the gut microbiota of long-term responders to PD-1 antibody therapy. [80] In contrast, low baseline serum propionic and butyric acid were associated with longer progression-free survival in patients with metastatic melanoma and metastatic prostate cancer receiving cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies. [81] Due to differences in the methodologies applied and modest size of patient populations included, no clear conclusions can be drawn from the divergent results across the abovementioned studies. Adequate enterocyte function, reflected by high plasma citrulline levels ($\geq$20 μM) at baseline, correlated with favorable response to ICI, longer progression-free, and overall survival in patients with advanced NSCLC receiving anti-PD-1 therapy. [13] The effects of ICI therapy on the intestinal immune system have been investigated in more detail in the context of ICI-induced colitis. In ICI-induced colitis, fecal calprotectin and lactoferrin levels are elevated. [11,82–84] ICI-induced colitis is characterized by a heavy CD8 + T cell mucosal infiltrate. [12,85] In the ongoing DEFENCE study, colon biopsies and blood samples are obtained at baseline and during ICI treatment to determine the effects of ICI on the physical gut wall and the intestinal immune system activation in relation to ICI tumor response. [86]

Future perspective: Exploiting the gut wall to predict and potentiate tumor response to ICI

Compelling data suggest that gut microbiota composition and functionality are relevant to tumor response to ICI. This raises the question of whether this may also be the case for the gut wall. To study this hypothesis, the gut wall phenotypes of responders and non-responders to ICI should be defined and compared. This can be done by measuring physical gut barrier integrity, intestinal permeability, and intestinal inflammation markers at baseline and during ICI treatment. In addition, the interplay between gut wall immune composition and activity status and gut microbiota, as well as tumor and patient characteristics should be taken into account. Determining PD-1 and CTLA-4 expression of cells in the gut wall may also be of interest, since these ICI targets have a role in maintaining intestinal immune system homeostasis. [87,88] If data suggest a role for the gut wall in the response to ICI, and specific gut wall phenotypes are associated with response to ICI, interventions to promote such beneficial phenotypes should be considered.

Together, the data obtained from exploring the role of the gut wall in tumor response to ICI might lead to novel markers and therapeutic targets with which to predict and potentiate the response to ICI.

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Author contribution

All authors contributed to manuscript conception, drafting of the manuscript, provided critical review and revisions, and approved the final version of the manuscript.

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Sara Hone Lopez: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Mathilde Jalving:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Rudolf S.N. Fehrmann:** Conceptualization, Methodology, Writing – review & editing. **Wouter B. Nagengast:** Conceptualization, Writing – review & editing. **Elisabeth G.E. de Vries:** Conceptualization, Methodology, Writing – review & editing. **Jacco J. de Haan:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

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