



The Controversial Role of Intestinal Mast Cells in Colon Cancer

Rosa Molfetta  and Rossella Paolini * 

Department of Molecular Medicine, Istituto Pasteur Italia—Fondazione Cenci Bolognetti, Sapienza University of Rome, 00161 Rome, Italy

* Correspondence: rossella.paolini@uniroma1.it; Tel.: +39-06-49255670

Abstract: Mast cells are tissue-resident sentinels involved in large number of physiological and pathological processes, such as infection and allergic response, thanks to the expression of a wide array of receptors. Mast cells are also frequently observed in a tumor microenvironment, suggesting their contribution in the transition from chronic inflammation to cancer. In particular, the link between inflammation and colorectal cancer development is becoming increasingly clear. It has long been recognized that patients with inflammatory bowel disease have an increased risk of developing colon cancer. Evidence from experimental animals also implicates the innate immune system in the development of sporadically occurring intestinal adenomas, the precursors to colorectal cancer. However, the exact role of mast cells in tumor initiation and growth remains controversial: mast cell-derived mediators can either exert pro-tumorigenic functions, causing the progression and spread of the tumor, or anti-tumorigenic functions, limiting the tumor's growth. Here, we review the multifaceted and often contrasting findings regarding the role of the intestinal mast cells in colon cancer progression focusing on the molecular pathways mainly involved in the regulation of mast cell plasticity/functions during tumor progression.

Keywords: colorectal cancer; mast cells; tumor microenvironment



Citation: Molfetta, R.; Paolini, R. The Controversial Role of Intestinal Mast Cells in Colon Cancer. *Cells* **2023**, *12*, 459. <https://doi.org/10.3390/cells12030459>

Academic Editor: Volker Blank

Received: 16 December 2022

Revised: 24 January 2023

Accepted: 26 January 2023

Published: 31 January 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Colorectal cancer (CRC) is the third most common malignancy and one of the leading causes of cancer-related mortality, counting almost 1 million annual deaths world-wide, according to the International Association of Cancer Registries [1,2]. The majority of CRC cases are associated with the sporadic mutations linked to risk factors or lifestyle; 10–30% of the cases, instead, present family history, while less than 5% of patients show hereditary forms of the disease [3–5]. A diet rich in meat, cigarette smoke, alcohol consumption, as well as chronic inflammation in patients with inflammatory bowel disease (IBD) all represent critical independent risk factors for CRC development [6–10]. CRC pathogenesis and progression are driven by distinct genetic features and events of genomic instability which lead to different CRC phenotypes characterized by chromosomal instability, the hypermethylation of promoter CpG island sites (CpG island methylator phenotype, CIMP), and the high level of microsatellite instability [3,11,12]. Along with CRC classifications based on the features of cancer cells, including microsatellite instability and TNM (Tumor–Node–Metastasis) staging, the WHO has introduced the “immunoscore” as a prognostic value for predicting disease-specific recurrence and survival [13–16]. Among the parameters, this score includes the density of tumor-infiltrating cytotoxic and memory T cells, which are associated with favorable prognosis [17], whereas scores reporting the frequency of innate immune cells, including mast cells (MCs), are limited [18].

Initially neglected, MCs are progressively becoming crucial players in CRC because increasing evidence supports their capability to affect tumor progression [19–21].

Nonetheless, despite the many works that have been published in the last year, the ultimate role of MCs in tumors is far from being understood. The findings are characterized by apparently contradictory data, which actually are consequent of the plastic nature of

MCs that are extremely sensitive to microenvironmental cues to which they suddenly respond. Hence, the effect of MCs cannot be limited to the dichotomy presence/absence but it is caused by their localization, density, activation and degranulation state, secretion of cytokines and/or proteases, and proximity to other immune and cancer cells [22]. MCs could also represent an important tool to predict cancer outcome, but, before they can be employed as prognostic/predictive markers or even as targets for novel therapeutic approaches, a deeper characterization of their biology and the identification of the specific profiles associated with their activation and localization are necessary.

In this review, we provide an overview of the features of intestinal MCs and their potential roles in the development of CRC with a particular focus on the interplay between MCs and tumor cells in tumorigenesis.

2. Phenotypic and Functional Heterogeneity of Intestinal MCs

MCs are innate immune cells that originate from bone marrow precursors, enter the circulation as committed progenitors (MCp), and migrate into peripheral tissues where they further differentiate under the influence of the local microenvironment [23]. Mature MCs are strategically distributed in close proximity to blood and lymphatic vessels as well as nerves to respond to pathogens and other ingested or inhaled agents [24–26]. Indeed, MCs express a wide array of receptors that allow them to recognize invading pathogens and respond to different stimuli coming from the microenvironment [27,28]. MCs are able to integrate environmental signals and in response to all of them release different granule-stored or newly synthesized chemical mediators and cytokines [29,30].

In the gut, MCs are the main sentinels of the host defense involved in the maintenance of homeostasis as well as in orchestrating local inflammation [31].

Compared to other peripheral tissues, the gut is a peculiar site since it presents an abundant reservoir of murine MCp that constitutively home to this organ thanks to the expression of the integrin $\alpha 4\beta 7$ and the chemokine receptor CXCR2 [32]. Committed murine MCp in the gut have been characterized as $\text{Lin}^- \text{c-Kit}^{\text{lo}} \text{Fc}\epsilon\text{RI}\alpha^{\text{lo}} \alpha 4\beta 7^+$ cells and under the influence of local factors, differentiate into fully mature MCs upregulating $\text{Fc}\epsilon\text{RI}\alpha$ while downregulating $\alpha 4\beta 7$ [33].

The two main subsets of MCs have been identified in the murine intestine based on the expression of MC proteases [34]. Mucosal MCs (MMCs), positive for MCP-1 and MCP-2, are found in the lamina propria close to the epithelium and produce lower levels of histamine and higher amounts of cysteinyl leukotrienes compared to the larger connective tissue MCs (CTMCs) found in the submucosa (Figure 1, left panel). CTMCs contain the chymase mMCP-4, the elastase mMCP-5, the tryptases mMCP-6 and -7, and the metallopeptidase carboxypeptidase A3 (CPA3) in their granules [34,35]. A third MC subtype was recently identified in mice: the interepithelial mucosal MCs (ieMMC) [36]. Although much remains to be learned about the differing functions of lamina propria and ieMMCs, both of them are rare in normal mouse intestinal mucosa but are increased during the immune responses to intestinal helminth infections and in food allergies [36].

MC heterogeneity was also reported in the human gastrointestinal tract (Figure 1, right panel). The tryptase-positive and chymase-negative MC population is mainly present in the lamina propria (MC_T), while the main MC subset in the submucosa (MC_{TC}) is characterized by the expression of both enzymes [34,37,38]. A rare population of MCs exclusively expressing chymase was also identified in both lamina propria and submucosa [38], but its role is still unclear.

However, mouse and human MC classifications are simplistic since they do not reflect the high level of intestinal MC plasticity due to the constant change in the local microenvironment. Using single-cell RNAseq technology, Dwyer and coauthors have elucidated tissue-specific MC peculiarity, revealing at least three distinct connective tissue MC subsets [39].

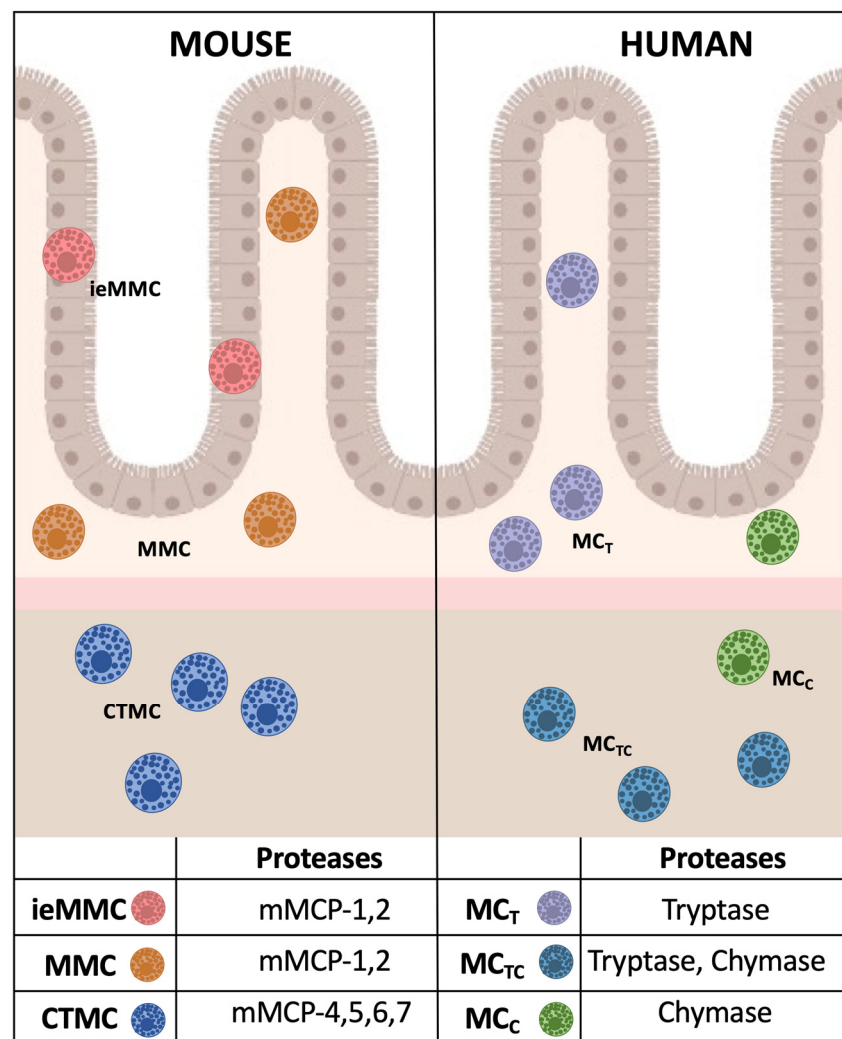


Figure 1. Mast cell subsets in murine and human gut. Mast cell subsets identified in murine intestine (**left**) and human intestine (**right**), and their distribution are represented with different colors. Proteases expressed by the different MC subsets are listed in the table below. ieMMC: intraepithelial mucosal mast cells, MMC: mucosal mast cells, CTMC: connective tissue mast cells, MC_T, MC_{TC}, MC_C: Mast cells expressing tryptase, tryptase and chymase, chymase only, respectively.

3. Role of Intestinal MCs in Immune Homeostasis and Infections

Different MC subsets may regulate the intestinal barrier function in homeostatic conditions and upon infections. Mice deficient for MCP-4 show a reduced intestinal permeability and epithelial cell migration [40], highlighting a role for CTMCs in homeostatic conditions.

Upon parasite infection, a high degree of MC plasticity is well underlined. MMC is the main subset that expands and increases the intestinal permeability to facilitate the expulsion of nematode through the action of MCP-1 [41]. During the acute phase of the *Trichinella spiralis* infection, MCs dramatically increase in number and change from a connective to a mucosal phenotype, mainly expressing the chymase family members MCP-1, MCP-2, and MCP-10. MCP-1 directly participates in the clearance of infection since the delayed expulsion of the adult helminth and increased deposition of muscle larvae have been reported in MCP-1-deficient mice [42]. In the recovery phase, MCs slowly revert back to their initial protease phenotype and restore their physiologic number [43].

By contrast, Shin and co-authors underline a selective role of connective tissue MCs in the chronic phase of *T. spiralis* infection. Indeed, they showed that the tryptase MCP-6 is important for the recruitment of eosinophil to *T. spiralis* larvae and for the infection's clearance [44].

A different scenario characterizes an acute infection with a high-dose of the nematode *Trichuris muris* that results in a persistent accumulation of MCs with mucosal phenotype in the large-intestinal epithelium [45], having long-term consequences on the barrier integrity.

The apparent discrepancy between the two infection models can be explained by the different location of an infection (small versus large intestine) and/or by a selective change in the resident microbial communities.

The MC plasticity, intended as the ability to rapidly sense a changing environment and consequently adapt to the specific received triggers, can explain the activated MC phenotype described in different human gastrointestinal disorders. Several studies have reported an increased number of MCs in the mucosa of patients affected by celiac disease, IBD, irritable bowel syndrome, and mucosal MCs resulted to be fundamental mediators of the pathology-associated inflammation [46].

Of note, the large majority of intestinal MCs are in direct contact with nerves and the MC/nerve crosstalk provides a neuroimmune network necessary to control the physiological and pathological response of the gut [47,48].

MCs locally release histamine and tryptase that may impact on the intestinal neurons through histamine receptors and the proteinase-activated receptor (PAR-2), thus inducing the muscle contraction and pain that characterize intestinal inflammation [49,50]. On the other hand, upon cytokine priming, human MCs express neurokinin receptor 1, thus becoming responsive to substance P, while murine MCs can sense several neuropeptides including adenosine triphosphate, somatostatin, calcitonin gene-related peptide, and substance P [51].

Even though a direct effect of neuropeptides on MC activation is more evident in murine models, the increased neuropeptide amounts in IBD patients suggests a possible role for MC/intestinal neuron cooperation in the pathogenesis of the disease.

4. The Ambiguous Role of Intestinal MCs in Colorectal Cancer Development

The link between the persistent inflammation and tissue transformation is now solid and best represented by CRC development in patients affected by IBD [50]. Indeed, the presence of morphologically activated or degranulated MCs in the colon during the florid phase of the inflammatory process suggests their possible role in the transition from inflammation to carcinoma.

However, the precise role of the different intestinal MC subsets during CRC development is still a matter of debate [19].

4.1. Evaluating MC Infiltration in Human Patients with CRC

By in situ detection of MCs, several studies have highlighted a correlation between an increased MC density and a poor prognosis [52–56]. In a more recent finding, a link between the frequency of circulating MC progenitors and advanced stages of CRC disease was also reported [57].

Of note, MCs have been observed mainly at the tumor margins and at peri-vascular regions [54,55], and their presence was associated with an increased blood vessel density in the tumor microenvironment (TME) [58].

Despite the finding that support a pro-tumorigenic role for MCs, other studies have reported a correlation between a high MC density and better clinical outcomes [59–61].

It is likely that age, sex, and racial disparities [62] as well as the method(s) used for detecting the MC frequency in tissues may account for the described discrepant results.

Regarding the phenotypic features of MCs among normal tissues and colorectal cancer, Tan and co-authors have found no differences in the proportion of the MC_{TC} subtype and of the MC_T subset, making their percentage approximately 75% and 25%, respectively [60].

However, most studies on the density of tumor-infiltrating MCs were performed through in situ detection of tryptase-positive cells in the invasive front of colonic adenocarcinomas without discrimination between MC_{TC} and MC_T subsets [55,58,63,64]. Tryptase represents one of the most powerful angiogenic mediators released by human MCs [65]. In a human colon carcinoma cell line, Yoshii et al. demonstrated that tryptase activates

PAR-2 on tumor cells and that this activation in turn led to the production of PGE2 and the induction of cell proliferation [66].

However, no conclusive data exist about the role of human tryptase in the carcinogenesis process, emphasizing the need to examine the impact of MCs and their proteases in CRC development from different perspectives.

4.2. Mouse Models to Study the Role of MCs in CRC Development

Several mouse models have been used to dissect the role of intestinal murine MCs during colon inflammation and tumor progression. Depending on the specific tumor model and on the experimental settings under investigation, heterogeneous MC functions have been proposed either to sustain or resolve the tumor progression (Figure 2) [19,67].

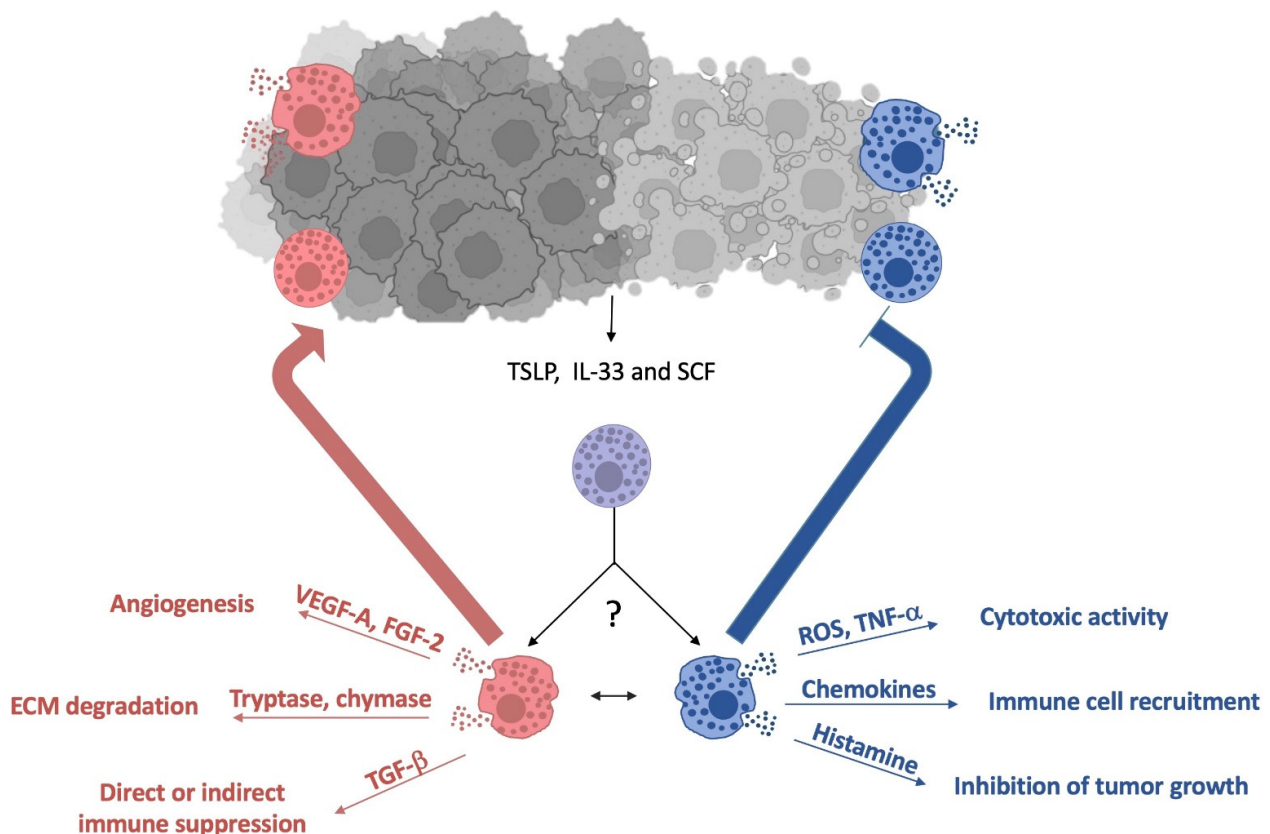


Figure 2. The dichotomous role of MCs during CRC. MCs infiltrating colonic tumor can directly interact with cancer cells or recognize tumor-released factors, such as TSLP, IL-33 and SCF, tuning their phenotype/activity. Different MC subsets can exert either pro-tumorigenic (red arrow) or anti-tumorigenic (blue arrow) properties through the secretion of preformed and newly synthesized mediators, the main of which are depicted. TSLP: thymic stromal lymphopoietin; IL-33: Interleukin-33, SCF: stem cell factor, VEGF: vascular endothelial growth factor; FGF: fibroblast growth factor, TGF: transforming growth factor, ROS: reactive oxygen species, TNF: tumor necrosis factor.

Among the studies supporting a role for MCs in the development of CRC, Gounaris and co-authors demonstrated that MCs and their progenitors accumulate in the colonic polyps of adenomatous polyposis coli mutant mice ($APC^{\Delta 468}$) in a T cell-independent manner [68]. They observed that the depletion of MCs, by using $APC^{\Delta 468}$ mice lethally irradiated and reconstituted with c-kit defective BM ($Kit^{W-sh/W-sh}$), leads to a decrease in the frequency and size of colonic tumors, suggesting that MCs and their soluble mediators are the essential components for polyp development. In particular, the authors proposed that the MC-derived tumor necrosis factor α (TNF α) acts in an autocrine fashion to amplify

the local MC pool at the site of the tumor's formation and directly contributes to the adenomatous polyp growth [68].

These results are consistent with a previous study demonstrating a reduced susceptibility of MC-deficient B6Kit(W)/Kit(W-v) mice to chemically induced intestinal tumors [69], and with other evidence suggesting that MCs acquire a pro-tumorigenic role during the development of colitis-associated CRC [70,71].

However, there is also evidence in which MCs appear to play a protective role in CRC tumorigenesis. For example, Sinnamon and co-authors demonstrated that in the absence of MCs, the frequency and size of adenomas increased in mice carrying a heterozygous mutation in the adenomatous polyposis coli gene (ApcMin/+ mice) [72]. Similarly, Haribabu and colleagues reported that an accumulation of MC in the small intestine of ApcMin/+ mice mediated immune surveillance through a selective recruitment of anti-tumor CD8+ T-cells, reducing the intestinal tumor burden [73].

A more recent work from Sakita and colleagues provided evidence that *in vivo* MCs could either promote or inhibit the development of colon tumors according to the type of microenvironment stimuli, being tumorigenic in colitis-induced CRC and protective in murine models of sporadic CRC [74].

Finally, it is important to underline that murine small intestinal tumors have a different immunological milieu than colonic tumors. In the case of MC subsets, during the progression from adenoma to carcinoma, a decreased number of ieMMCs have been reported in colorectal lesions but not in small intestinal tumors [75].

Thus, it is likely to be concluded that the MC activity during the CRC development may impact either in a beneficial or harmful fashion depending on the genetic background, specific tumor models, and regional diversity in the microenvironment composition.

5. Gut Microenvironment “Education” and MC Switch during Inflammation and Colon Cancer Development

Similar to the case of macrophages, MCs undergo to a sort of “microenvironment education” under the influence of cytokines, growth factors, and microbial components that tune the MC phenotype and functions in homeostatic and inflammatory conditions [22,76]; however, the molecular mechanism(s) are still undefined.

On the other hand, once activated, the MCs recruited in the initial phase of tumorigenesis release several mediators that directly modify the TME and/or indirectly regulate the local immune response [20,77].

5.1. Crosstalk between MCs and Microbiome

Emerging evidence support a mutual influence between MCs and gut microbiota, as is well documented by the use of germ-free (GF) mouse models [76,78,79]. Commensal bacteria through the interaction with Toll-like receptor (TLR) 2 and 4 promote the expression of CXCR2 ligands by intestinal epithelial cells, which, in turn, is responsible for MC maturation and their recruitment into intestine [78]. Accordingly, upon oral sensitization with ovalbumin GF mice did not develop the symptoms of a food allergy despite the production of high IgE levels [79].

The ability of bacteria and fungi to elicit an MC activation is further supported by the *in vitro* data demonstrating that a coculture of MCs with some bacteria strains or *Candida Albicans* induce MC degranulation and pro-inflammatory cytokine production, as well as the release of VEGF [76]. MC activation, in turn, may facilitate the elimination of microorganisms either through the secretion of pro-inflammatory cytokines or the production of MC extracellular traps [80,81].

On the other hand, other microorganisms are able to inhibit FcεRI-mediated intracellular signals *in vitro* and *in vivo*, thus dampening the MC functions [76].

The ability of gut microbiota to shape the MC functions suggests that dysbiosis may cause the intestinal accumulation of MCs in inflammatory conditions, including

celiac disease, Crohn's disease, and ulcerative colitis, and that the increased intestinal permeability may further facilitate an MC-microbiota crosstalk [50].

Experimental evidence from the past years have also highlighted a key role for the intestinal microbiota in malignant gastrointestinal diseases [82]. Remarkably, similar alterations in the microbiota composition (e.g., higher abundance of *E. coli*) has been reported in Crohn's disease individuals and in patients affected by colon cancer [83,84], suggesting that a shared dysbiosis may contribute to IBD-associated CRC.

However, the microbial mechanisms associated with human CRC pathogenesis during the crosstalk between MCs and microbiome remain undescribed.

5.2. Bidirectional Interaction between MCs and Cancer Cells

During an inflammatory state, a molecular mechanism behind the phenotypic/functional switch of MCs could be the result of their interactions with epithelial cells and/or the soluble factors that these cells produce, including the alarmins thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33 that deserve a particular mention [85–88].

In the intestine, TSLP and IL-33 control the balance between the host defense and wound repair [89,90]. In particular, the capability of murine MCs to resolve IL-33-mediated inflammation appears to be critical in promoting tissue repair through MC-mediated protease and cytokine production [70,90].

TSLP and IL-33 released either by gut epithelial or immune cells can also play a direct role in tumorigenesis [91,92]. Using a xenograft mouse model of colon cancer, Yue and coauthors demonstrated that the peritumoral administration of TSLP reduces tumor growth by inducing the apoptosis of human colon cancer cells in a TSLPR-dependent manner [91].

On the other hand, during CRC progression, the abnormal expression of IL-33 in the TME activates tumor stroma to promote intestinal polyposis [92].

Transformed cells by releasing IL-33 can then elicit pro-inflammatory functions in MCs to reprogram them into a pathogenic state [93].

In the context of small bowel cancer, during the transition from inflammation to cancer, it was recently reported that distinct MC subsets expand and guide tumor progression [94]. Specifically, Saadalla et al. reported that mucosal MCs, the same MC subtype that expand during an acute *Trichinella spiralis* infection, accumulate in benign polyps in the presence of IL-10, IL-13, and IL-33 and are maintained in an IL-10-dependent manner. However, during the transition of polyps to adenocarcinoma, a different subset characteristic of connective tissue MC expands and accumulates inside the tumor stroma in an IL-33-dependent manner [94], supporting cancer's ability to change the MC activity toward a pro-cancer function. Accordingly, in the ApcMin/+ mouse model, an IL-33 deficiency inhibited the intestinal tumor burden and decreased the MC density, as well as the release of MC-derived proteases and cytokines [92,95].

Moreover, in an azoxymethane (AOM)-induced colonic tumor model, the MCs recruited to epithelial cells during an acute inflammation play a role in the resolution of colon damage but acquire a pro-tumorigenic role during epithelial cell transformation [70].

It is likely to be concluded that MCs acquire a different behavior when faced with normal, damaged, or transformed epithelial cells. Such deviated immune responses would benefit the progression of cancer through promoting chronic inflammation molecular pathways over cytotoxic pathways.

MCs represent an abundant source of several angiogenic and lymphangiogenic factors that have been shown to play a role in inflammatory and neoplastic angiogenesis [96–99]. Of note, the important role of MCs as producers of the angiogenic factor VEGF-A has been recently underlined by a transcriptomic analysis of tumor-infiltrating myeloid cells in different human cancers, including CRC [100].

MC-secreted factors facilitate tumor vascularization not only by a direct angiogenic effect but also by stimulating MCs themselves and other inflammatory cells in the TME to release novel angiogenic mediators and cytokines.

MCs release matrix metalloproteinases 9 and specific proteases (tryptase and chymase) that degrade the components of the extracellular matrix, promoting the spread of a tumor and metastasis [98]. Moreover, by releasing adenosine and amphiregulin, MCs can suppress the protective immune responses against cancer [101,102].

On the other hand, MCs represent the only cell type able to store preformed TNF- α in their granules [103] and, upon degranulation, can also exhibit anti-tumor activity through direct tumor cell cytotoxicity mediated by TNF- α and reactive oxygen species.

To deeply investigate the interplay between colon cancer cells and MCs, by using 2D and 3D human coculture models, Yu and co-authors provided evidence that support a bidirectional crosstalk in which cancer cells, mainly producing stem cell factor (SCF), support MC recruitment, while MCs release pro-tumorigenic mediators and increase colon cancer growth [104]. They also compared the transcriptomic profile of colon cancer-cocultured human MCs versus control MCs [105]. A list of deregulated genes has been identified, including *MMP-2*, *VEGF-A*, *PDGF-A*, *COX2*, *NOTCH1*, and *ISG15*, which all contribute to the enrichment of cancer-related pathways. To better validate the complex interaction between MC and TME, a 3D multicomponent coculture should be developed by the incorporation of other stromal/immune cells.

By a similar approach, utilizing whole-genome gene expression data from both mouse models and human cancer patients, Ko and coauthors demonstrated that the expression profile of “MC-dependent genes” (deregulated by MC deficiency but largely recovered upon MC engraftment) differs between normal and tumor from lung, breast, and colon tissues [106].

However, further studies are needed to validate the exact role of individual MC-dependent genes in CRC development.

5.3. Crosstalk between MCs and Other Immune Cells during CRC Progression

The activation of MCs leads to the release of a plethora of factors that act on other immune cell types in the TME and influence their recruitment, rate of proliferation, and their state of activation, differentiation, and polarization [20].

Eissmann and co-authors recently demonstrated a vicious signaling axis between IL-33, MCs, and macrophages to sustain angiogenesis and the growth of gastric cancer: tumor epithelial-derived IL-33 activates MCs to produce a chemotactic cytokine expression signature, which promotes a selective accumulation of tumor-associated macrophages (TAMs) [107]. They found that the ablation of MCs or macrophages in tumor-bearing mice were associated with a vascular collapse and tumor hypoxia. Importantly, in gastric cancer patients, this MC activation signature correlates with decreased patient survival.

In CRC, earlier studies have demonstrated the presence of both MC and TAMs in the stromal tumor front [63,108]. They are located in close proximity and promote tumor growth-releasing pro-inflammatory and angiogenetic growth factors [108,109].

Accordingly, using the piroxicam/IL-10 $^{-/-}$ mouse model of progressive colitis, Khan and co-authors found that MCs and TAMs may communicate and through their crosstalk, promote cancer cell invasion [110]. Upon the activation of the PI3K/AKT signaling, cascade MCs acquire the ability to attract CD11b $^{+}$ cells that in turn promote tumor cell proliferation and invasion.

Taken together, these findings support the hypothesis that the progression from chronic inflammation to CRC can be influenced by the interaction between stromal, MCs, and TAMs and that the inhibition of PI3 Kinase could antagonize such a vicious loop.

In murine polyposis and human CRC, MCs also established with Treg an intricate interaction that regulates the functions of both cell types in a reciprocal manner [111,112]. Interestingly, MCs induce conventional Tregs to switch function, generating a potent immune suppressive but proinflammatory Treg population that shuts down IL-10 and promotes MC expansion and degranulation [113].

Another mechanism by which MCs could promote immune evasion is through the interaction with myeloid-derived suppressor cells (MDSCs).

Activated MCs, by the release of nitric oxide, IL-6, and TGF- β , increases the recruitment and activity of MDSC, which in turn results in a strong inhibition of T-cell proliferation and consequent tumor-induced tolerance [114]. More specifically, in the APC Δ 468 murine model, it was reported that MCs support the MDSC activity in driving the immune escape with a subsequent increase in the polyp development [115,116].

Since MDSCs can enhance MC activation [116], within the TME, a pro-tumor positive feedback loop between MC and MDSC can be also envisaged and likely contributes to immune evasion.

6. Concluding Remarks

Many questions related to the role of intestinal MCs in CRC progression remain unresolved.

To investigate the role of MCs within the immunologic milieu of CRC, “mast cell-deficient” mice have been derived primarily on the C57BL/6 background and, to a lesser extent, on BALB/c, and work with such animals produces results that might be mainly restricted to those strains of inbred mice. Additionally, most findings came from murine models of c-Kit mutations that do not affect exclusively MCs but can also influence the basophil numbers and functions, as well as intestinal γ/δ T cells.

It is also important to mention that a non-negligible proportion of genetically engineered mouse models in CRC research (e.g., Apc-mutated) develop tumors predominantly in the small intestine, which is in sharp contrast to the human situation. Moreover, murine small intestinal tumors have a different immunological milieu than colonic tumors and murine MCs might therefore affect the adenoma-carcinoma progression differently depending on the intestinal region considered.

Thus, advanced functional studies in MC-deficient mouse models and the second generation of genetically engineered mouse models for intestinal cancer (e.g., tumor initiation plus Cre-mediated immune cell manipulation) will be required for ultimately determining the MC role in intestinal cancers. In particular, considering the great relevance of MC heterogeneity in intestinal cancer, it will be important to choose mouse models in which the specific targeting of all, or of one specific, MC subtypes is assured.

Another current goal is to better understand whether progenitors generate distinct intestinal MC subsets, meaning anti-tumorigenic and pro-tumorigenic MCs, and/or whether individual MCs have sufficient plasticity to exhibit distinct features based on their responsiveness to particular TME signals. The application of single-cell RNA sequencing platforms will allow for a high-resolution characterization of an intestinal MC signature that accompanies a colonic tumors' initiation and growth and may help to solve these questions.

Mast cell secretory granules contain various bioactive mediators, including tryptase, chymase, and carboxypeptidase A. However, the contribution of specific MC proteases during CRC progression is still largely unclear.

Further studies will be also needed to fully investigate the effects of the microbiota on intestinal MC functions in CRC tumorigenesis.

Finally, a better characterization of intestinal MCs at various stages of colonic disease would help to define to what extent one can safely enhance the positive functions of MCs, or inhibit their harmful activities, in order to offer novel potential targets for a therapeutic intervention in CRC progression.

Author Contributions: R.M. and R.P. wrote the manuscript and prepared the figures. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the Italian Association for Cancer Research (AIRC IG-24955) and the Istituto Pasteur Italia-Fondazione Cenci Bolognetti (2020-366).

Conflicts of Interest: The authors declare no commercial or financial conflict of interest.

Abbreviations

Adenomatous polyposis coli (APC); azoxymethane (AOM); colorectal cancer (CRC); inflammatory bowel disease (IBD); mast cell (MC); interleukin-33 (IL-33); mast cell progenitors (MCp); proteinase-activated receptor (PAR-2); stem cell factor (SCF); tumor-associated macrophage (TAM); tumor microenvironment (TME); tumor necrosis factor (TNF); thymic stromal lymphopoietin (TSLP).

References

- Keum, N.; Giovannucci, E. Global burden of colorectal cancer: Emerging trends, risk factors and prevention strategies. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 713–732. [[CrossRef](#)]
- Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [[CrossRef](#)]
- Fearon, E.R.; Vogelstein, B. A genetic model for colorectal tumorigenesis. *Cell* **1990**, *61*, 759–767. [[CrossRef](#)]
- Kanth, P.; Grimmitt, J.; Champine, M.; Burt, R.; Samadder, J.N. Hereditary Colorectal Polyposis and Cancer Syndromes: A Primer on Diagnosis and Management. *Am. J. Gastroenterol.* **2017**, *112*, 1509–1525. [[CrossRef](#)]
- Fidelle, M.; Yonekura, S.; Picard, M.; Cogdill, A.; Hollebecque, A.; Roberti, M.P.; Zitvogel, L. Resolving the Paradox of Colon Cancer Through the Integration of Genetics, Immunology, and the Microbiota. *Front. Immunol.* **2020**, *11*, 600886. [[CrossRef](#)]
- Chan, A.T.; Giovannucci, E.L. Primary Prevention of Colorectal Cancer. *Gastroenterology* **2010**, *138*, 2029–2043.e10. [[CrossRef](#)] [[PubMed](#)]
- Dahm, C.C.; Keogh, R.H.; Spencer, E.A.; Greenwood, D.C.; Key, T.J.; Fentiman, I.S.; Shipley, M.J.; Brunner, E.J.; Cade, J.E.; Burley, V.J.; et al. Dietary fiber and colorectal cancer risk: A nested case-control study using food diaries. *J. Natl. Cancer Inst.* **2010**, *102*, 614–626. [[CrossRef](#)]
- Beaugerie, L.; Itzkowitz, S.H. Cancers Complicating Inflammatory Bowel Disease. *New Engl. J. Med.* **2015**, *372*, 1441–1452. [[CrossRef](#)] [[PubMed](#)]
- Dashti, S.G.; Buchanan, D.D.; Jayasekara, H.; Ait Ouakrim, D.; Clendenning, M.; Rosty, C.; Winship, I.M.; Macrae, F.A.; Giles, G.G.; Parry, S.; et al. Alcohol consumption and the risk of colorectal cancer for mismatch repair gene mutation carriers. *Cancer Epidemiol. Biomark. Prev.* **2017**, *26*, 366–375. [[CrossRef](#)] [[PubMed](#)]
- Murphy, N.; Ward, H.A.; Jenab, M.; Rothwell, J.A.; Boutron-Ruault, M.C.; Carbonnel, F.; Kvaskoff, M.; Kaaks, R.; Kühn, T.; Boeing, H.; et al. Heterogeneity of Colorectal Cancer Risk Factors by Anatomical Subsite in 10 European Countries: A Multinational Cohort Study. *Clin. Gastroenterol. Hepatol.* **2019**, *17*, 1323–1331. [[CrossRef](#)] [[PubMed](#)]
- Boland, C.R.; Goel, A. Microsatellite Instability in Colorectal Cancer. *Gastroenterology* **2010**, *138*, 2073–2087. [[CrossRef](#)] [[PubMed](#)]
- Advani, S.M.; Advani, P.S.; Brown, D.W.; DeSantis, S.M.; Korphaisarn, K.; VonVille, H.M.; Bressler, J.; Lopez, D.S.; Davis, J.S.; Daniel, C.R.; et al. Global differences in the prevalence of the CpG is-land methylator phenotype of colorectal cancer. *BMC Cancer* **2019**, *19*, 964. [[CrossRef](#)] [[PubMed](#)]
- Mlecnik, B.; Bindea, G.; Angell, H.K.; Maby, P.; Angelova, M.; Tougeron, D.; Church, S.E.; Lafontaine, L.; Fischer, M.; Fredriksen, T.; et al. Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability. *Immunity* **2016**, *44*, 698–711. [[CrossRef](#)]
- Lanzi, A.; Pagès, F.; Lagorce-Pagès, C.; Galon, J. The consensus immunoscore: Toward a new classification of colorectal cancer. *Oncoimmunology* **2020**, *9*, 1789032. [[CrossRef](#)]
- Nagtegaal, I.D.; Odze, R.D.; Klimstra, D.; Paradis, V.; Rugge, M.; Schirmacher, P.; Washington, K.M.; Carneiro, F.; Cree, I.A. The 2019 WHO classification of tumours of the digestive system. *Histopathology* **2020**, *76*, 182–188. [[CrossRef](#)]
- Quezada-Marín, J.I.; Lam, A.K.; Ochiai, A.; Odze, R.D.; Washington, K.M.; Fukayama, M.; Rugge, M.; Klimstra, D.S.; Nagtegaal, I.D.; Tan, P.H.; et al. Gastrointestinal tissue-based molecular biomarkers: A practical categorisation based on the 2019 World Health Organization classification of epithelial digestive tumours. *Histopathology* **2020**, *77*, 340–350. [[CrossRef](#)]
- Galon, J.; Costes, A.; Sanchez-Cabo, F.; Kirilovsky, A.; Mlecnik, B.; Lagorce-Pagès, C.; Tosolini, M.; Camus, M.; Berger, A.; Wind, P.; et al. Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome. *Science* **2006**, *313*, 1960–1964. [[CrossRef](#)]
- Fionda, C.; Scarno, G.; Stabile, H.; Molfetta, R.; Di Censo, C.; Gismondi, A.; Paolini, R.; Sozzani, S.; Santoni, A.; Sciumè, G. NK Cells and Other Cytotoxic Innate Lymphocytes in Colorectal Cancer Progression and Metastasis. *Int. J. Mol. Sci.* **2022**, *23*, 7859. [[CrossRef](#)]
- Heijmans, J.; Büller, N.; Muncan, V.; Brink, G.V.D. Role of mast cells in colorectal cancer development, the jury is still out. *Biochim. Biophys. Acta (BBA) Mol. Basis Dis.* **2012**, *1822*, 9–13. [[CrossRef](#)]
- Varricchi, G.; Galdiero, M.R.; Loffredo, S.; Marone, G.; Iannone, R.; Marone, G.; Granata, F. Are mast cells MASTers in cancer? *Front Immunol.* **2017**, *8*, 424. [[CrossRef](#)]
- Rigoni, A.; Colombo, M.; Pucillo, C. Mast cells, basophils and eosinophils: From allergy to cancer. *Semin. Immunol.* **2018**, *35*, 29–34. [[CrossRef](#)] [[PubMed](#)]
- Varricchi, G.; de Paulis, A.; Marone, G.; Galli, S.J. Future Needs in Mast Cell Biology. *Int. J. Mol. Sci.* **2019**, *20*, 4397. [[CrossRef](#)]

23. Chen, C.-C.; Grimaldeston, M.A.; Tsai, M.; Weissman, I.L.; Galli, S.J. Identification of mast cell progenitors in adult mice. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11408–11413. [[CrossRef](#)] [[PubMed](#)]
24. Galli, S.J.; Tsai, M. Mast cells in allergy and infection: Versatile effector and regulatory cells in innate and adaptive immunity. *Eur. J. Immunol.* **2010**, *40*, 1843–1851. [[CrossRef](#)] [[PubMed](#)]
25. Voehringer, D. Protective and pathological roles of mast cells and basophils. *Nat. Rev. Immunol.* **2013**, *13*, 362–375. [[CrossRef](#)]
26. Reber, L.L.; Sibilano, R.; Mukai, K.; Galli, S.J. Potential effector and immunoregulatory functions of mast cells in mucosal immunity. *Mucosal Immunol.* **2015**, *8*, 444–463. [[CrossRef](#)]
27. Kawakami, T.; Galli, S.J. Regulation of mast-cell and basophil function and survival by IgE. *Nat. Rev. Immunol.* **2002**, *2*, 773–786. [[CrossRef](#)]
28. Marone, G.; Galli, S.J.; Kitamura, Y. Probing the roles of mast cells and basophils in natural and acquired immunity, physiology and disease. *Trends Immunol.* **2002**, *23*, 425–427. [[CrossRef](#)]
29. Frossi, B.; Mion, F.; Tripodo, C.; Colombo, M.P.; Pucillo, C.E. Rheostatic Functions of Mast Cells in the Control of Innate and Adaptive Immune Responses. *Trends Immunol.* **2017**, *38*, 648–656. [[CrossRef](#)]
30. Lecce, M.; Molfetta, R.; Milito, N.D.; Santoni, A.; Paolini, R. FcεRI Signaling in the Modulation of Allergic Response: Role of Mast Cell-Derived Exosomes. *Int. J. Mol. Sci.* **2020**, *21*, 5464. [[CrossRef](#)]
31. Kurashima, Y.; Goto, Y.; Kiyono, H. Mucosal innate immune cells regulate both gut homeostasis and intestinal inflammation. *Eur. J. Immunol.* **2013**, *43*, 3108–3115. [[CrossRef](#)] [[PubMed](#)]
32. Abonia, J.P.; Austen, K.F.; Rollins, B.J.; Joshi, S.K.; Flavell, R.A.; Kuziel, W.A.; Koni, P.A.; Gurish, M.F. Constitutive homing of mast cell progenitors to the intestine depends on autologous expression of the chemokine receptor CXCR2. *Blood* **2005**, *105*, 4308–4313. [[CrossRef](#)] [[PubMed](#)]
33. Arinobu, Y.; Iwasaki, H.; Gurish, M.F.; Mizuno, S.I.; Shigematsu, H.; Ozawa, H.; Tenen, D.G.; Austen, K.F.; Akashi, K. Developmental checkpoints of the basophil/mast cell lineages in adult murine hema-topoiesis. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 18105–18110. [[CrossRef](#)]
34. Gurish, M.F.; Austen, K.F. Developmental Origin and Functional Specialization of Mast Cell Subsets. *Immunity* **2012**, *37*, 25–33. [[CrossRef](#)] [[PubMed](#)]
35. Collington, S.J.; Williams, T.J.; Weller, C.L. Mechanisms underlying the localisation of mast cells in tissues. *Trends Immunol.* **2011**, *32*, 478–485. [[CrossRef](#)]
36. Vogel, P.; Janke, L.; Gravano, D.M.; Lu, M.; Sawant, D.V.; Bush, D.; Shuyu, E.; Vignali, D.A.; Pillai, A.; Rehg, J.E. Globule Leukocytes and other Mast Cells in the Mouse Intestine. *Vet Pathol.* **2018**, *55*, 76–97. [[CrossRef](#)]
37. Albert-Bayo, M.; Paracuellos, I.; González-Castro, A.M.; Rodríguez-Urrutia, A.; Rodríguez-Lagunas, M.J.; Alonso-Cotoner, C.; Santos, J.; Vicario, M. Intestinal Mucosal Mast Cells: Key Modulators of Barrier Function and Homeostasis. *Cells* **2019**, *8*, 135. [[CrossRef](#)]
38. Weidner, N.; Austen, K. Heterogeneity of Mast Cells at Multiple Body Sites: Fluorescent Determination of Avidin Binding and Immunofluorescent Determination of Chymase, Tryptase, and Carboxypeptidase Content. *Pathol. Res. Pract.* **1993**, *189*, 156–162. [[CrossRef](#)]
39. Dwyer, D.F.; Barrett, N.A.; Austen, K.F.; The Immunological Genome Project Consortium. Expression profiling of constitutive mast cells reveals a unique identity within the immune system. *Nat. Immunol.* **2016**, *17*, 878–887. [[CrossRef](#)]
40. Groschwitz, K.R.; Ahrens, R.; Osterfeld, H.; Gurish, M.F.; Han, X.; Åbrink, M.; Finkelman, F.D.; Pejler, G.; Hogan, S.P. Mast cells regulate homeostatic intestinal epithelial migration and barrier function by a chymase/Mcpt4-dependent mechanism. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 22381–22386. [[CrossRef](#)]
41. McDermott, J.R.; Bartram, R.E.; Knight, P.A.; Miller, H.R.; Garrod, D.R.; Grecis, R.K. Mast cells disrupt epithelial barrier function during enteric nematode infection. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 7761–7766. [[CrossRef](#)]
42. Knight, P.A.; Wright, S.H.; Lawrence, C.E.; Paterson, Y.Y.; Miller, H.R. Delayed expulsion of the nematode *Trichinella spiralis* in mice lacking the mucosal mast cell-specific granule chymase, mouse mast cell protease-1. *J. Exp. Med.* **2000**, *192*, 1849–1856. [[CrossRef](#)]
43. Friend, D.S.; Ghildyal, N.; Austen, K.F.; Gurish, M.F.; Matsumoto, R.; Stevens, R.L. Mast cells that reside at different locations in the jejunum of mice infected with *Trichinella spiralis* exhibit sequential changes in their granule ultrastructure and chymase phenotype. *J. Cell Biol.* **1996**, *135*, 279–290. [[CrossRef](#)] [[PubMed](#)]
44. Shin, K.; Watts, G.F.; Oettgen, H.C.; Friend, D.S.; Pemberton, A.D.; Gurish, M.F.; Lee, D.M. Mouse mast cell tryptase mMCP-6 is a critical link between adaptive and innate immunity in the chronic phase of *Trichinella spiralis* infection. *J. Immunol.* **2008**, *180*, 4885–4891. [[CrossRef](#)] [[PubMed](#)]
45. Sorobetea, D.; Holm, J.B.; Henningsson, H.; Kristiansen, K.; Svensson-Frej, M. Acute infection with the intestinal parasite *Trichuris muris* has long-term consequences on mucosal mast cell homeostasis and epithelial integrity. *Eur. J. Immunol.* **2017**, *47*, 257–268. [[CrossRef](#)] [[PubMed](#)]
46. Bischoff, S.C. Physiological and pathophysiological functions of intestinal mast cells. *Semin. Immunopathol.* **2009**, *31*, 185–205. [[CrossRef](#)] [[PubMed](#)]
47. Buhner, S.; Schemann, M. Mast cell-nerve axis with a focus on the human gut. *Biochim. et Biophys. Acta (BBA) Mol. Basis Dis.* **2011**, *1822*, 85–92. [[CrossRef](#)]

48. Schemann, M.; Camilleri, M. Functions and Imaging of Mast Cell and Neural Axis of the Gut. *Gastroenterology* **2013**, *144*, 698–704.e4. [[CrossRef](#)]
49. Tsujii, K.; Andoh, T.; Lee, J.-B.; Kuraishi, Y. Activation of Proteinase-Activated Receptors Induces Itch-Associated Response Through Histamine-Dependent and -Independent Pathways in Mice. *J. Pharmacol. Sci.* **2008**, *108*, 385–388. [[CrossRef](#)]
50. Bischoff, S.C. Mast cells in gastrointestinal disorders. *Eur. J. Pharmacol.* **2016**, *778*, 139–145. [[CrossRef](#)]
51. van der Kleij, H.P.; Ma, D.; Redegeld, F.A.; Kraneveld, A.D.; Nijkamp, F.P.; Bienenstock, J. Functional expression of neurokinin 1 receptors on mast cells induced by IL-4 and stem cell factor. *J. Immunol.* **2003**, *171*, 2074–2079. [[CrossRef](#)] [[PubMed](#)]
52. Gulubova, M.; Vlaykova, T. Prognostic significance of mast cell number and microvascular density for the survival of pa-tients with primary colorectal cancer. *J. Gastroenterol. Hepatol.* **2009**, *24*, 1265–1275. [[CrossRef](#)]
53. Malfettone, A.; Silvestris, N.; Saponaro, C.; Ranieri, G.; Russo, A.; Caruso, S.; Popescu, O.; Simone, G.; Paradiso, A.; Mangia, A. High density of tryptase-positive mast cells in human colorectal cancer: A poor prognostic factor related to protease-activated receptor 2 expression. *J. Cell. Mol. Med.* **2013**, *17*, 1025–1037. [[CrossRef](#)] [[PubMed](#)]
54. Suzuki, S.; Ichikawa, Y.; Nakagawa, K.; Kumamoto, T.; Mori, R.; Matsuyama, R.; Takeda, K.; Ota, M.; Tanaka, K.; Tamura, T.; et al. High infiltration of mast cells positive to tryptase predicts worse outcome following resection of colorectal liver metastases. *BMC Cancer* **2015**, *15*, 840. [[CrossRef](#)] [[PubMed](#)]
55. Hu, G.; Wang, S.; Cheng, P. Tumor-infiltrating tryptase⁺ mast cells predict unfavorable clinical outcome in solid tumors. *Int. J. Cancer* **2017**, *142*, 813–821. [[CrossRef](#)]
56. Mao, Y.; Feng, Q.; Zheng, P.; Yang, L.; Zhu, D.; Chang, W.; Ji, M.; He, G.; Xu, J. Low tumor infiltrating mast cell density confers prognostic benefit and reflects immunoactivation in colorectal cancer. *Int. J. Cancer* **2018**, *143*, 2271–2280. [[CrossRef](#)]
57. Zhao, P.; Zhou, P.; Tang, T.; Si, R.; Ji, Y.; Hu, X.; Li, A.; Jiang, Y. Levels of circulating mast cell progenitors and tumour-infiltrating mast cells in patients with colorectal cancer. *Oncol. Rep.* **2022**, *47*, 89. [[CrossRef](#)]
58. Ammendola, M.; Sacco, R.; Sammarco, G.; Donato, G.; Montemurro, S.; Ruggieri, E.; Patrino, R.; Marech, I.; Cariello, M.; Vacca, A.; et al. Correlation between Serum Tryptase, Mast Cells Positive to Tryptase and Microvascular Density in colo-rectal Cancer Patients: Possible Biological-Clinical Signifi-cance. *PLoS ONE* **2014**, *9*, e99512. [[CrossRef](#)]
59. Nielsen, H.J.; Hansen, U.; Christensen, I.J.; Reimert, C.M.; Brünner, N.; Moesgaard, F. Independent prognostic value of eosinophil and mast cell infiltration in colorectal cancer tissue. *J. Pathol.* **1999**, *189*, 487–495. [[CrossRef](#)]
60. Tan, S.Y.; Fan, Y.; Luo, H.S.; Shen, Z.X.; Guo, Y.; Zhao, L.J. Prognostic significance of cell infiltrations of immunosurveillance in colorectal cancer. *World J. Gastroenterol.* **2005**, *11*, 1210–1214. [[CrossRef](#)]
61. Mehdawi, L.; Osman, J.; Topi, G.; Sjölander, A. High tumor mast cell density is associated with longer survival of colon can-cer patients. *Acta Oncol.* **2016**, *55*, 1434–1442. [[CrossRef](#)]
62. Curran, T.; Sun, Z.; Gerry, B.; Findlay, V.J.; Wallace, K.; Li, Z.; Paulos, C.; Ford, M.; Rubinstein, M.P.; Chung, D.; et al. Differential immune signatures in the tumor microenvironment are associated with colon cancer racial disparities. *Cancer Med.* **2021**, *10*, 1805–1814. [[CrossRef](#)]
63. Xia, Q.; Wu, X.J.; Zhou, Q.; Jing-Zeng Hou, J.H.; Pan, Z.Z.; Zhang, X.S. No relationship between the distribution of mast cells and the survival of stage IIIB colon cancer patients. *J. Transl. Med.* **2011**, *9*, 88. [[CrossRef](#)]
64. Flores de Los Rios, P.A.; Soto Domínguez, A.; Arellano-Pérez Vertti, R.D.; Castelán Maldonado, E.E.; Velázquez Gauna, S.E.; Morán Martínez, J.; Salas Treviño, D.; García Garza, R. Differential expression of mast cell granules in samples of metastatic and non-metastatic colorectal cancer in patients. *Acta Histochem.* **2020**, *122*, 151618. [[CrossRef](#)]
65. Moon, T.C.; Lee, E.; Baek, S.-H.; Murakami, M.; Kudo, I.; Kim, N.S.; Lee, J.M.; Min, H.-K.; Kambe, N.; Chang, H.W. Degranulation and cytokine expression in human cord blood-derived mast cells cultured in serum-free medium with recombinant human stem cell factor. *Mol. Cells* **2003**, *16*, 154–160.
66. Yoshii, M.; Jikuhara, A.; Mori, S.; Iwagaki, H.; Takahashi, H.K.; Nishibori, M.; Tanaka, N. Mast Cell Tryptase Stimulates DLD-1 Carcinoma Through Prostaglandin- and MAP Kinase-Dependent Manners. *J. Pharmacol. Sci.* **2005**, *98*, 450–458. [[CrossRef](#)] [[PubMed](#)]
67. Segura-Villalobos, D.; Ramírez-Moreno, I.G.; Martínez-Aguilar, M.; Ibarra-Sánchez, A.; Muñoz-Bello, J.O.; Anaya-Rubio, I.; Padilla, A.; Macías-Silva, M.; Lizano, M.; González-Espinosa, C. Mast Cell–Tumor Interactions: Molecular Mechanisms of Recruitment, Intratumoral Communication and Potential Therapeutic Targets for Tumor Growth. *Cells* **2022**, *11*, 349. [[CrossRef](#)]
68. Gounaris, E.; Erdman, S.E.; Restaino, C.; Gurish, M.F.; Friend, D.S.; Gounari, F.; Lee, D.M.; Zhang, G.; Glickman, J.N.; Shin, K.; et al. Mast cells are an essential hematopoiet-ic component for polyp development. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 19977–19982. [[CrossRef](#)]
69. Wedemeyer, J.; Galli, S.J. Decreased susceptibility of mast cell-deficient Kit(W)/Kit(W-v) mice to the development of 1, 2-dimethylhydrazine-induced intestinal tumors. *Lab Invest.* **2005**, *85*, 388–396. [[CrossRef](#)]
70. Rigoni, A.; Bongiovanni, L.; Burocchi, A.; Sangaletti, S.; Danelli, L.; Guarnotta, C.; Lewis, A.; Rizzo, A.; Silver, A.R.; Tripodo, C.; et al. Mast Cells Infiltrating Inflamed or Transformed Gut Alternatively Sustain Mucosal Healing or Tumor Growth. *Cancer Res* **2015**, *75*, 3760–3770. [[CrossRef](#)]
71. Lee, J.-H.; Jeon, Y.-D.; Xin, M.; Lim, J.-Y.; Lee, Y.-M.; Kim, D.-K. Mast cell modulates tumorigenesis caused by repeated bowel inflammation condition in azoxymethane/dextran sodium sulfate-induced colon cancer mouse model. *Biochem. Biophys. Rep.* **2022**, *30*, 101253. [[CrossRef](#)]

72. Sinnamon, M.J.; Carter, K.J.; Sims, L.P.; Lafleur, B.; Fingleton, B.; Matrisian, L.M. A protective role of mast cells in intestinal tumor-igenesis. *Carcinogenesis* **2008**, *29*, 880–886. [[CrossRef](#)]
73. Bodduluri, S.R.; Mathis, S.; Maturu, P.; Krishnan, E.; Satpathy, S.R.; Chilton, P.M.; Mitchell, T.C.; Lira, S.; Locati, M.; Mantovani, A.; et al. Mast Cell-Dependent CD8+ T-cell Recruitment Mediates Immune Surveillance of Intestinal Tumors in ApcMin/+ Mice. *Cancer Immunol. Res.* **2018**, *6*, 332–347. [[CrossRef](#)]
74. Sakita, J.Y.; Elias-Oliveira, J.; Carlos, D.; Santos, E.D.S.; Almeida, L.Y.; Malta, T.M.; Brunaldi, M.O.; Albuquerque, S.; Silva, C.L.A.; Andrade, M.V.; et al. Mast cell-T cell axis alters development of colitis-dependent and colitis-independent colorectal tumours: Potential for therapeutically targeting via mast cell inhibition. *J. Immunother. Cancer* **2022**, *10*, e004653. [[CrossRef](#)]
75. Groll, T.; Silva, M.; Sarker, R.S.; Tschurtschenthaler, M.; Schnalzger, T.; Mogler, C.; Denk, D.; Schölch, S.; Schraml, B.U.; Ruland, J.; et al. Comparative Study of the Role of Interepithelial Mucosal Mast Cells in the Context of Intestinal Adenoma-Carcinoma Progression. *Cancers* **2022**, *14*, 2248. [[CrossRef](#)]
76. De Zuani, M.; Dal Secco, C.; Frossi, B. Mast cells at the crossroads of microbiota and IBD. *Eur. J. Immunol.* **2018**, *48*, 1929–1937. [[CrossRef](#)]
77. Oldford, S.A.; Marshall, J.S. Mast cells as targets for immunotherapy of solid tumors. *Mol. Immunol.* **2015**, *63*, 113–124. [[CrossRef](#)]
78. Kunii, J.; Takahashi, K.; Kasakura, K.; Tsuda, M.; Nakano, K.; Hosono, A.; Kaminogawa, S. Commensal bacteria promote migration of mast cells into the intestine. *Immunobiology* **2011**, *216*, 692–697. [[CrossRef](#)]
79. Schwarzer, M.; Hermanova, P.; Srutkova, D.; Golias, J.; Hudcovic, T.; Zwicker, C.; Sinkora, M.; Akgün, J.; Wiedermann, U.; Tuckova, L.; et al. Germ-Free Mice Exhibit Mast Cells With Impaired Functionality and Gut Homing and Do Not Develop Food Allergy. *Front. Immunol.* **2019**, *10*, 205. [[CrossRef](#)]
80. Gendrin, C.; Shubin, N.J.; Boldenow, E.; Merrillat, S.; Clauson, M.; Power, D.; Doran, K.S.; Abrink, M.; Pejler, G.; Rajagopal, L.; et al. Mast cell chymase decreases the severity of group B Streptococcus infections. *J. Allergy Clin. Immunol.* **2018**, *142*, 120–129.e6. [[CrossRef](#)]
81. Campillo-Navarro, M.; Leyva-Paredes, K.; Donis-Maturano, L.; González-Jiménez, M.; Paredes-Vivas, Y.; Cerbulo-Vázquez, A.; Serafín-López, J.; García-Pérez, B.; Ullrich, S.E.; Flores-Romo, L.; et al. *Listeria monocytogenes* induces mast cell ex-tracellular traps. *Immunobiology* **2017**, *222*, 432–439. [[CrossRef](#)]
82. Tilg, H.; Adolph, T.E.; Gerner, R.R.; Moschen, A.R. The Intestinal Microbiota in Colorectal Cancer. *Cancer Cell* **2018**, *33*, 954–964. [[CrossRef](#)] [[PubMed](#)]
83. Pascal, V.; Pozuelo, M.; Borruel, N.; Casellas, F.; Campos, D.; Santiago, A.; Martinez, X. A microbial signature for Crohn’s dis-ease. *Gut* **2017**, *66*, 813–822. [[CrossRef](#)] [[PubMed](#)]
84. Quaglio, A.E.V.; Grillo, T.G.; De Oliveira, E.C.S.; Di Stasi, L.C.; Sasaki, L.Y. Gut microbiota, inflammatory bowel disease and colorectal cancer. *World J. Gastroenterol.* **2022**, *28*, 4053–4060. [[CrossRef](#)] [[PubMed](#)]
85. Kobori, A.; Yagi, Y.; Imaeda, H.; Ban, H.; Bamba, S.; Tsujikawa, T.; Saito, Y.; Fujiyama, Y.; Andoh, A. Interleukin-33 expression is specifically en-hanced in inflamed mucosa of ulcerative colitis. *J. Gastroenterol.* **2010**, *45*, 999–1007. [[CrossRef](#)]
86. Sedhom, M.A.; Pichery, M.; Murdoch, J.R.; Foligné, B.; Ortega, N.; Normand, S.; Mertz, K.; Sanmugalingam, D.; Brault, L.; Grandjean, T.; et al. Neutralisation of the interleukin-33/ST2 pathway ameliorates experimental colitis through enhancement of mucosal healing in mice. *Gut* **2012**, *62*, 1714–1723. [[CrossRef](#)]
87. Varricchi, G.; Pecoraro, A.; Marone, G.; Criscuolo, G.; Spadaro, G.; Genovese, A.; Marone, G. Thymic Stromal Lymphopoietin Isoforms, Inflammatory Disorders, and Cancer. *Front. Immunol.* **2018**, *9*, 1595. [[CrossRef](#)]
88. Corren, J.; Ziegler, S.F. TSLP: From allergy to cancer. *Nat. Immunol.* **2019**, *20*, 1603–1609. [[CrossRef](#)]
89. Reardon, C.; Lechmann, M.; Brüstle, A.; Gareau, M.G.; Shuman, N.; Philpott, D.; Ziegler, S.F.; Mak, T.W. Thymic Stromal Lymphopoietin-Induced Expression of the Endogenous Inhibitory Enzyme SLP1 Mediates Recovery from Colonic Inflammation. *Immunity* **2011**, *35*, 223–235. [[CrossRef](#)]
90. He, Z.; Song, J.; Hua, J.; Yang, M.; Ma, Y.; Yu, T.; Feng, J.; Liu, B.; Wang, X.; Li, Y.; et al. Mast cells are essential intermediaries in regulating IL-33/ST2 sig-naling for an immune network favorable to mucosal healing in experimentally inflamed colons corresponding author. *Cell Death Dis.* **2018**, *9*, 1173. [[CrossRef](#)]
91. Yue, W.; Lin, Y.; Yang, X.; Li, B.; Liu, J.; He, R. Thymic stromal lymphopoietin (TSLP) inhibits human colon tumor growth by pro-moting apoptosis of tumor cells. *Oncotarget* **2016**, *7*, 16840–16854. [[CrossRef](#)]
92. Maywald, R.L.; Doerner, S.K.; Pastorelli, L.; De Salvo, C.; Benton, S.M.; Dawson, E.P.; Lanza, D.G.; Berger, N.A.; Markowitz, S.D.; Lenz, H.J.; et al. IL-33 activates tumor stro-ma to promote intestinal polyposis. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, E2487–E2496. [[CrossRef](#)] [[PubMed](#)]
93. Eissmann, M.F.; Buchert, M.; Ernst, M. IL33 and Mast Cells—The Key Regulators of Immune Responses in Gastrointestinal Cancers? *Front Immunol.* **2020**, *11*, 1389. [[CrossRef](#)] [[PubMed](#)]
94. Saadalla, A.M.; Osman, A.; Gurish, M.F.; Dennis, K.L.; Blatner, N.R.; Pezeshki, A.; McNagny, K.M.; Cheroutre, H.; Gounari, F.; Khazaie, K. Mast cells promote small bowel cancer in a tumor stage-specific and cytokine-dependent manner. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 1588–1592. [[CrossRef](#)] [[PubMed](#)]
95. He, Z.; Chen, L.; Souto, F.O.; Canasto-Chibuque, C.; Bongers, G.; Deshpande, M.; Harpaz, N.; Ko, H.M.; Kelley, K.; Furtado, G.C.; et al. Epithelial-derived IL-33 promotes intestinal tumorigenesis in Apc Min/+ mice. *Sci. Rep.* **2017**, *7*, 5520. [[CrossRef](#)]
96. Marone, G.; Varricchi, G.; Loffredo, S.; Granata, F. Mast cells and basophils in inflammatory and tumor angiogenesis and lym-phangiogenesis. *Eur. J. Pharmacol.* **2016**, *778*, 146–151. [[CrossRef](#)]

97. Crivellato, E.; Nico, B.; Ribatti, D. Mast cells and tumour angiogenesis: New insight from experimental carcinogenesis. *Cancer Lett.* **2008**, *269*, 1–6. [[CrossRef](#)]
98. Maltby, S.; Khazaie, K.; McNagny, K.M. Mast cells in tumor growth: Angiogenesis, tissue remodelling and immune-modulation. *Biochim. et Biophys. Acta (BBA) Rev. Cancer* **2009**, *1796*, 19–26. [[CrossRef](#)]
99. Cristinziano, L.; Poto, R.; Criscuolo, G.; Ferrara, A.L.; Galdiero, M.R.; Modestino, L.; Loffredo, S.; de Paulis, A.; Marone, G.; Spadaro, G.; et al. IL-33 and Superantigenic Activation of Human Lung Mast Cells Induce the Release of Angiogenic and Lymphangiogenic Factors. *Cells* **2021**, *10*, 145. [[CrossRef](#)]
100. Cheng, S.; Li, Z.; Gao, R.; Xing, B.; Gao, Y.; Yang, Y.; Qin, S.; Zhang, L.; Ouyang, H.; Du, P.; et al. A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. *Cell* **2021**, *184*, 792–809.e23. [[CrossRef](#)]
101. Huang, B.; Lei, Z.; Zhang, G.-M.; Li, D.; Song, C.; Li, B.; Liu, Y.; Yuan, Y.; Unkeless, J.; Xiong, H.; et al. SCF-mediated mast cell infiltration and activation exacerbate the inflammation and immunosuppression in tumor microenvironment. *Blood* **2008**, *112*, 1269–1279. [[CrossRef](#)] [[PubMed](#)]
102. Zaiss, D.M.W.; van Loosdregt, J.; Gorlani, A.; Bekker, C.P.J.; Gröne, A.; Sibilio, M.; van Bergen en Henegouwen, P.M.P.; Roovers, R.C.; Coffey, P.J.; Sijts, A.J.A.M. Amphiregulin Enhances Regulatory T Cell-Suppressive Function via the Epidermal Growth Factor Receptor. *Immunity* **2013**, *38*, 275–284. [[CrossRef](#)] [[PubMed](#)]
103. Olszewski, M.B.; Groot, A.J.; Dastyk, J.; Knol, E.F. TNF trafficking to human mast cell granules: Mature chain-dependent endocytosis. *J. Immunol.* **2007**, *178*, 5701–5709. [[CrossRef](#)] [[PubMed](#)]
104. Yu, Y.; Blokhuis, B.; Derks, Y.; Kumari, S.; Garssen, J.; Redegeld, F. Human mast cells promote colon cancer growth via bidirectional crosstalk: Studies in 2D and 3D coculture models. *Oncoimmunology* **2018**, *7*, e1504729. [[CrossRef](#)] [[PubMed](#)]
105. Yu, Y.; Blokhuis, B.R.; Garssen, J.; Redegeld, F.A. A Transcriptomic Insight into the Impact of Colon Cancer Cells on Mast Cells. *Int. J. Mol. Sci.* **2019**, *20*, 1689. [[CrossRef](#)]
106. Ko, E.-A.; Sanders, K.M.; Zhou, T. A transcriptomic insight into the impacts of mast cells in lung, breast, and colon cancers. *Oncoimmunology* **2017**, *6*, e1360457. [[CrossRef](#)]
107. Eissmann, M.F.; Dijkstra, C.; Jarnicki, A.; Pheesse, T.; Brunner, J.; Poh, A.R.; Etemadi, N.; Tsantikos, E.; Thiem, S.; Huntington, N.D.; et al. IL-33-mediated mast cell activation promotes gastric cancer through macrophage mobilization. *Nat. Commun.* **2019**, *10*, 2735. [[CrossRef](#)]
108. Erreni, M.; Mantovani, A.; Allavena, P. Tumor-associated Macrophages (TAM) and Inflammation in Colorectal Cancer. *Cancer Microenviron.* **2010**, *4*, 141–154. [[CrossRef](#)]
109. Khazaie, K.; Blatner, N.R.; Khan, M.W.; Gounari, F.; Gounaris, E.; Dennis, K.; Bonertz, A.; Tsai, F.-N.; Strouch, M.J.T.; Cheon, E.; et al. The significant role of mast cells in cancer. *Cancer Metastasis Rev.* **2011**, *30*, 45–60. [[CrossRef](#)]
110. Khan, M.W.; Keshavarzian, A.; Gounaris, E.; Melson, J.E.; Cheon, E.C.; Blatner, N.R.; Chen, Z.E.; Tsai, F.-N.; Lee, G.; Ryu, H.; et al. PI3K/AKT Signaling Is Essential for Communication between Tissue-Infiltrating Mast Cells, Macrophages, and Epithelial Cells in Colitis-Induced Cancer. *Clin. Cancer Res.* **2013**, *19*, 2342–2354. [[CrossRef](#)]
111. Gri, G.; Piconese, S.; Frossi, B.; Manfroi, V.; Merluzzi, S.; Tripodo, C.; Viola, A.; Odom, S.; Rivera, J.; Colombo, M.P.; et al. CD4+CD25+ Regulatory T Cells Suppress Mast Cell Degranulation and Allergic Responses through OX40-OX40L Interaction. *Immunity* **2008**, *29*, 771–781. [[CrossRef](#)] [[PubMed](#)]
112. Gounaris, E.; Blatner, N.R.; Dennis, K.; Magnusson, F.; Gurish, M.F.; Strom, T.B.; Beckhove, P.; Gounari, F.; Khazaie, K. T-regulatory cells shift from a pro-protective anti-inflammatory to a cancer-promoting proinflammatory phenotype in polyposis. *Cancer Res.* **2009**, *69*, 5490–5497. [[CrossRef](#)] [[PubMed](#)]
113. Blatner, N.R.; Bonertz, A.; Beckhove, P.; Cheon, E.C.; Krantz, S.B.; Strouch, M.; Weitz, J.; Koch, M.; Halverson, A.L.; Bentrem, D.J.; et al. In colorectal cancer mast cells contribute to systemic regulatory T-cell dysfunction. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 6430–6435. [[CrossRef](#)] [[PubMed](#)]
114. Danelli, L.; Frossi, B.; Gri, G.; Mion, F.; Guarnotta, C.; Bongiovanni, L.; Tripodo, C.; Mariuzzi, L.; Marzinotto, S.; Rigoni, A.; et al. Mast Cells Boost Myeloid-Derived Suppressor Cell Activity and Contribute to the Development of Tumor-Favoring Microenvironment. *Cancer Immunol. Res.* **2015**, *3*, 85–95. [[CrossRef](#)] [[PubMed](#)]
115. Cheon, E.C.; Khazaie, K.; Khan, M.W.; Strouch, M.J.; Krantz, S.B.; Phillips, J.; Blatner, N.R.; Hix, L.M.; Zhang, M.; Dennis, K.L.; et al. Mast cell 5-lipoxygenase activity promotes intestinal polyposis in APC Δ 468 mice. *Cancer Res.* **2011**, *71*, 1627–1636. [[CrossRef](#)] [[PubMed](#)]
116. Morales, J.K.; Saleem, S.J.; Martin, R.K.; Saunders, B.L.; Barnstein, B.O.; Faber, T.W.; Pullen, N.A.; Kolawole, E.M.; Brooks, K.B.; Norton, S.K.; et al. Myeloid-derived suppressor cells enhance IgE-mediated mast cell responses. *J. Leukoc. Biol.* **2013**, *95*, 643–650. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.