gastrointestinal disorders

MDPI

Review

Lamina Propria and GALT: Their Relationship with Different Gastrointestinal Diseases, Including Cancer

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Abstract: The structural integrity of the gastrointestinal tract is important because it dictates the functionality of this system. Regarding this, gut-associated lymphoid tissue (GALT) has a significant role in immunity. Most cancer research focuses on organized lymphoid structures and less on diffuse structures such as the lamina propria (LP). Therefore, this paper aims to investigate the link between the LP and cancer in humans. The interstitial matrix and loose connective tissue layer located directly under the epithelium is known as the LP. In this area, there are a lot of IgA+ plasma cells (PCs), T and B lymphocytes, macrophages, dendritic cells (DCs), and stromal cells (SCs). Antigens from the lumen are picked up by LP DCs and presented directly to B cells, which may cause IgA class switching and differentiation in the presence of T cells. In humans, the GALT of the mucosa has been proposed as the source of a unique malignancy known as "GALT carcinoma", which is thought to represent the "third pathway of colorectal carcinogenesis". However, present colorectal cancer classifications do not define GALT carcinoma as a separate histologic category.

Keywords: lamina propria; GALT; gastrointestinal tract; colorectal

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1. Introduction

The host's mucosal surfaces serve as one of the primary barriers against infections and the systemic spread of the local microbiota. Human type I mucosal surfaces include those of the respiratory system, gastrointestinal (GI) tract, and female upper reproductive systems. Type II mucosal surfaces are located in the mouth, alimentary canal, and lower reproductive systems of females, according to their distinctive characteristics. In humans, these two kinds of mucosal surfaces make up around 400 m^2 of surfaces [1]. Essentially, a basic columnar epithelium covers the mucosal surfaces, has polymeric immunoglobulin receptors (pIgRs), and contains essential secretory antibodies, such as immunoglobulin A (sIgA). IgG becomes more prevalent than IgA; the majority of the isotypes is the stratified squamous (non-keratinized) epithelium, and pIgR is not found in type II mucosal layers [1]. The gut-associated lymphoid tissue (GALT) and the gastrointestinal tract constitute a particular system that is constantly exposed to contradicting signals. The organism comes into contact with the most critical antigens in this area. It must be able to rapidly differentiate between commensal bacteria from the gut microbiota and invasive pathogens in addition to its roles in food intake; digestion; nutritional absorption from food, water, and electrolyte exchange; and hormone synthesis [2]. The majority of the intestinal mucosal immune system is found in the lamina propria, which is placed underneath the intestinal epithelial layer [3]. The different innate and adaptive immune cell types found here include dendritic

cells, macrophages, innate lymphoid cells (ILCs), CD4+ T cells (Th1, Th17, Treg cells), CD8+ T cells, isolated lymphoid follicles (ILFs), and IgA-secreting plasma cells. These cells work together to protect against pathogen invasion and maintain the gut mucosal barrier (Figure 1).

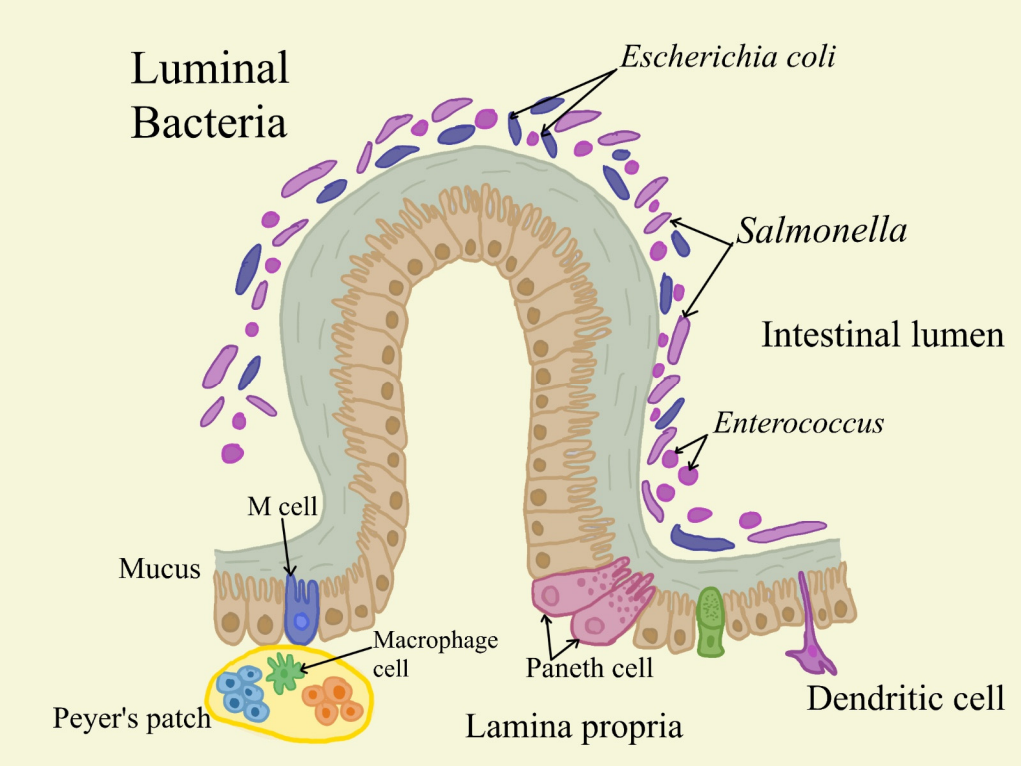

Figure 1. The organization of the lamina propria. The layer of loose connective tissue and interstitial matrix directly beneath the epithelium is known as the LP. M cells, dendritic cells, Paneth cells, macrophages, and Peyer's patches are presented. When dendritic cells collect antigens through the epithelial layer and carry them to Peyer's patches, they improve the activation of adaptive immune cells. In the intestinal tract, M cells are located adjacent to Peyer's patches (PPs), which are lymphoid organs. The PPs' B and T cells, DCs, and macrophages receive dietary antigens or microbiological particles from M cells.

The ability of lamina propria T cells to initiate pro- and anti-inflammatory responses in response to cues from the luminal milieu is thus demonstrated [4]. Uncontrolled inflammatory responses to commensal bacteria or dietary antigens are the main causes of tissue damage and ongoing intestinal inflammation in patients with inflammatory bowel disease (IBD) [5]. The mucosal immune system is tightly controlled to stay in a healthy state. For the maintenance of colon homeostasis, local Tregs are essential [6]. Numerous bacterial metabolites, including tryptophan metabolites, some secondary bile acid conjugates, and short chain fatty acids (SCFAs), are responsible for the triggering of colonic Tregs [7–11]. The immune system and commensal microorganisms interact and change over time. Food affects this interaction by giving gut bacteria substrates, and certain foods can directly affect immune cells. Therefore, this paper aims to investigate the link between the LP and cancer in humans.

2. Methodology Used in This Review

For this review, different phrases and keywords were utilized to methodically evaluate research articles and reviews that were collected from several global databases. Lamina propria, GALT, gastrointestinal tract, and colorectal were among the keywords used. The data included in this review were issued between 2010 and the present.

The original figure was made using the Sketchbook app on an iPad (fifth generation), Air iPadOs 18.1.1 software.

To achieve the aims of this study, several topics were examined, including the relationship between the lamina propria, microbiota, and inflammation, the effects of inflammation states on lamina propria functionality, the intricate association of specific lamina propria components and colorectal cancer (CRC), and the impact of different microbial metabolites on the lamina propria in terms of inflammation and tumorigenesis development.

The gut immune system is made up of innate and adaptive processes. One of the main causes of gastrointestinal (GI) illnesses, which are quite common worldwide and pose a severe threat to public health, is the immune system's inefficient or incorrect operation. Microorganism-induced gastrointestinal infections, along with disorders including diverticular disease (DD), inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS), fall under this category [12].

In order to identify microbial components and initiate prompt defense responses, innate immunity uses physical barriers, antimicrobial peptides, and pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs). Conversely, adaptive immunity—which involves B and T cells—offers immunological memory and long-term immunity, guaranteeing a precise response to repeated exposure to infections. Immunity and gut health are maintained by both innate and adaptive pathways [13].

Both common lymphoid organs (such as the spleen or lymph nodes) and unique formations known as tertiary lymphoid tissue can experience immunological responses. When an infection or inflammation affects an area, these structures develop unnaturally (ectopically). Similarly to secondary lymphoid organs, immune system cells congregate and arrange there to form germinal centers for B cells, which produce antibodies, and particular locations for T cells, which organize the immunological response. This happens when the body needs to combat a localized infection or inflammation, even when it is not in the typical immune activity sites [14].

It is known that innate immune cells, such as neutrophils, macrophages, and myeloid-derived suppressor cells, contribute to the advancement of cancer across a wide range of tumor forms. These days, B cells are also essential for creating the persistent inflammation linked to de novo carcinogenesis. With the buildup of IgG immune complexes, the activation of innate immune cells, such as tumor-associated macrophages (TAMs), via the Fc gamma receptor (FcR) and polarization to an immunosuppressive phenotype, is probably antibody-dependent [15].

A thick layer of mucus and a single layer of epithelial cells securely connected by junctional complexes make up the intestinal mucosal barrier [16]. This barrier prevents pathogens and harmful substances from passing from the stomach lumen into the systemic circulation [17]. As a physical barrier, the mucus layer, mainly made of mucins released by goblet cells, traps microorganisms and makes it easier to remove them [3]. Leaky gut syndrome, characterized by increased intestinal permeability, may be a contributing factor to many GI pathologies and systemic conditions like metabolic syndrome, neurodegenerative diseases, or autoimmune disorders. It is brought on by changes in the intestinal mucosal barrier. Indeed, autoimmune pathology treatments like dimethyl fumarate may be a novel prospective treatment for inflammatory and immune-mediated intestinal illnesses, as well as for improving psoriasis or multiple sclerosis [18].

According to new research, a leaky gut is linked to autoimmune diseases. Positive linear correlations between serum occludin/zonulin antibodies and circulating autoantibodies may be utilized to detect autoimmune disorders, as human patients with increased intestinal permeability have greater levels of circulating autoantibodies [19].

In colorectal cancer (CRC), a group of immune and inflammatory cells is seen infiltrating the affected tissue, consisting of lymphocytes (essential immune cells), neutrophils (cells responsible for rapid response to infections), and macrophages (cells that engulf and destroy pathogens). These cells, after their entrance, can accumulate at the edge where the tumor interacts with the surrounding healthy tissue, an area essential for cancer progression

or control. In this malignancy, infiltrating T cells play a protective effect and are strongly linked to improved clinical outcomes [20].

It has been shown that tumor-infiltrating lymphocytes are not only dotted between tumor cells but also dispersed throughout the stroma. Additionally, they form aggregates that resemble tertiary lymphoid tissue [21].

3. Lamina Propria Dendritic Cells in a Healthy State

The body's reaction to a given antigen can either be pro- or anti-inflammatory, and this is mostly determined by dendritic cells (DCs) (Table 1). For local proliferation, DCs that are repopulating tissues from monocyte precursors depend on a granulocyte–macrophage colony-stimulating factor (GM-CSF). Conventional DCs (cDCs), which originate from the CDP, live in secondary lymphoid tissues and show high levels of CD11c, along with variable levels of CD8α and CD11b [22].

Table 1. The lamina propria components' role in gut homeostasis.

Components		Role	Reference
LPDCs		▪ Determines whether the immune response to an antigen will be pro-inflammatory or anti-inflammatory. ▪ Maintains the immune balance. ▪ Prevents autoimmune reactions. ▪ Tolerance to intestinal antigens.	[22]
	CDP	▪ Peripheral tolerance, thus preventing unjustified autoimmune or inflammatory reactions.	[23]
		▪ Source of pDCs and role in the immune response by producing type I interferons, vital for antiviral defense and regulation of the immune system.	[24]
	Mature CD	▪ Capable of presenting antigens to T lymphocytes, initiating immune responses when necessary.	
	$CD103^+$	▪ Maintains immune tolerance and prevents autoimmune reactions.	[25,26]
	$CD103^-$	▪ Stimulates the production of inflammatory mediators IL-6, TNF-α.	[27]
	ILCs ILC1 ILC2 ILC3	▪ Detects signals from the environment and contributes to the rapid activation of the innate immune response. ▪ Modulation of the immune defense that supports the rapid stimulation of the immune system against infections. ▪ Mucous membrane protection. ▪ Depending on the situation, cytokine production—IL-5, IL-13, and IFN-γ—assists in creating an inflammatory or anti-inflammatory milieu and controls the activity of other immune cells. ▪ Development of lymphoid tissue—helps organize and mature T and B cells—thus generating an adaptive immune response. ▪ Interaction with microbiota—maintains the balance between gut flora and immune responses. ▪ Maintains tissue homeostasis. ▪ Include natural killer cells, are distinguished by their ability to produce interferon gamma (IFN-γ). ▪ Are found in both lymphoid and non-lymphoid tissues and are usually a mark of inflammation, secreting IL-5 and IL-13. ▪ Are the most numerous subpopulation in ILCs identified in the intestines of rodents and humans. ▪ Are primarily responsible for producing IL-17 and IL-22 when local signaling molecules like IL-23 and IL-1b are activated.	[28] [29,30] [29] [31]

Table 1. *Cont.*

Components	Role	Reference
ILFs	▪ Immune defense structures—protection against pathogens. ▪ Source of immune cells, B lymphocytes in ILFs produce antibodies, especially immunoglobulin A (IgA). ▪ Generation of antibodies and activation of B and T cells are facilitated by the induction of the adaptive immune response. ▪ Monitoring and maintains the balance between beneficial microbiota and immune responses.	[32]

LPDCs—dendritic cells; CDP—common progenitor of dendritic cells; pDC—plasmacytoid dendritic cells; IL-6—interleukin—6; TNF-α—tumor necrosis factor-alpha; $CD103^+$—positive dendritic cells; $CD103^-$—negative dendritic cells; ILCs—innate lymphoid cells; ILFs—isolated lymphoid follicles.

The CDP is also the source of plasmacytoid DCs (pDCs) that are specialized for generating type I interferons. The developed state of DCs has significant effects on immunity in addition to functional subsets of DCs. Mature DCs that have previously come into touch with inflammatory stimuli and microbial products are highly specialized for antigen presentation. Because they are in a good position to stimulate antigen-specific T cells and express large amounts of co-stimulatory molecules, mature DCs typically reside in secondary lymphoid organs [24]. The peripheral tolerance to gastrointestinal luminal antigens and the self is constantly and directly maintained by LPDCs. LPDCs exhibit a variety of functionally unique characteristics, similar to LP macrophages.

LPDCs require chemokine receptor 1 (CX3CR1) to extend their processes beyond the epithelial cell layer to collect luminal antigens [23]. LPDCs can be divided into two main categories, namely $CD103^+$ and $CD103^-$. The CD103 LPDC stimulates the generation of Foxp3+ regulatory T cells through the production of retinoic acid and the transformation of growth factor-β (TGF) [25,26]. Nonetheless, following activation with TLR ligands like IL-6 and tumor necrosis factor-α (TNF-α), $CD103^-$ LPDCs increase the production of inflammatory mediators and promote inflammation [27]. Their presence is particularly important in decreasing unnecessary inflammation because the absence of $CD103^+$ CX3CR1− LPDCs enhances epithelium damage during colitis [33].

4. Innate Lymphoid Cells in a Healthy State

Another cellular group present in the lamina propria consists of innate lymphoid cells (ILCs). While ILCs share physical similarities with lymphocytes [28], they lack antigen-specific receptors generated through V(D)J recombination. Particularly prevalent in mucous membranes like the skin, lungs, and gastrointestinal tract, ILCs sense and combine environmental cues to quickly trigger the innate immune response, releasing effector chemicals that support tissue homeostasis and mucosal immune defense [34]. ILCs are the innate equivalent of the T cells that have an important role in developing and maintaining the sub-epithelial lymphoid tissue of the intestines. They share a common progenitor with lymphocytes but are distinct from them because they lack T cell receptors and they are constantly producing their cytokines, unlike T cells' activation-required production. They can be divided into three main groups (Table 1). Group 1 ILCs, which include natural killer cells, are distinguished by their ability to produce interferon gamma (IFN-γ). Areas of mucosal inflammation are home to a large number of transcription factor (T-bet+) group 1 ILCs [29,30]. Both lymphoid and non-lymphoid tissues include group 2 ILCs, which often indicate inflammation by secreting IL-5 and IL-13. However, group 2 ILCs are generated by the transcription factors GA-TA3 and RAR-related orphan receptor alpha (RORα), and their characteristic cytokines are IL-5 and IL-13 [29]. In group 3, ILC3s are found in the greatest abundance at the mucosal barrier surfaces and exhibit receptor-related orphan receptors (RORs). The so-called lymphoid tissue inducer (LTi) cells represent an ILC3 subtype [35].

The most recent classification of ILCs was put forth in 2018 as cytotoxic NK cells, non-cytotoxic helper ILC1, ILC2, and ILC3, and LTi cells, based on a deeper comprehension of the mechanisms of development and the molecules involved in the tasks of the T cell and ILC subset [35–37]. Since ILCs and T cells have similar transcription factors and cytokine

production capabilities, they are also thought to be their innate functional counterparts. Cytotoxic CD8+ T cells, CD4+ T helper (Th) cells 1, Th2, and Th17/Th22 are represented by NK cells, ILC1, ILC2, and ILC3, respectively [36,38].

The most common subpopulation of ILCs found in human and rodent intestines is ILC3s (Table 1). IL-17 and IL-22 are produced when local signaling molecules such as IL-23 and IL-1b are activated. This maintains tissue homeostasis and facilitates the innate immune response to intracellular and external infections [31].

ILC3s are split into CCR6+ILC3s and CCR6-ILC3s based on C-C chemokine receptor type 6 (CCR6) expression. Most CCR6-ILC3 cells, which are further separated into NCR+ILC3 and NCR-ILC3 cells, are found in the lamina propria. NCR-ILC3 primarily expresses IL-17 and less IL-22, constituting only 15% of intestinal ILC3. On the other hand, NCR+ILC3 expresses more IL-22 and less IL-17 and accounts for around 70% of intestinal ILC3 [37].

Immune homeostasis and the intestinal epithelial barrier depend on ILC3. Through the secretion of cytokines such as IL-22 and IL-17, ILC3 contributes significantly to this vital function. To restore mucus-producing goblet cells, reduce colonic inflammation, and control intestinal mucosal wound healing, IL-22 stimulates the production of mucins involved in the composition of the mucus layer by activating STAT3 in epithelial cells [39]. By using the aryl hydrocarbon receptor (AHR) to detect genotoxic phytochemicals, IL-22 triggers a DNA damage response in epithelial stem cells, halting the genesis of cancer and malignant transformation (Table 1). NCR-ILC3 is the primary source of IL-17, which is involved in immune-inflammatory and anti-infective responses and stimulates the production of cytokines and chemokines to draw neutrophils to the infection site [40].

Notably, ILC1s, ILC3s, and ILC3/NKs are present in the healthy gut but not ILC2s. ILC1-like and ILC2 subsets unique to tumors were also found in CRC patients. Little is known about the function of helper-like ILCs in carcinogenesis and cancer immunity, and it seems to depend on the tumor microenvironment. Large quantities of pro-inflammatory cytokines, like TNF-alpha and IFN-γ, are produced by ILC1s and promote carcinogenesis. Nevertheless, in specific tumor microenvironments, IFN-g can also inhibit tumor growth [41]. In most tumor environments, ILC2s are harmful [42].

Intestinal malignancies have been connected to dysregulated ILC responses. Low levels of ILC2s are found in a variety of human disease disorders [43,44]. On the other hand, ILC3s, which typically densely populate the colon at a steady state, are unusually low in CRC patients, while ILC1s are abundant in the intestines. Decreases in the ILC3/ILC1 ratio have indeed been connected to the severity of CRC. Under tumor circumstances, nothing is known about the makeup, diversity, and functional state of the baseline helper-like ILC landscape in the human gut [45,46] (Table 1).

Two other subsets were shown to be present in helper-like ILCs from CRC patients, an ILC2 (ctILC2) subset and an ILC1-like subset exclusive to CRC tissue. The blood of patients with colorectal cancer showed higher frequencies of helper-like ILCs that expressed SLAMF1. It was found that ctILCs are the only cells that express SLAMF1 (signaling lymphocytic activation molecule family member 1, CD150) [46].

5. Isolated Lymphoid Follicles in a Healthy State

Isolated lymphoid follicles (ILFs) fall into two categories, namely submucosal ILFs (SM-ILFs), which protrude in the lamina but are also found in the submucosa, and mucosal ILFs (M-ILFs), which are found only in the lamina propria. Where SM-ILFs are mostly found in the colon, M-ILFs are typically detected in the ileum and distal colon [47]. Lymphocytes make up about 90% of the cells in ILFs, with a slightly greater percentage of T cells than B cells. Cytokine-producing T cell subsets are also present in the GALT-free lamina propria. It also contains a large number of dendritic cells, which offer antigens to T cells as they move through the lymphatic system to mesenteric lymph nodes [48].

The majority of the lymphocytes in the large intestine's lamina propria are B cells, in contrast to the small intestine [49]. Dimeric IgA is produced by the lamina propria B

cells in response to the polymeric immunoglobulin receptor. Epithelial cells subsequently transcytose the IgA, allowing it to enter the intestinal lumen [50]. Gastrointestinal IgA synthesis plays a critical function at baseline by blocking commensal microbes from escaping the epithelium and enhancing M cells' absorption of luminal bacteria, even though gastrointestinal infections can also create antigen-specific IgA [51] (Table 1).

Additionally, it has been shown that the number, diameter, and cellular composition of sub-epithelial lymphoid follicles are closely related to the extent of epithelial damage in colonic inflammation [52]. The more ILFs in the surrounding mucosa, the more severe the epithelial destruction that occurs.

A number of papers have examined the relationship between colonic cancers in rodents and lymphoid aggregates [53,54]. According to the findings, proliferative activity is noticeably higher in the colonic crypts connected to intestinal lymphoid follicles (ILFs). Genetically compromised epithelial cells may also be impacted by this elevated activity. Because of this, colonic mucosa with ILFs is more likely to develop cancer than mucosa without ILFs.

Tissue-derived dendritic cells have been observed to migrate from the site of inflammation via lymphatic arteries to secondary lymphoid organs, where they engage in interactions with lymphocytes in a variety of inflammatory models [55]. In intestinal lymphoid follicles (ILFs), follicular dendritic cells may be an important transformation site for migrating bone marrow-derived stem cells and the surrounding sub-epithelial myofibroblasts because of their dual nature. This suggests a possible mechanism for adaptability and change in relation to tumor formation and inflammation.

Throughout the colonic lamina propria, sub-epithelial myofibroblasts (SEMFs) form a syncytium that combines with the pericytes encircling the blood vessels [56]. Two phases of epithelial healing require SEMFs [57] (Table 1). The first process, known as restitution [58], enables the quick repair of the epithelial layer and is in charge of healing superficial, mild, or moderate lesions. The second one applies when the damage is deeper and more serious, necessitating full restoration of the tissues underlying the epithelium as well as the basement membrane, which sustains the structure of the epithelium [59].

SEMFs show up early in the course of cancer. A poor clinical prognosis is a direct result of the mutual connection between cancer cells and SEMFs, which occurs through direct cell–cell interactions and paracrine signals [52].

TLRs (Toll-like receptors) are expressed on the intestinal epithelium, endothelial cells, and stromal cells, as well as on cells of the monocyte/macrophage system and some types of T cells in ILFs. Additionally, TLRs can bind endogenous ligands such as extracellular matrix components, heat shock proteins, and necrotic cells [52].

It has also been demonstrated that human colon cancer cells produced and were functionally active TLR4. Producing immunosuppressive factors and apoptosis resistance may be crucial in facilitating the immunological escape of human colon carcinoma cells. It may also facilitate the growth and migration of cancer cells [60].

According to experimental research, intestinal lymphoid follicles (ILFs) may play a role in the formation of adenocarcinomas in colon cancer. Tumor-infiltrating lymphocytes, on the other hand, are linked to a better prognosis in colorectal cancer (CRC) in humans, as well as high DNA microsatellite instability, a feature of several malignancies [61]. According to these findings, ILFs play a defensive rather than tumor-promoting role in the early stages of colorectal cancer (Table 1).

In addition, Gutfeld et al. [32] found that cells in ILFs, as well as other inflammatory and endothelial cells in the colon, express a protein called serum amyloid A, which increases in the presence of trauma, infection, or cancer. Serum amyloid A expression points to a potential involvement in the onset of colorectal cancer.

6. T Cell Trafficking to the GALT and Gut

In intestinal infections, naïve T cells from the blood must arrive at particular sites in the gut, where they prepare to respond to antigens. Peyer's patches, PPs, and mesenteric lymph

nodes (MLNs) are examples of these GALT locations. Dendritic cells, which are immune cells that transport antigens from the gut to the PP's ganglia, present them with digestive tract antigens in this situation. Furthermore, mesenteric lymph nodes (mLNs) are home-gut migratory DCs that contribute to the polarization of naïve T cells toward Th1, Th2, Th9, Th17, T follicular helper (Tfh), or regulatory T (Treg) cells. Immunogenic or tolerogenic immune responses are the areas of expertise for each of these cells. In this manner, they identify the type of answer from the helper T (Th) [62]. Furthermore, migratory DCs induce the expression of gut-homing receptors like CCR9 or α4β7 by antigen-specific T lymphocytes, which enables the cells to return to the intestinal tract [63]. This process activates T cells and makes them Th1 and/or Th17 effector cells, which are prepared to combat infections [64] (Table 2).

Table 2. The impact of dismicrobism on CRC.

Impact	Ref
▪ Impairs intercellular tight junctions, allowing for the penetration of antigens, which causes GALT activation and consequent tissue damage. ▪ Imbalance of bacterial flora—dismicrobism leads to an increased abundance of potentially pathogenic bacteria, which can affect how the immune system responds to pathogens and antigens in the gut. ▪ Inflammation and cancer—persistent inflammation can lead to changes in the cellular structure of the intestinal mucosa, favoring the evolution from dysplasia to carcinoma. ▪ Diet—a significant impact on the composition of the intestinal microbiome, a diet rich in sugars and fats can exacerbate dismicrobism and negatively affect gastrointestinal metabolism and the balance of the immune system. While genetic variables accounted for only 12% of the gut microbiota makeup, changed dietary behaviors had a significant impact (57%). MALT lymphomas—closely associated with the presence of *Helicobacter* bacteria.	[65–77]

According to different research, antigen-carrying dendritic cells (DCs) from the intestinal mucosa and Peyer's patches are carried to the MLNs by the associated lymphatic vessels. These nodes may be the primary site where naïve T cells first encounter specific antigens in the gut, triggering their activation. After activation, T cells become effector cells, that is, cells capable of causing an immune response, including in cases of disease or infection [64].

High endothelial venules (HEVs) facilitate the movement of these T cells from the circulation to certain lymphoid regions, including lymph nodes. Specialized blood arteries like these aid in drawing immune cells to tissues and delivering them there so they may carry out their anti-infection duties [78] (Table 2). The HEVs that are associated with Peyer's patches contain a molecule called MAdCAM-1, which helps attach lymphocytes to these blood vessels. In contrast, HEVs in mesenteric lymph nodes express both MAdCAM-1 and PNAd, another adhesion molecule. L-selectin, a protein on the surface of T cells, binds to these molecules to help lymphocytes anchor to HEVs, thereby initiating a process called "rolling", which is crucial for T cell migration.

In mesenteric nodes, naïve T cells can use another molecule, α4β7, to attach to MAdCAM-1. This interaction contributes to the firm adhesion and arrest of lymphocytes, which allows them to enter the MLNs and Peyer's patches [79–81]. Once naïve CD4+ T cells reach these areas, they encounter specific enteric antigens presented by dendritic cells, which collaborate with major histocompatibility complex II (MHC II).

T cells multiply, shed L-selectin, and express more adhesion molecules that aid in their homecoming in the gut during the early activation phase. These molecules, like CCR9 and α4β7, interact with CCL25 and MAdCAM-1 in the post-capillary venules to help T

cells migrate to the small intestine. This mechanism is necessary for T cells to respond to antigens at the site of infection or inflammation [82].

Following their entry into the intestinal tissues, effector T cells come into contact with the particular antigens they have previously identified. More diverse specialized antigen-presentation cells (APCs), including dendritic cells (DCs), B cells, and macrophages, are presenting antigens this time. The effector T cells react to the antigen considerably more quickly and intensely after this second exposure. Cytokines, which are crucial for the immunological and inflammatory response, are produced in large quantities as a result of this process. These include IFN-γ (interferon-gamma), IL-17, TNF-α (tumor necrosis factor-alpha), lymphotoxin-α, and IL-2 [83].

This accelerated response helps to more effectively defend against infection and coordinate inflammatory reactions, thereby helping to eliminate pathogens from the gut.

7. Dismicrobism

In healthy people, stomach acidity plays a crucial role in preventing bacteria from colonizing the gut. The acidic environment in the stomach acts as a natural barrier, killing or inhibiting the growth of bacteria before they reach the intestine. This process ensures that the intestinal bacterial flora remains balanced, preventing overpopulation with potentially harmful bacteria. Gastric acidity is thus an important defense mechanism against infections and intestinal microbiota imbalances. The microbiota performs various physiological tasks, including regulating intestinal lymphoid tissue, producing chemicals that aid in colonic mucosa tropism, inhibiting the growth of pathogenic microbes, and synthesizing amino acids [65] (Table 2).

Dismicrobism leads to the imbalance of the normal bacterial flora in the gut. The immune system's response to infections may be impacted when this equilibrium is upset. Specifically, GALT may be activated by this imbalance. GALT activation sets off immunological responses in the gut that, if left unchecked, might result in inflammation or other immune diseases [66] (Table 2).

Changed dietary patterns had a significant effect (57%) on the composition of the gut microbiome, explaining more than half of the observed variation, while genetic factors played a much smaller role, contributing to only a small proportion (12%). The Western diet, characterized by a high consumption of sugar and fat, can cause dysbiosis, that is, an imbalance of intestinal bacteria. This imbalance negatively affects both gastrointestinal metabolism, i.e., the way the body processes and uses nutrients, and the balance of the immune system [67]. Over time, this type of eating can contribute to digestive disorders and immune problems [68]. Because vegetarianism is high in fiber, microbes produce more short-chain fatty acids, which lowers gut pH and inhibits the growth of potentially harmful bacteria, including *E. coli* and *Enterobacteriaceae* [69] (Table 2).

7.1. Mucosal-Associated Lymphoid Tissue (MALT) Lymphomas

It is believed that mucosal-associated lymphoid tissue (MALT) lymphomas develop in the marginal zone and are closely linked to *Helicobacter.* Approximately 90% of MALT lymphomas are associated with *Helicobacter* infection [70].

Inflammation and high endothelial venule-like cysts, which are linked to lymphocyte recruitment and present in other chronic inflammatory diseases, including rheumatoid arthritis and colitis, are precursors to MALT lymphoma, which is also caused by H. helmanii, which is present in both humans and mice. Numerous investigations on animals have demonstrated that the number and activity of immune cells may be significantly impacted by either a single species or a mixture of bacteria [71]. For instance, segmented filamentous bacterial inoculation altered T cell activity, resulting in various reactions, such as increased IL-10, IL-17, and IFN-γ. Immune cell populations changed systemically as a result of Sphingomonas yanoikuyae inoculation. In mice, Bacteroides fragilis can trigger a Th17 response, which has since been demonstrated to be necessary for carcinogenesis [72]. Additionally, bacteria have the direct ability to modify pathways linked to inflamma-

tion. Increased TNF-α- and IFN-γ-associated pathways were observed upon inoculation with either *B. longum*, *B. thetaiotaomicron*, or both of these common human commensal bacteria [78].

The primary genetic abnormalities linked to mucosa-associated lymphoid tissue (MALT) lymphomas, a broad category of B cell-originated lymphoid neoplasms that typically present as indolent clinical behavior in adult patients, are examined with MALT. In addition to sharing numerous clinicopathological characteristics and developing in multiple anatomical sites, these lymphomas differ greatly in their etiology and genetic alterations. In MALT lymphomas, t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21), and t(3;14)(p14.1;q32) are the four most common chromosomal translocations [84]. In MALT lymphomas, chromosomal translocations occur often, albeit their frequency varying depending on the site. Other chromosomal number abnormalities have also been observed. However, they most likely result from secondary genetic processes [84].

Though many other genes may be involved, the most common mutations in MALT lymphomas are found in TNFAIP3, CREBBP, KMT2C, TET2, SPEN, KMT2D, LRP1B, PRDM1, EP300, TNFRSF14, NOTCH1/NOTCH2, and B2M. Some mutations are more prevalent in particular forms of lymphoma, much like chromosomal translocations. Similarly, MALT lymphomas from various anatomical regions are known to use immunoglobulin genes differently. The understanding of the pathogenic pathways in forming MALT lymphomas has improved over the past ten years due to numerous studies that have examined the roles of microRNA, transcriptomics, and epigenetic modifications. These developments enhance the idea of precision medicine in MALT lymphomas and provide the opportunity for focused, directed treatment for those identified as having MALT lymphomas [84].

7.2. Dismicrobism in CRC

A study found that the luminal compartment of CRC patients had more *Enterococcus*, *Escherichia*, *Shigella*, *Klebsiella*, *Streptococcus*, and *Peptostreptococcus* bacteria than controls. In contrast, the *Lachnospiraceae* family (butyrate-producing bacteria) had fewer bacteria [85].

Research on the microbiota in the intermediate stages of colorectal cancer (CRC) showed that patients with adenoma had a higher abundance of *Firmicutes*, *Bacteroidetes*, and *Proteobacteria* on the intestinal mucosal surface than those without adenoma [66].

Intestinal mucosal inflammation is a pathogenic backdrop in around 1–2% of CRC patients [73]. This "inflammatory background" of the colonic mucosa can develop into a less severe (low-grade) or more severe (high-grade) dysplasia, which leads to "in situ" carcinoma and ultimately "invasive" carcinoma through neoplastic transformation. The suppression of colon tumor formation after anti-IL-17 antibody treatment suggests that mice colonized with enterotoxigenic *B. fragilis* have colonic Th17 inflammatory infiltrates implicated in the generation of colon cancers [86].

The immune system is regulated in part by the commensal microbiota. Heat shock proteins (Hsps), which are proteins made by cells in reaction to stressors like infection or inflammation, can be influenced by these bacteria. Hsp60 and Hsp70, in particular, are autoantigens that can activate immune-regulatory mechanisms [87].

The bacterial fermentation of indigestible carbohydrates produces short-chain fatty acids (SCFAs), especially butyrate, which are growth signals and nutrients for the intestinal epithelium and may help prevent colorectal cancer [74]. Butyrate stops apoptosis and the ensuing mucosal shrinkage in healthy colonocytes [75].

Fortunately, butyrate plays a protective role in colon cancer cells. It helps prevent the development of cancer through several mechanisms; it promotes cell differentiation (the process by which cells become specialized), reduces the uncontrolled proliferation of cancer cells, induces apoptosis (programmed cell death), and inhibits angiogenesis (the formation of new blood vessels that feed tumors) [88].

In addition, the intestinal microbiota produces anticancer chemicals like sulforaphane, butyrate, N-acetyl cysteine, and ally1 mercaptan through the metabolism of some foods,

such as garlic or cruciferous vegetables (broccoli, cabbage, cauliflower). These substances lower the risk of cancer and safeguard the gut microbiota. Therefore, by interfering with HDAC activity, metabolites generated from microbes can reverse the carcinogenetic process by inducing cell cycle arrest and tumoral cell apoptosis [89].

Consuming omega-3 polyunsaturated fatty acids has been shown in experiments to reduce the risk of sporadic colorectal cancer. In models of familial adenomatous polyposis, eicosapentaenoic free fatty acid inhibits the growth and production of polyps [82].

8. CRC Carcinogenesis

Colorectal cancer is the second leading cause of cancer-related deaths globally. Tumor-infiltrating T cells correspond to Chron 's-like lymphoid reaction (CLR), a peritumoral lymphoid aggregate at the tumor's edge. Those CLRs are unique tertiary lymphoid organs linked to a more favorable prognosis and a lower chance of metastasis.

The immuno-phenotype of CLR in both metastatic and non-metastatic CRC can be predicted by ILF features. CD20+ B cells within ILFs are associated with improved prognosis of CRC in liver metastasis patients [77].

ILC3s invade tumors, and their cytokine synthesis and activation have pro-tumorigenic consequences. In addition to IL-17A, CRC has been linked to the stimulation of IL-22 synthesis through ILC3-activating IL-1, and IL-23 expression is more significant in CRC tissues [77].

Due to their ability to penetrate tumors and alter the tumoral microenvironment, ILC3s have been implicated in a growing number of malignancies, including colorectal cancer [90]. ILC3s encourage tumor growth by using inflammatory chemicals such as IL-17 and IL-22. The gut microbiota may regulate this pathway through the secretion of IL-23 and IL-7 by macrophages. Intestinal flora may activate macrophages to release IL-23 and IL-7, hence controlling this pathway. Furthermore, Th17 cells and immunological competence will become dysregulated as a result of MHC II deletion in ILC3, which will accelerate tumor growth [34]. To support tumors, ILC3 can also develop into ILCregs and release IL-10. However, by regulating the microbial and immunological environments and promoting the formation of lymphoid tissue, ILC3 may prevent the growth of tumors. In order to suppress tumor cells, ILC3 releases CXCL10, which draws CD4T and CD8T cells into the tumor cells and causes them to release granzyme, perforin, and IFN-γ. The flexibility of ILC3 between ILC1 and ex-ILC3 increases the generation of IFN-γ. It is also possible that the newly identified capacity of ILC3 to develop into NK cells is an anti-tumor mechanism [91] (Table 3).

Table 3. General changes induced by CRC on gut physiology.

Specification	Changes	Ref
Alteration of the intestinal microbiome	An increase in pathogenic bacteria and a decrease in beneficial bacteria.	[77,84–95]
Chronic Inflammation	Generates an inflammatory environment that can lead to chronic inflammation of the intestinal mucosa and contribute to tumor progression.	
Intestinal barrier dysfunction	Affects the integrity of intercellular junctions, increasing intestinal permeability.	
Changes in intestinal motility	Causes both diarrhea and constipation, depending on the location and stage of the cancer.	
Nutrient metabolism disorder	CRC can affect the way the body digests and absorbs nutrients.	
Changes in the immune response	Reduces the body's ability to fight infections and may allow tumors to develop.	
Altered metabolite production	The presence of CRC can influence the production of metabolites, such as short-chain fatty acids (SCFAs) that have an important role in intestinal health and in the regulation of the immune response.	

Intestinal injuries cause both innate and adaptive immune cells to produce CPEB4, which is required for the translation of cytokine mRNAs, including the one encoding interleukin-22. Therefore, CPEB4 mediates repair and remodeling following acute inflammatory tissue injury and aids in the resolution of intestinal inflammation. It is also required for the development of GALT and intestinal immunological homeostasis. CPEB4 is constantly overexpressed by inflammatory cells in patients with IBD and colorectal cancer, which encourages the formation of tumors [92].

To better understand how the CPEB4 protein influences the functioning of the intestinal barrier, the researchers used a genetically modified mouse model in which the CPEB4 gene was completely disabled (total knockout). Peyer's patches and cryptopatches, which support the intestinal immunological barrier, were smaller and less numerous in CPEB4KO mice, indicating a change in GALT [92]. Peyer's patches of CPEB4KO mice showed an abnormal T and B lymphocyte composition, with a higher frequency of CD19+ B lymphocytes and a lower frequency of total CD3+ T lymphocytes because of a decrease in T-helper CD4+ and cytotoxic CD8+ T cells. In CPEB4KO animals, the frequency of CD3+ T lymphocytes in the colonic lamina propria was significantly decreased, while the frequency of CD19+ B lymphocytes increased (Table 4).

Table 4. Specific changes induced by CRC on gut physiology.

Specification	Changes	Ref
Crohn's lymphoid reaction (CLR)	The accumulation of immune cells at the edge of the tumor.	[94]
T and B lymphocytes	In the colonic lamina propria, CPEB4KO animals showed a marked decrease in CD3+ T lymphocyte frequency and an increase in CD19+ B lymphocyte frequency.	[92]
ILFs	Can predict CLR immunophenotype in metastatic and non-metastatic CRC. The B cells in these follicles can help control cancer.	[92–95]
ILC3s	Can promote tumors by secreting inflammatory cytokines but can also inhibit tumor progression by recruiting T cells and secreting substances that attack cancer cells.	

In intestinal immune cells, CPEB4 controls specific cytokines (signaling proteins) like IL-17a, IL-17f, and IL-22, which are necessary for a robust immune response. These cytokines aid in preserving the immune system's equilibrium and providing infection protection when present in moderate and well-regulated amounts. However, immunological responses fall out of balance if over- or under-expressed, which causes persistent inflammation and disturbance of lymphoid tissue. CPEB4 levels have risen sharply in inflammatory cells associated with chronic intestinal inflammation, including Crohn's disease and ulcerative colitis. This buildup exacerbates chronic inflammation in many disorders and is linked to an overabundance of Th17 immune response activation [94]. People who have inflammation are more likely to acquire cancer because it often encourages the different stages of carcinogenesis. As a result, individuals with chronic IBD are more likely to develop CRC. CPEB4 knockdown rats had a decreased incidence of CRC, but they also exhibited more prolonged inflammation and trouble healing injured intestinal epithelia. A poor prognosis is linked to CPEB4 overexpression in entire (including tumoral niche) CRC samples. Like inflammation, impaired IL-22 translation is associated with the CPEB4 depletion phenotype in CAC. Therefore, it has been reported that Th17 cells and Th17 cytokines, including IL-17A, IL-21, and IL-22, are mostly pro-tumorigenic in CRC [95] (Table 4).

9. Conclusions and Future Perspectives

This review tried to highlight the role of the lamina propria through its components in maintaining health and the changes occurring as a result of inflammation and, ultimately, colorectal cancer. However, compared to the other parts of this lymphoid tissue, the lamina propria from GALT has not been thoroughly investigated. All of the lamina propria cells are important in improving inflammation and preventing cancer. Moreover, different cells, such as T cells, can respond quickly and specifically to the gut microenvironment stimuli and initiate anti- and pro-inflammatory actions.

1. Consequently, the intestinal LP contains a wide variety of DCs. Moreover, LPDCs control the intestinal environment and luminal contents to maintain homeostasis by producing advantageous mediators, preventing pro-inflammatory responses, and actively promoting adaptive immunological tolerance. While some LPDCs actively encourage tolerance, others prefer to amplify adaptive inflammatory responses to foreign antigens. An imbalance throughout all of these physiological systems, however, can swing the balance in favor of IBD and chronic intestinal inflammation.
2. Moreover, there is evidence linking dysregulated ILC responses to intestinal cancers. ILC2s are found in trace amounts in different human clinical situations [43,44]. Conversely, ILC1s are disproportionately plentiful in the intestines, and ILC3s, which normally densely populate the colon at a steady state, are abnormally low in CRC patients. ILC3/ILC1 ratio decreases have been connected to the severity of colorectal cancer.
3. According to experimental findings, ILFs in the early stages of colorectal cancer play a defensive rather than tumor-promoting role in relation to other lamina cells.
4. Lamina propria T cells, after their activation, become effector cells, in the sense that they can initiate an immune response, including in cases of disease or infection [61].

For the mucosal immune system to remain healthy, it must be strictly regulated. The presence of local Tregs is essential in colon homeostasis [6]. SCFAs and tryptophan metabolites are among the several bacterial metabolites that trigger colonic Tregs [7–11]. The body's defense system is significantly regulated by the commensal microbiome. These bacteria can regulate the expression of heat shock proteins (Hsps), which are proteins that cells produce in reaction to stressors like inflammation or infection.

In addition, the intestinal microbiota metabolizes aliments like garlic and cruciferous vegetables to produce anticancer compounds, including ally1 mercaptan, butyrate, sulforaphane, and N-acetyl cysteine. These compounds lower the risk of cancer and sustain the gut microbiota.

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