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Review Article

Tumor-Infiltrating Immune Cells in Colorectal Cancer

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A B S T R A C T

Colorectal cancer encompasses a heterogeneous group of malignancies that differ in pathophysiological mechanisms, immune response and infiltration, therapeutic response, and clinical prognosis. Numerous studies have highlighted the clinical relevance of tumor-infiltrating immune cells among different types of colorectal tumors yet vary in cell type definitions and cell identification strategies. The distinction of immune signatures is particularly challenging when several immune subtypes are involved but crucial to identify novel intercellular mechanisms within the tumor microenvironment. In this review, we compile human and non-human studies on tumor-infiltrating immune cells and provide an overview of immune subtypes, their pathophysiological functions, and their prognostic role in colorectal cancer. We discuss how differentiating immune signatures can guide the development of immunotherapeutic targets and personalized treatment regimens. We analyzed comprehensive human protein biomarker profiles across the entire immune spectrum to improve interpretability and application of tumor studies and to ultimately enhance immunotherapy and advance precision medicine for colorectal cancer patients.

Introduction

Colorectal cancer (CRC) is the second most deadly cancer worldwide [1] and a growing global socioeconomic burden [2]. While healthcare systems are facing increasing CRC incidence in developing countries and younger age of onset in developed countries [3], breakthrough immunotherapies are promising but effective for only a small subset of CRC patients [4,5]. Moreover, CRC is highly heterogeneous with variable outcomes even within the same tumor stage [6]. Immune infiltration signatures have been shown to be a CRC heterogeneity factor that is linked to clinical outcomes [7] and that may offer more robust predictive biomarkers than those used in existing clinical staging [8]. A deeper understanding of CRC-infiltrating immune cells may enhance staging strategies, identify novel immunotherapeutic targets, and ultimately improve clinical outcomes for CRC patients.

CRC staging is based on local Tumor spread, lymph Node infiltration, and distant Metastasis (TNM classification), along with factors such as primary tumor location and molecular mutations [9–12]. This staging classification guides therapeutic strategies with treatments ranging from surgical resection in limited stages [9,12,13] to a combination of chemotherapies with targeted therapies in advanced tumor stages [10,11]. The immunotherapy pembrolizumab, which inhibits the immune checkpoint protein (ICP) programmed cell death protein 1 (PD-1), is approved by the US Food Drug Administration (FDA) for CRC patients carrying advanced tumors with mismatch repair deficiency (MMRd)/microsatellite instability (MSI) [4,11]. These MMRd/MSI tumors have higher mutation rates and exhibit increased neoantigen expression that can lead to adaptive immune cell recruitment into the tumor [4,5,14,15]. However, over 95% of advanced CRC tumors are mismatch repair proficient (MMRp)/microsatellite stable (MSS) tumors [16] with low mutational burden, which makes them less responsive to anti-PD-1 therapy [11]. These tumors evade the immune detection through other mechanisms such as major histocompatibility complex (MHC) downregulation [17]. MSS tumors show different immune infiltration patterns that are distinct from MSI tumors and also correlate with clinical stages and outcomes [7], which highlights their potential to expand current clinical staging systems. Since tumors and the host immune system constantly adapt to each other, it is crucial for staging classifications and precision treatment to account for this evolving relationship. This can be achieved by incorporating parameters such as individual tumor-infiltrating immune cell signatures into treatment algorithms. A classification system that captures both tumor and host perspectives can allow development of more effective treatments tailored to each patient.

In this review, we summarize myeloid and lymphoid tumor-infiltrating immune cells in CRC, highlight their prognostic role, and analyze their protein biomarker profiles (Tables 1 and 2) to enable the immediate study and differentiation of tumor-infiltrating immune cells in human CRC specimens. We emphasize the importance of utilizing the whole spectrum of tumor-infiltrating immune cells to reflect individual immune responses for identifying prognostic biomarkers, advancing predictive classifications, developing novel immunotherapies, and eventually improving personalized medicine for CRC patients.

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Table 1
Human protein biomarker profiles of immune cells in the myeloid lineage.

Cell lineage	Lineage markers	Immune cell	Protein biomarkers
MDSCs [24–26]	Lin$^-$ (CD3, CD19, CD56) Lin$^+$ (CD11b, CD33)	M-MDSCs	HLA-DR$^{low/-}$ CD15$^-$, CD14$^+$, CD66b$^-$, CXCR1$^+$, CD84$^+$
		PMN-MDSCs	HLA-DR$^{low/-}$, CD15$^+$, CD14$^-$, CD66b$^+$, OLR1$^+$, CD84$^+$
		e-MDSCs	HLA-DR$^-$, CD15$^-$, CD14$^-$
Macrophages [65]	Lin$^+$ (CD11b, CD14, CD68, CSFR1)	M1-like	CD86$^+$, iNOS^{+*}, MARCO$^+$, SOCS1^{+*}, FCγR1A$^+$
		M2-like	CD163$^+$, CD206$^+$, FCϵR2$^+$, ARG1^{+*}
Alternative Macrophages Classification [47]	N/A	IFN-TAMs	CD11b$^+$, CD14$^+$, HLA-DR^{low}, CD68$^+$, CD86^{++}, CD80^{++}, PD-L1^{++}, PD-L2^{++}, MHC-II^{++}, KLKR1$^+$, LAMP1$^+$, TLR4$^+$, MCR1$^-$, SIGLEC$^-$
		Inflam-TAMs	N/A[1]
		LA-TAMS	CD163$^{low/-}$, CD206$^{+/low}$, CD80$^+$, CD9$^+$, TFRC$^+$, CD72$^+$
		Angio-TAMs	CD163^{++}, CD206^{++}, CD52^{++}, CXCR4$^+$, TREM1$^+$
		Reg-TAMs	CD206$^+$, GPNMB$^+$, TREM2$^+$, ADGRE1^{++}, CX3CR1$^+$, ARG1^{+*}
		Prolif-TAMs	N/A[1]
		RTM-like TAMs	CD163^{low}, CD206^{low}, CD68$^+$, MT1^{+*}
Dendritic Cells [71,79,82]	Lin$^-$ (CD3, CD19, CD20, CD56) Lin$^+$ (CD45, HLA-DR)	pDC	CD2$^+$, CD123$^+$, CD45RA$^+$, LILRA4$^+$, CLEC4C$^+$, CD1c$^-$, CD11c$^-$, CD14$^-$, CD141$^-$
		cDC1	CD141$^+$, CADM1$^+$, XCR1$^+$, CLEC9A$^+$
		cDC2	Lin$^+$ (CD1c, FCϵR1A, CD127a)
		cDC2A	CD5$^+$
		cDC2B (DC3)	CD14$^+$, CD163$^+$
Neutrophils [102,117,123,124, 247]	Lin$^+$ (MPO, CCR1, CD11b, CD15, FCγR3A, CD13, CD10, CD66b) Lin$^-$ (HLA-DR, CD33)	N1	CD206$^-$
		N2	CD206$^+$

The table summarizes the protein marker profiles of myeloid immune cells discussed in this review, grouped according to the subtype's lineage association.
Abbreviations: MDSCs, Myeloid-derived suppressor cells; Lin, lineage markers; CD, cluster of differentiation; PMN, polymorphonuclear; HLA-DR, human leukocyte antigen DR isotype; CXCR, C-X-C motif chemokine receptor; OLR1, Oxidized low-density lipoprotein receptor 1; CSFR1, colony stimulating factor 1 receptor; iNOS, inducible nitric oxid synthase; MARCO, macrophage receptor with collagenous structure; SOCS, suppressor of cytokine signaling proteins; FCγR, Fc gamma receptor; FCϵR, Fc epsilon receptor; ARG1, arginase 1; TAMs, tumor associated macrophages; IFN-TAMs, interferon-primed TAMs; Inflam-TAMs, inflammatory cytokine-enriched TAMs; LA-TAMs, lipid-associated TAMs; Angio-TAMs, pro-angiogenic TAMs; Reg-TAMs, immune regulatory TAMs; Prolif-TAMs, proliferating TAMs; RTM-like TAMs, resident tissue macrophage like TAMs; PD-L1, programmed cell death ligand 1; MHC-II, major histocompatibility complex type II; KLKR1, killer cell lectin like receptor K1; LAMP1, lysosomal associated membrane protein 1; TLR4, Toll-like receptor 4; MCR1, mobilized colistin resistance gene 1; SIGLEC, sialic acid binding Ig like lectin; TFRC, transferrin receptor; TREM, triggering receptor expressed on myeloid cells; GPNMB, glycoprotein NMB; ADGRE1, adhesion G protein-coupled receptor E1; CX3CR1, C-X3-C motif chemokine receptor 1; MT1, metallothionein 1; DC, dendritic cell; pDC, plasmacytoid DC; cDC, conventional DC; LILRA4, leukocyte immunoglobulin like receptor A4; CLEC, C-type lectin domain; CADM1, cell adhesion molecule 1; XCR1, X-C motif chemokine receptor 1; MPO, myeloperoxidase; CCR, C-C motif chemokine receptor; N, neutrophil.
[*] intracellular only.
[++] high expression.
[1] Protein markers unavailable because these subtypes were identified by transcriptomic markers only.

Immune Infiltration Predicts Clinical Outcomes

Although CRC was once viewed as cold tumor without significant immune cell infiltration [17], Galon et al. demonstrated in 2006 that the constellation and frequency of tumor-infiltrating immune cells correlate with CRC prognosis [18]. This study revealed that the immune infiltrating profile predicts clinical outcomes independently of MSI status and TNM stage [18]. Using this as a foundation, they subsequently developed the Immunoscore as an additional staging metric [19] and showed that it is stronger than MSI status in predicting patient survival in CRC [8]. The Immunoscore metric, which is a ratio that involves the numeration of two lymphocyte populations [19], was validated in 2018 as a dependable indicator of the recurrence risk in patients with colon cancer [20]. Despite these advances, immune infiltration in CRC remains highly heterogeneous [6] and is challenging to represent by solely considering two lymphocyte populations.

To elucidate CRC heterogeneity, Guinney et al. (2015) analyzed large gene expression datasets of bulk CRC specimens to define four consensus molecular subtypes (CMSs) that differ in molecular profile, neoantigen load, tumor progression, immune infiltration, and metabolic and histological behavior [7]. They found that tumor molecular profiles, which contain multiple single molecular markers including but not limited to MSI and Kirsten Rat Sarcoma viral oncogene homolog (KRAS) mutation status, were sufficient to classify tumors into associated CMSs. As one of their examples, 76% of CMS1 tumors exhibited an MSI profile, while 24% of CMS1 tumors did not, showing that an MSI tumor can be classified into a different subtype depending upon the rest of the molecular profile [7]. They additionally reported that CMSs were associated with distinct immune signatures and identified significant correlations between CMS and clinical outcomes [7], which suggests that tumor-individual MSI-independent factors play a role in tumor immunology and clinical outcomes.

The Immunoscore metric and CMS classification showed that MSI-independent immunological factors are important in CRC prognosis [7,8] and that the current MSI status-based clinical staging can be improved. Both approaches identify either two immune populations or bulk immune information to classify CRC tumors. However, the tumor microenvironment (TME) is more diverse and contains numerous individual cell types. CRC tumors classified as "immune-exclusive" may contain rare immune cell types and cellular interactions that these approaches cannot detect. To enhance precision, CRC classification must include a combination of robust mechanistic rationales [21] and incorporate novel predictive markers as new rare cell types and cellular interactions are discovered and clinically validated. Therefore, a detailed understanding of tumor-infiltrating immune cells will guide the identification of additional prognostic cell types and novel predictive biomarkers to extend previous work and pave the way for more precise clinical staging of CRC patients.

Table 2
Human protein biomarker profiles of immune cells in the lymphoid lineage.

Cell lineage	Lineage markers	Immune cell	Protein biomarkers
ILCs [130,131,248]	$CD45^+$ Lin^- (TCR$\alpha\beta$, TCR$\gamma\delta$, CD3, CD19, CD14, CD123, CD34, CD303, FCϵR1)	Group 1 ILCs	Lin^+ (IL12RB2, T-bet*)
		NK cells	$CD56^+$, $NCR1^+$, $EOMES^{+*}$, $CD16^{+1}$
		ILC1	$CD127^{+2}$
		Group 2 ILCs	Lin^+ (GATA-3*, CD127)
		ILC2	$ICOS^+$, $CRTH2^+$, $IL17RB^+$, $IL1R^+$, $CD161^+$
		Group 3 ILCs	Lin^+ (RORγt*, CD127, CD117, IL1R, IL23R, CD254)
		NCR^+ ILC3	$NKp44^+$
		NCR^- ILC3	$NKp44^-$
		LTi-ILC	$NKp44^-$
T cells [143,215,249]	Lin^+ (CD45, CD3)	TCR$\alpha\beta$ T-cells	Lin^+ (TCR$\alpha\beta$)
		Cytotoxic T-cells	$CD8^+$
		T-helper cells	$CD4^+$
		Th1	T-bet^{+*}, $CXCR3^+$, $CCR6^-$
		Th2	$GATA3^{+*}$, $IRF4^{+*}$, $CCR6^-$, $CCR4^+$, $CD294^+$
		Th9	$PU.1^{+*}$, $IRF4^{+*}$
		Th17	$ROR\gamma t^{+*}$, $IRF4^{+*}$, $CCR6^+$, $CCR4^+$, $CD161^+$, IL-$23R^+$
		Th22	AHR^{+*}, $FOXO4^+$, $CCR6^+$, $CCR4^+$, $CCR10^+$
		Tfh	Bcl-6^{+*}, $CXCR5^+$, $ICOS^+$, PD-1^+
		Treg	$FoxP3^{+*}$, $CTLA4^+$, $CD25^+$, $CD127^{low}$
		NKT-cells	$CD56^+$
		TCR$\gamma\delta$ T-cells	Lin^+ (TCR$\gamma\delta$)
		Vδ1	V$\delta1^+$
		Vγ9Vδ2	V$\delta2^+$, V$\gamma9^+$
B cells [226,234]	Lin^+ (CD45, CD19)	naive	$CD20^+$, IgD^+, $CD27^-$
		unswitched memory	$CD20^+$, IgD^+, $CD27^+$
		switched memory	$CD20^+$, IgA^+/IgG^+/IgE^+, $CD27^+$
		IL-10^+ regulatory	$CD73^-$, $CD25^+$, $CD71^+$
		plasma cell	$CD20^-$, $BCMA^+$, $CD27^+$, $CD138^+$, $CD38^+$
		plasmablast	$CD20^-$, $CD27^+$, $CD138^-$, $CD38^{++}$
		germinal center	$CD20^+$, $CD27^-$, $CXCR5^+$

The table summarizes the protein biomarker profiles of lymphoid immune cells discussed in this review, grouped according to the subtype's lineage association. Abbreviations: ILCs, innate lymphoid cells; TCR, T cell receptor; FCϵR, Fc epsilon receptor; NK cells, natural killer cells; NCR, natural cytotoxicity receptor; LTi, lymphoid tissue inducer; IL12RB2, interleukin 12 receptor subunit beta 2; T-bet, T-box transcription factor 21; EOMES, Eomesodermin; GATA-3, G-A-T-A 3 nucleotide sequence binding protein; ICOS, inducible T-cell costimulator; CRTH2, chemoattractant receptor-homologous molecule on T-helper type 2 cells; IL17RB, interleukin 17 receptor B; IL1R, interleukin 1 receptor; IL23R, interleukin 23 receptor; NKp44, natural killer specific molecule also known as natural cytotoxity triggering receptor 2 (NCR2); Th, T-helper cell; Tfh, follicular helper T-cell; Treg, regulatory T cell; NKT, natural killer T cell; Vδ, also known as TCR delta variable; Vγ, TCR gamma variable; CXCR, C-X-C motif chemokine receptor; CCR, C-C motif chemokine receptor; IRF, interferon regulatory factor; ROR, RAR related orphan receptor; AHR, acryl hydrocarbon receptor; FOXO4, Forkhead box O4; Bcl-6, B-cell lymphoma 6; PD-1, programmed cell death protein 1; CTLA4, cytotoxic T-lymphocyte associated protein 4; IgD, immunoglobulin D; IgA, immunoglobulin A; IgG, immunoglobulin G; IgE, immunoglobulin E; IL-10, interleukin 10; BCMA, B-cell maturation antigen.
* intracellular only.
++ high expression.
1 CD16 is expressed by highly cytotoxic NK cells.
2 Minority of ILC1s do not express CD127.

Myeloid Lineage

The myeloid lineage derives from the common myeloid progenitor in the bone marrow and accounts for the majority of innate immune cells (Fig. 1) that include dendritic cells, macrophages, and granulocytes. These cells recognize pathogens with pattern-recognition receptors (PRRs), which are nonspecific receptors that recognize common pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Myeloid cells are also antigen-presenting cells (APCs) that interact with innate and adaptive lymphoid cell populations in order to eliminate, recruit, and/or activate them. In the context of solid tumors, literature also describes myeloid-derived suppressor cells (MDSCs) as an infiltrating myeloid subtype in the TME. We direct the curious reader to references [22,23] for more details on the fundamentals of cancer and general immunology.

Myeloid-derived suppressor cells

MDSCs are immature myeloid cells that can be categorized into two main groups by their nuclear morphology and surface markers: mononuclear MDSCs (M-MDSCs) and polymorphonuclear MDSCs (PMN-MDSCs) (Table 1) [24–26]. Initially, researchers considered M-MDSCs as a subtype of macrophages and PMN-MDSCS as a subtype of neutrophils. Since both M-MDSCs and PMN-MDSCs exhibited extraordinarily high immunosuppressive activity, they were ultimately combined under the name MDSCs [24,27]. Researchers found MDSCs mainly in pathologically altered tissues [24,28] and assumed that these cells develop from macrophages and neutrophils via constant overstimulation by myeloid-growth factors and inflammatory cytokines (Fig. 1)[24]. Consequently, MDSCs exhibit pronounced immunosuppressive properties with tumorigenic and prometastatic effects in solid tumors such as CRC [24,25,29–34].

CRC studies associate the majority of MDSCs with MSI tumors [35] as well as T cell inhibition and poor prognosis (Fig. 2) [31,36–40]. However, a small subset termed early-stage MDSCs (e-MDSCs)[26] have an unknown prognostic role. The exact identification of MDSCs remains challenging due to their surface marker overlap with macrophages and neutrophils, and requires additional suppression assays for precise differentiation [26]. By identifying exclusive surface markers and MDSC-specific marker profiles, future research can precisely differentiate these cells from other myeloid cells to investigate their prognostic role in intact tissues. Since MDSCs can revert to less immunosuppressive myeloid cells under certain conditions [41,42], inhibiting or reprogramming MDSCs may be a promising future cancer therapy approach [24,42,43].

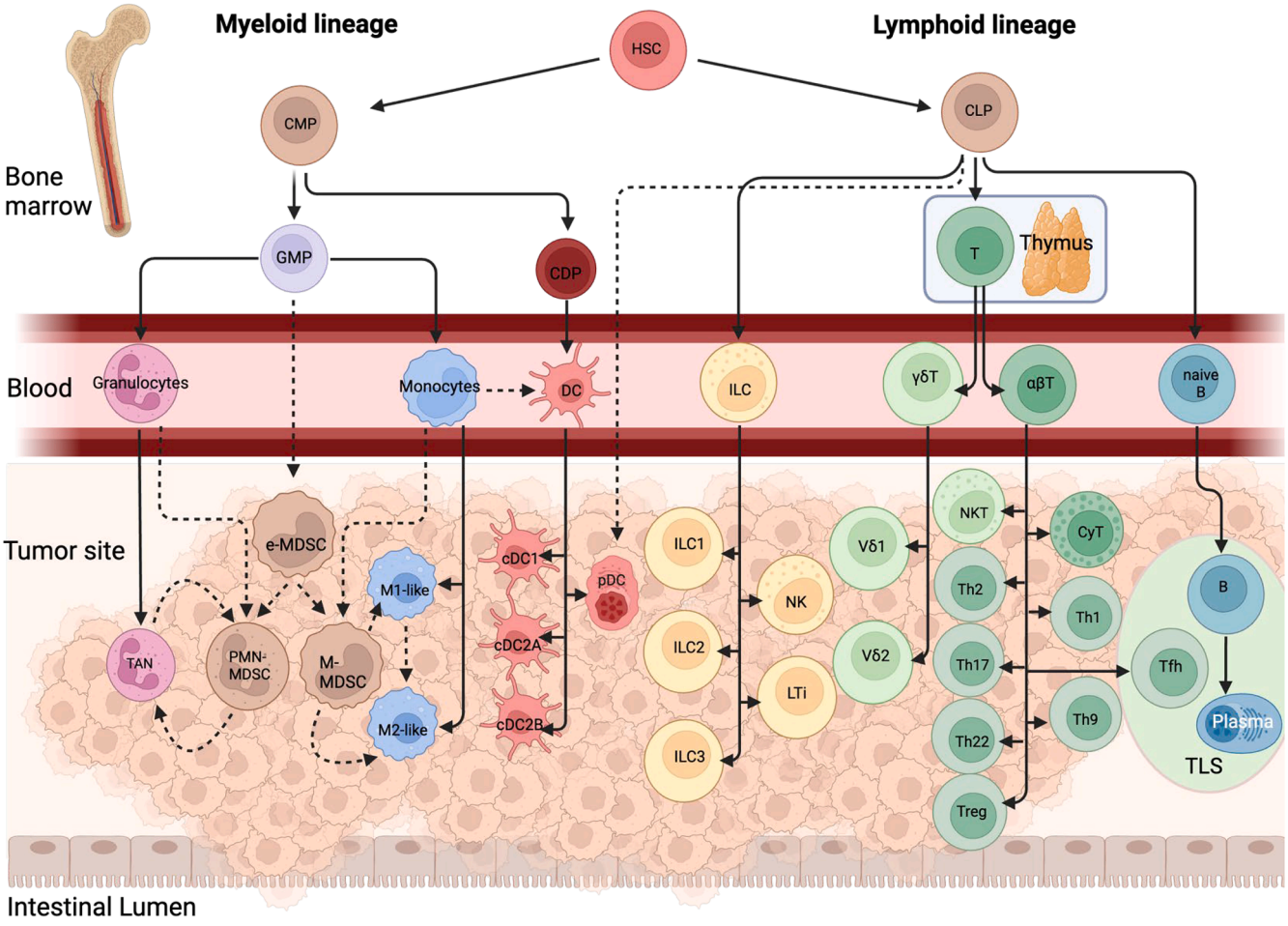

Fig. 1. Immune cell lineage development and tumor infiltration.
The schematic illustrates immune cell lineage development and the spectrum of tumor-infiltrating immune cells. Hematopoietic development takes place in the bone marrow, where the myeloid lineage develops from the common myeloid progenitor (CMP) and the lymphoid lineage from the common lymphoid progenitor (CLP). After entering blood circulation, immune cells distribute into lymphoid organs, as well as distant tissues such as the tumor microenvironment, guided by chemotactic signals. Immune cells differentiate into distinct subtypes depending on signals from other immune cells, lymphoid tissue, and tumor microenvironment. Solid line: primary development; dotted line: functional differentiation; HSC: hematopoietic stem cell; GMP: granulocyte-macrophage progenitor; CDP, common dendritic progenitor; T, T cells; DC, dendritic cells; ILC, innate lymphoid cells; $\gamma\delta$T: TCR$\gamma\delta^+$ T-cells; $\alpha\beta$T, TCR$\alpha\beta^+$ cells; B, B cells; TAN, tumor-associated neutrophils; e-MDSC, early-stage MDSCs; PMN-MDSC, polymorphonuclear MDSCs; M-MDSCs, mononuclear MDSCs; M1-like, M1-like macrophages; M2-like, M2-like macrophages; cDC, conventional dendritic cells; pDC, plasmacytoid dendritic cells; NK, natural killer cells; LTi, lymphoid tissue inducer cells; NKT, natural killer T cells; Th, T-helper cells; Treg, regulatory T cells; CyT, cytotoxic T cells; Tfh, follicular helper T cells; Plasma, plasma cells; TLS: tertiary lymphoid structure. Created with BioRender.com.

Macrophages

Under physiological conditions, macrophages play an important role as tissue-resident cells that perform pathogen phagocytosis and elimination and that regulate inflammation and fibrosis [44,45]. Macrophages can activate T cells by PRR-mediated pathogen phagocytosis and subsequent antigen presentation on MHC-II. They also orchestrate immune responses through the secretion of cytokines, chemokines, growth factors, and complement factors as well as through direct cell-cell interaction via cell surface receptors and ligands [45]. Macrophages have immune-activating and immune-suppressive properties while maintaining tissue clearance and homeostatic functionalities [44–46].

Tumor-associated macrophages (TAMs, Fig. 1) exhibit plasticity and functionality that are distinct from macrophages in healthy tissue [47–49]. TAMs are regulated by tumor cells, fibroblasts, extracellular matrix, metabolites, and numerous other factors in the microenvironment. They can initiate fibroblast and immune cell differentiation and can control tumor progression and metastasis [49]. Previously, literature classified TAMs as M1-like and M2-like macrophages based on their *in vitro* response to stimulation and release of cytokines and chemokines [50,51]. M1-like macrophages have pro-inflammatory and anti-tumor properties, while M2-like macrophages are tumorigenic and immunosuppressive [49,50]. Despite this *in vitro* identification strategy [52], many studies do not distinguish between M1-like and M2-like macrophages [53–56] and report that TAMs mainly contribute to tumor progression [53]. In CRC, TAM infiltration correlates with MSI tumors [35], good prognosis, and prolonged survival (Fig. 2) [53,57,58]. When considering specific TAM subtypes, many studies confirm the *in vitro* behavior and associate M1-like macrophages with favorable prognosis and M2-like macrophages with poor prognosis (Fig. 2) [59–61]. Other studies report that M2-like macrophages correlate with prolonged survival in CRC [62,63]. Since both M1 and M2 subtypes proportionally express the same type of biomarker, their differentiation may require multiple biomarkers to capture accurately the subtype polarity [64]. Therefore, a comprehensive lineage identification strategy that incorporates multiple biomarkers is necessary to describe macrophage polarity and unravel differences in their prognostic role in CRC [17,25,65].

In the last decade, many articles proposed improved terminology for TAMs that can reflect comprehensively the macrophage diversity

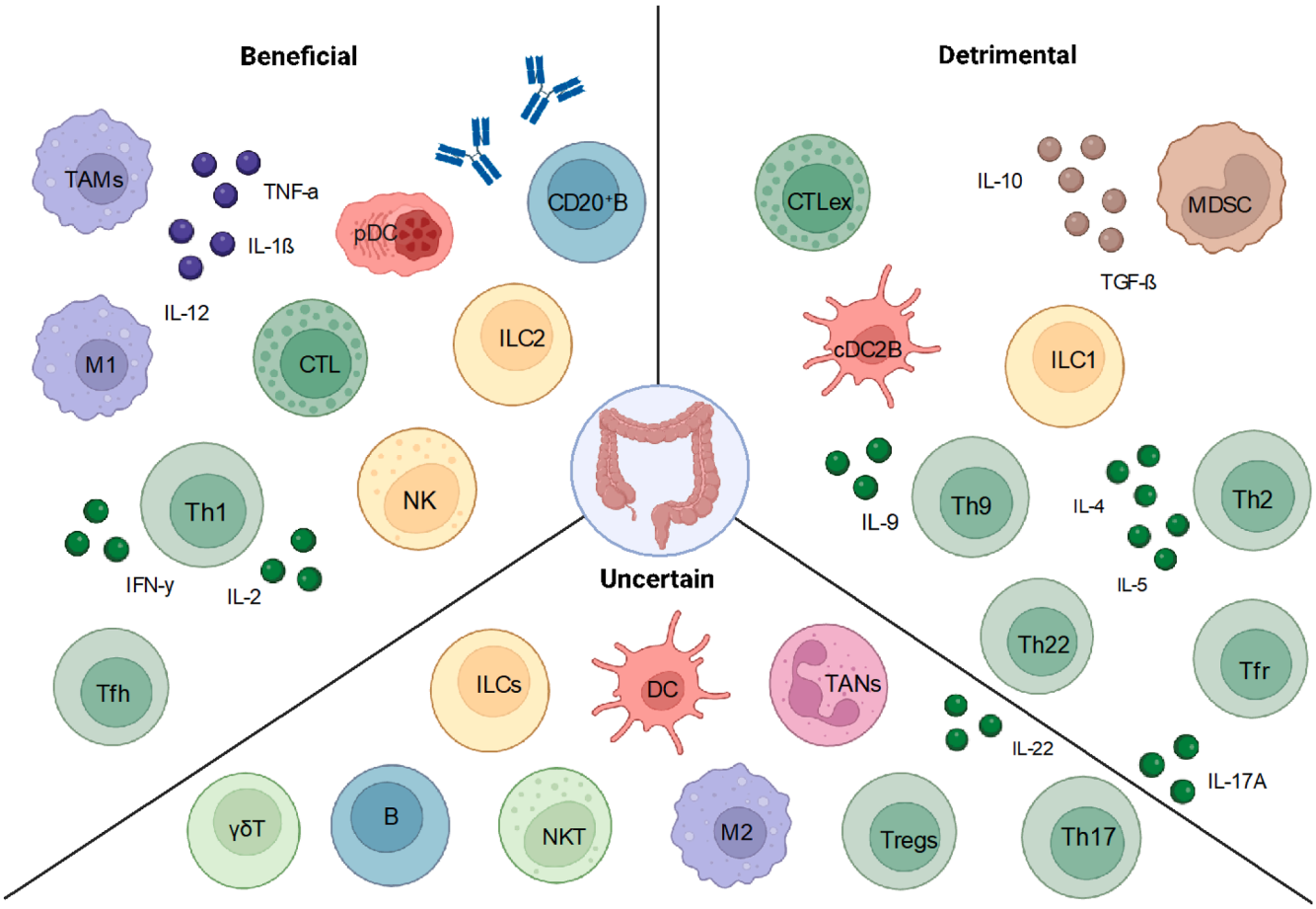

Fig. 2. Influence of tumor-infiltrating immune cells and their cytokines on progression and prognosis of CRC.
The figure illustrates the influence of tumor-infiltrating immune cells and cytokines on progression and prognosis of CRC. Immune cells that have been associated with good prognosis in colorectal cancer include tumor-associated macrophages (TAMs) broadly, M1-like macrophages, plasmacytoid dendritic cells (pDC), natural killer (NK) cells, cytotoxic T lymphocytes (CTLs), T-helper 1 (Th1) cells, follicular helper T cells (Tfh), and $CD20^+$ B cells. Type 2 innate lymphoid cells (ILC2) have antitumor effects in CRC. Immune cells that have been clearly associated with poor prognosis in CRC include myeloid-derived suppressor cells (MDSCs) and exhausted cytotoxic T lymphocytes (CTLex). Conventional dendritic cells type 2A (cDC2A), type 1 innate lymphoid cells (ILC1), Th2, Th9, Th22, and follicular regulatory T (Tfr) cells have tumor-promoting properties in CRC. Immune cells in the "uncertain" category have either been associated with both good and poor prognosis or have not been adequately described in the context of CRC prognosis or tumor progression. TANs: tumor-associated neutrophils; $\gamma\delta$T: TCR$\gamma\delta^+$ T-cells; B: B cells; NKT: natural killer T-cells; Tregs: regulatory T-cells. Created with BioRender.com.

existing outside of the M1/M2 classification [45,66–68]. In 2014, Murray et al. (2014) proposed a spectrum model for macrophage classification [68] that is translatable to both murine and human studies, considers macrophage origin, and offers uniform definitions with activation markers [68]. Recently, Ma et al. (2022) reviewed numerous publications on single-cell high-throughput technologies and proposed a new TAM terminology that divides macrophages into seven functional subtypes found in several malignancies: interferon-primed TAMs, immune regulatory TAMs, inflammatory cytokine-enriched TAMs, lipid-associated TAMs, pro-angiogenic TAMs, resident-tissue macrophages-like TAMs, and proliferating TAMs. They classified these TAM subtypes according to their transcriptomic and protein-expressing signatures [47]. These subtypes have also been found in CRC [47,69,70], but their prognostic role remains unknown and requires further investigation. We have compiled the protein markers in Table 1 for CRC-relevant TAMs and listed them according to historical as well as proposed nomenclature. As the library of TAM protein signatures increases, researchers can refine TAM terminology to investigate the individual behaviors of TAM subtypes more precisely and examine their prognostic role in CRC.

Dendritic cells

Dendritic cells are highly specialized APCs that integrate innate and adaptive immune responses [71]. They phagocytose pathogens in peripheral tissues, migrate to lymph organs, and activate adaptive immune cells by antigen-presentation. Dendritic cells present extracellular antigens via MHC-II and intracellular antigens via MHC-I, but some dendritic cells can also perform cross-presentation. Cross-presentation is a pathway by which a dendritic cell endocytoses an infected or pathologically altered cell to process the endocytosed cell's contents for eventual MHC-I presentation to a complementary $CD8^+$ cell. Cross-priming describes the successful interaction between the dendritic cell's MHC-I and the T cell's CD8 that leads to the induction of effector $CD8^+$ T cells for recognizing and destroying altered cells. Dendritic cells are functionally different from other immune cells and APCs; they also exhibit a unique developmental and phenotypic diversity [72–74], which allows them to be classified by their origin, phenotype, localization, and/or function [72]. Since the biomedical community has not yet recognized an official universal classification system for dendritic cells, ongoing studies use different classification strategies to propose new subtypes [73,75–78]. In terms of their origin, the majority of dendritic cells emerge from the myeloid lineage while the remaining

dendritic cells derive from either the lymphoid lineage or both lineages (Fig. 1) [71,73,79–81].

In this review, we classify dendritic cells based on their functional state to represent protein profiles (Table 1) which correlate with cellular interactions that may ultimately contribute to prognosis predictors. This paradigm encompasses two main groups of subtypes: the conventional dendritic cells (cDCs) and the plasmacytoid dendritic cells (pDCs) [71,79]. Within cDCs are two primary subtypes: cDC type 1 (cDC1) and cDC type 2 (cDC2) [79]. cDC1s specialize in cross-presentation and activate cytotoxic T cells via MHC-I while prominently expressing the surface molecules C-type lextin domain family 9 member a (CLEC9A) and X-C motif chemokine receptor 1 (XCR1). cDC2s further classify into cDC2A (or DC2) and cDC2B (or DC3), both capturing extracellular antigens and initiating $CD4^+$ T-helper cell responses via MHC-II [79]. While also carrying MHC-II [82], pDCs produce high amounts of Type I interferons (IFNs) [79] and secrete several more mediators that contribute to both pro- and anti-inflammatory processes [80,82]. Similarly, studies in human cancer have demonstrated both pro- and antitumor properties for dendritic subtypes [71]. For example, cDC1s correlate with favorable prognoses across several malignancies [71,83–87], while cDC2 subtypes exhibit varied prognostic associations—cDC2As promote tumorigenesis and cDC2Bs show antitumor properties [71]. Additionally, pDC infiltration often correlates with poor prognosis and adverse outcomes in cancer patients [71,88–92].

Early studies investigating CRC show conflicting correlations between dendritic cell tumor infiltration and prognosis that depend on co-infiltrating immune cells, maturation status, and general dendritic cell markers (Fig. 2) [93–97]. However, recent studies now incorporate dendritic subtypes into their analysis. A recent study from Kießler et al. correlated pDC infiltration with prolonged survival in CRC [98], while another study compared primary tumors with CRC liver metastasis using single-cell RNA sequencing analysis to find that DC3 (cDC2B) cells predominantly infiltrate liver metastasis [99]. By enhancing the library of biomarkers for dendritic subtype identification, future studies can incorporate diverse dendritic cell activity and functionality states that are suppressed by the TME [25,100]. These studies can enable future investigation of the dendritic subtype-related prognostic roles in CRC. Due to the dendritic cells' critical role in recognizing altered tumor cells by cross-presentation and in activating potent adaptive immune responses, future therapeutics may target the restoration of dendritic cell functionality for CRC therapy.

Neutrophils

Neutrophils are granulocytes derived from myeloid precursors in the bone marrow (Fig. 1) [101]. Neutrophils constitute the largest group of leukocytes in the blood and rapidly migrate into inflamed tissues in response to signaling from endothelial cells [101]. At the inflammatory site, they initiate an immune response by releasing antimicrobial enzymes, reactive oxygen species (ROS), and inflammatory cytokines. Neutrophils eliminate pathogens through PRR-mediated phagocytosis and through the release of ROS. A distinctive property of neutrophils is their ability to generate neutrophil extracellular traps (NETs) during programmed cell death (NETosis), which form a meshwork of proteins and nucleotide strands in the extracellular space. These NETs capture pathogens and facilitate their recognition and elimination by other immune cells.

Tumor-associated neutrophils downregulate their pro-inflammatory properties and enhance immunosuppressive abilities by secreting various mediators [102,103]. Tumor-associated neutrophils can increase the mutational burden of cancer cells by releasing oxidative enzymes [103] while promoting tumor progression and metastasis through the induction of angiogenesis and extracellular matrix remodeling [102,103]. At the tumor site, neutrophils undergo NETosis to shield cancer cells from a cytotoxic immune response [104,105]. Distant from the primary tumor site, neutrophil NETs can capture circulating cancer cells in the bloodstream to facilitate cancer cell migration and metastasis [106,107]. Despite these tumor-promoting properties, Fridlender et al. (2009) demonstrated that blocking transforming growth factor beta (TGF-β) signaling converts neutrophils into an anti-tumor phenotype [108], which eliminates cancer cells and initiates an effective immune response [103]. Building on this discovery, they categorized tumor-associated neutrophils into N1 and N2 neutrophils in a manner similar to the M1/M2 polarization of macrophages. N1 neutrophils produce pro-inflammatory chemokines and cytokines that counteract tumor growth while N2 neutrophils exhibit anti-inflammatory properties that support tumorigenesis [108]. Moreover, another study revealed that interferon beta (IFN-β) converts N2 neutrophils back to the N1 phenotype [109]. These findings underscore the dynamic polarization of tumor-associated neutrophils and suggest potential paths for developing novel immune-modulating therapies.

Depending on their localization, circulating neutrophils can be distinguished from tumor-infiltrating neutrophils. Most cancer studies have focused on the prognostic role of circulating neutrophils using the neutrophil-to-lymphocyte ratio, which directly correlates with worse prognosis in multiple cancers [102,110–112] including CRC [102,113–116]. However, the role of tumor-infiltrating neutrophils in CRC is uncertain. One CRC study reported that tumor-infiltrating neutrophils correlated with poor prognosis [117], while other studies associated high neutrophil infiltration with good prognosis (Fig. 2) [118,119]. These results highlight the need to differentiate between tumor-infiltrating neutrophil subtypes to assess their significance in CRC.

Since the N1/N2 classification lacks human protein markers [102], one must distinguish neutrophil subtypes by combining common neutrophil markers with novel biomarkers. Other studies have identified distinct infiltrating neutrophil subtypes in liver cancer and non-small cell lung cancer by incorporating biomarkers that have been found in single-cell RNA profiles [120,121]. Another group combined CD206—a negative prognostic biomarker in macrophages [122]—with common neutrophil markers to differentiate between neutrophil subtypes in pancreatic cancer (Table 1) and found that $CD206^-$ neutrophils were associated with good prognosis while $CD206^+$ neutrophils were linked to poor prognosis [123,124]. In translating these approaches to CRC, future studies will aim to capture the diverse functionality of tumor-infiltrating neutrophils, enhance neutrophil subtype classification in human specimens, and elucidate the prognostic significance of neutrophils in CRC.

Lymphoid Lineage

The lymphoid compartment develops from the common lymphoid progenitor in the bone marrow and includes innate as well as adaptive cell types (Fig. 1). Innate lymphoid cells (ILCs) lack canonical adaptive antigen receptors and—similar to myeloid cells—react against a broad spectrum of intracellular and extracellular pathogens. ILCs include natural killer (NK) cells, helper-like ILCs (ILC1s, ILC2s, ILC3s), and lymphoid tissue inducer cells (LTis). In contrast, adaptive lymphocytes specifically bind to a corresponding antigen, induce antigen-specific immune responses, and maintain antigen-specific memory. Adaptive lymphoid cells include T-lymphocytes (T cells) and B-lymphocytes (B cells).

While adaptive immune responses typically start in lymph nodes with lymph follicles as the center of B cell activation and maturation, lymph follicle-like formations, known as tertiary lymphoid structures, can also be found near the tumor site. Within these lymphoid structures, dendritic cells interact with follicular helper T cells (Tfh) and B cells [125] to initiate an adaptive immune response by priming, maturating, and activating lymphocytes [126]. Tertiary lymphoid structures have also been found in colorectal tumor tissues [125,127] and are associated with a favorable prognosis [125,126,128,129].

Innate lymphoid cells

ILCs are a population of T-like cells that differ from adaptive immune cells by a lack of recombinant antigen receptors (Table 2) [130–132]. However, ILCs share properties with T cells; helper-like ILCs have similar properties to $CD4^+$ T helper cells, while NK cells share cytotoxic properties with $CD8^+$ T cells [130]. The leading nomenclature of ILCs defines functional subtypes based on secreted mediators, and this nomenclature divides these cells into three groups. Group 1 ILCs include ILC1s and NK cells that release Th1-related IFN-y without secreting Th2 and Th17 related cytokines; Group 2 ILCs include ILC2s, which are defined by their secretion of Th2-related cytokines such as IL-5 and IL-13; and Group 3 ILCs include LTi and ILC3 cells, which release Th17-related cytokines such as IL-17 and IL-22 [132].

Tumor-infiltrating ILCs exhibit both pro- and anti-tumor properties that depend on external signals, which can alter the tumor-promoting effect of each ILC subtype and stimulate the transition into other ILC subtypes [133]. For example, NK cells differentiate into ILC1s after being stimulated through TGF-β signaling [134], highlighting the plasticity of ILCs within the tumor microenvironment [133]. This plasticity is also evident in CRC, where distinct ILC subtypes differ from healthy gut ILCs in gene expression, tumor stage association, and functional features [135]. Researchers showed that the ratio of ILC3 infiltration shifts in favor of ILC1 infiltration in CRC tumors compared to healthy tissue [135,136], suggesting that decreased ILC3 presence along with increased ILC1 presence may contribute to CRC tumorigenesis or be a reaction to the progressing TME.

Although ILC subtypes are present in CRC, their prognostic significance remains uncertain (Fig. 2) because many identification strategies do not make use of standardized classification. For example, NK cells [137,138] and some ILC subtypes are associated with a favorable prognosis, including ILC2s [139] and signaling lymphocytic activation molecule family member 1 $(SLAMF1)^+$ ILCs [135]. However, NK cell markers like CD56 and CD57 are also expressed by other ILCs [132,140]. Many studies focus on the tumor effects of ILC-related cytokines, although it remains unclear whether their molecular effects on CRC tumors are either exclusive to ILCs or result from the broader activity of cell groups with similar abilities [141]. In an attempt to address this uncertainty, Shembrey et al. (2023) derived a novel NK cell classification specifically for human CRC that is based on exclusive gene signatures that correlate with a good prognosis [142]. Future studies that expand classifications to all ILCs must incorporate functional properties as well as the lack of recombinant antigen receptors to clearly differentiate and examine the prognostic role of ILC subtypes from other immune cells in CRC.

T-lymphocytes

T-lymphocytes (T cells) mature in the thymus of the young individual (Fig. 1), from where they travel to distant tissues and lymphoid organs. T cells belong to the adaptive immune system because of their antigen-specific surface receptors called T cell receptors (TCRs), which mediate antigen specific immune memory. The main group of TCRs consists of alpha and beta chains (TCR$\alpha\beta$, Table 2) and binds to complementary antigens that are presented on MHC by immune and non-immune cells. Depending on the co-receptor, TCR$\alpha\beta^+$ cells bind either to MHC-I (via CD8 on cytotoxic T cells, CTLs) or to MHC-II (via CD4 on T-helper (Th) cells), respectively. Another small population of T cells express a distinct class of TCR with a gamma and a delta chain (TCR$\gamma\delta$), which can recognize specific antigens independent of MHC I or II. In recent decades, numerous studies have investigated the role of T cells in cancer and demonstrated both T cell pro- and anti-tumor characteristics depend on their phenotype and function. T cell subtypes also infiltrate CRC tumors, where they show variable impact on tumor progression and patient outcomes depending on their phenotype [17,127,143,144].

TCR$\alpha\beta^+$ $CD8^+$ cytotoxic T cells

TCR$\alpha\beta^+$ $CD8^+$ cytotoxic T-lymphocytes (CTLs) recognize altered antigens that are presented on MHC-I by APCs, non-immune cells, and cancer cells. After being primed by a presented cognate antigen, the $CD8^+$ T cell recognizes the same antigen, becomes activated, and releases several cytotoxic enzymes to induce apoptosis in the target cell. Activated CTLs also release cytokines to enhance NK cell responses and recruit macrophages, which leads to a coordinated immune defense. Over the past three decades, CTLs have been considered the strongest effectors in anti-cancer immunity, and several immunotherapies were developed to target their surface proteins or synthetically modify their receptors to enhance anti-tumor activities [145]. Galon et al. (2006) were the first to identify distinct tumor-infiltrating lymphocytes in CRC that predict clinical outcomes. They demonstrated that high infiltration of $CD8^+$ T cells correlates with prolonged survival in CRC patients [146, 147] independently of tumor stage or MSI status [18]. Since then, several studies have been investigating the role of infiltrating CTLs in CRC and confirmed their strong correlation with favorable outcomes in CRC (Fig. 2) [18,148].

However, $CD8^+$ T cells can show a dysfunctional cell state characterized by expression of several immune checkpoint molecules [149–151], which negatively correlates with good prognosis in CRC [148]. This exhausted cell state is associated with advanced stage and liver metastasis [99,152] and suggests that CTL functionality is influenced by the TME. Immune checkpoint therapies prevent the interaction of checkpoint proteins to enable the normalization of CTL functionality and the restoration of an effective immune response within the tumor tissue [153]. Hence, these inhibitors show a therapeutic response especially in CTL-infiltrated tumors like MSI and DNA polymerase epsilon (POLE)-mutated CRC tumors that contain a high neoantigen load [14,154]. Future studies on infiltrating CTLs in CRC will ideally consider both cell lineage markers (Table 2) as well as activity and immune checkpoint protein markers (Table 3) to capture CTL functional states and exhaustion. Additional insights into the functional diversity of CTLs may identify novel CTL subtypes and enable the characterization of individual subtype contribution to CRC outcomes.

TCR$\alpha\beta^+$ $CD4^+$ T-helper cells

Unlike $CD8^+$ T cells, TCR$\alpha\beta^+$ T-helper (Th) cells use CD4 surface molecules as a coreceptor to bind antigens on MHC-II receptors, which are exclusively expressed by antigen presenting cells such as dendritic cells, macrophages, and B cells. When a naïve $CD4^+$ T cell is primed by an APC and recognizes its cognate antigen presented by a B cell, the Th cell releases several cytokines that activate the B cell, which leads to downstream antibody production and a targeted immune response. Th cells can be divided into distinct subtypes by their expressed transcription factors and secreted cytokines (Table 2, Fig. 1) that mediate different tumor-effects and are associated with prognosis.

Th1 cells can be distinguished from other T cells by the transcription factor T-box 21 expressed in T cells (T-bet). Th1 cells secrete signaling molecules IFN-γ, tumor necrosis factor alpha (TNF-α), and interleukin 2 (IL-2), which are associated with induction of apoptosis in cancer cells and recruitment of $CD8^+$ T cells. Th1 cell infiltration in CRC is consistently correlated with good prognosis (Fig. 2) [18,31,146,147].

Th2 cells express the transcription factor GATA-binding protein 3 (GATA-3) and secrete IL-4 and IL-5, which correlate with chronic inflammation and cancer progression [155]. Although Th2 cells are associated with distinct prognostic effects in several cancers [127, 156–161], few studies have investigated Th2 cell infiltration in CRC (Fig. 2) [147,162,163]. While a gene expression study by Tosolini et al. (2011) demonstrated strong correlations between Th1 profiles, Th17 profiles, and prognoses, they reported no predictive findings for Th2 infiltration [147]. Further studies demonstrated that Th1 cells can shift their phenotype to Th2 cells and promote cancer progression [163,164], suggesting that Th2 cells may contribute to the adenoma-carcinoma-sequence [165]. Future studies may identify

Table 3
Novel Immune Checkpoint Proteins: Prognostic Association in CRC and Clinical Trials.

Prognostic Association	ICP/Target	Eligibility	Phase	Status	NCT number	Last Updated
Detrimental	TIGIT	Advanced malignancies including MSS-CRC [250]	I	Recruiting	NCT04354246	2024
		LARC [251]	II	Active	NCT05009069	2024
	LAG-3	Advanced solid tumors including MSS-CRC [252]	I	Completed	NCT03250832	2024
		Advanced solid tumors including CRC [253]	I	Completed	NCT03849469	2023
		Advanced solid tumors including MSI-CRC [254]	I	Completed	NCT03538028	2020
		Advanced solid tumors including MSS-CRC [255,256]	II	Completed	NCT02720068	2024
		Localized or locally advanced MSI-CRC [257]	II	Recruiting	NCT06205836	2024
		Early-stage colon cancer [258]	II	Recruiting	NCT03026140	2024
		Advanced MSS-CRC [259]	II	Active	NCT03642067	2024
	TIM-3	Advanced CRC [260]	I	Recruiting	NCT06010901	2024
		Advanced solid tumors [261]	I	Recruiting	NCT02817633	2024
Beneficial	ICOS	N/A for CRC				
	VISTA	N/A for CRC				
	OX40	Advanced malignancies [262]	I/II	Completed	NCT03241173	2022
Controversial	BTLA	Advanced solid tumors including CRC [263]	I	Recruiting	NCT05789069	2023
		Advanced solid tumors including MSI-CRC [264]	I	Recruiting	NCT05427396	2022

The table provides a list of ongoing clinical trials targeting novel immune checkpoint proteins (ICPs), grouped by the prognostic association in CRC.
Abbreviations: ICP, immune checkpoint protein; NCT, national clinical trial; TIGIT, T-cell-Ig-and-ITIM-domain; MSS-CRC, microsatellite-stable colorectal cancer; LARC, locally advanced rectal cancer; LAG-3, Lymphocyte activation gene 3; CRC, colorectal cancer; MSI-CRC, microsatellite-unstable colorectal cancer; TIM-3, T cell immunoglobulin and mucin-domain containing-3; ICOS, Inducible T-cell co-stimulator; N/A, not available; VISTA, V-domain Ig-containing suppressor of T cell activation; OX40, Tumor necrosis factor receptor superfamily, member 4; BTLA, B- and T-lymphocyte attenuator.

biomarker molecules that classify Th2 cells into subtypes, which may refine our understanding of the role of Th2 cells in CRC.

Th9 cells are characterized by secretion of IL-9 and the expression of transcription factor PU.1. Th9 cells were recently recognized in cancer immunity and CRC [166,167]. One study reported that Th9 cells infiltrate CRC tumors and are correlated with high infiltration of $CD8^+$ T cells and PD-1 expression [168]. Another study discovered infiltrating Th9 cells in colitis-induced CRC, which suggests a tumor-promoting role due to the secretion of IL-9 (Fig. 2) [169]. Since other Th cells secrete IL-9 and express PU.1, the exact identification of Th9 cells remains challenging and their prognostic role in CRC is unknown.

Th17 cells are distinguished from other T cells by the transcription factor RAR-related orphan receptor gamma 2 (RORyt) and the secretion of IL-17 family cytokines [170,171]. In CRC, Th17 cells are often associated with poor prognosis (Fig. 2) [147] due to the pro-inflammatory and tumor-promoting role of IL-17A [172–175]. For example, MSS CRC tumors with low levels of IL-17A show an increased response to anti-PD-1 therapy in comparison to tumors with high levels of IL-17A [176]. Another study demonstrated that simultaneous anti-IL-17 and anti-PD-1 therapy decreased tumor growth and improved survival in mice with MSS CRC [177]. Besides IL-17A, Th17 cells can also secrete IL-17F, which has anti-tumor effects [178] and may contribute to recent findings suggesting that Th17 cells enhance CTL infiltration and correlate with better outcomes in CRC [179]. Since IL-17 cytokines are not exclusively produced by Th17 cells [173,180,181], more refined Th17 identification strategies are needed to examine their role in CRC.

Th22 cells differentiate from naïve T-cells by upregulating aryl hydrocarbon receptor (AHR), a transcription factor responsible for IL-22 production [182]. IL-22 is reported to promote cancer proliferation and is associated with progression in CRC [183,184]. Th22 cells infiltrate CRC tumors, and their density gradually increases as the tumor progresses to advanced stages [184,185]. This suggests that either Th 22 infiltration is caused by an altered TME or the tumor progression is caused by IL-22 production [184,185]. In contrast to these findings, a separate study reported that IL-22-producing T cells were associated with better outcomes in CRC patients and demonstrated that IL-22 recruits advantageous neutrophils with anti-tumor capabilities [186]. Similar to IL-17, IL-22 is not specific to Th22 cells [186]. Further studies are needed to refine the prognostic role of Th22 cells in CRC (Fig. 2).

Regulatory T cells (Tregs) express the IL-2 receptor alpha-chain (CD25) and the transcription factor forkhead box P3 (FoxP3) [187]. Using biomarkers such as CD45RA, Helios, and neuropilin-1 (Nrp1), Tregs can be further divided into subtypes [187]. Tregs release several immunoregulatory cytokines [187], and these cells can correlate with both good and poor prognosis in different cancers [188]. A systematic review of tumor-infiltrating Tregs reported that Tregs in CRC are often associated with prolonged survival and better outcomes [188]. Despite this beneficial association, many studies underline the prognostic heterogeneity of Tregs in CRC [99,189–192]. One study found that higher Treg infiltration in KRAS-mutated CRC correlates with poor prognosis [193]. Tregs promote tumor progression [191] and decrease the infiltration of favorable $CD8^+$ T cells into the tumor [191,194] when exhibiting a Th17-like profile and producing IL-17. Tregs with high expression of CD39 correlate with poor prognosis in CRC independently of MSI status or tumor stage [189]. Another study described two different prognostic $CD45RA^-$ $FoxP3^+$ Treg subtypes in CRC: Tregs with high expression of FoxP3 are associated with poor prognosis; low expression of FoxP3 is associated with good prognosis [192]. These results highlight that Tregs are diverse and exhibit different functions and phenotypes. The application of new markers to distinguish Treg subtypes may enable future studies to more clearly define and validate their prognostic role in CRC.

Follicular helper T-cells (Tfh) orchestrate the germinal center in tertiary lymphoid structures while supporting adaptive anti-tumor immune responses through B cell activation and antibody development (Fig. 1) [195]. Tfh cells exhibit the transcription factor B cell lymphoma 6 (Bcl-6) and the surface receptor C-X-C chemokine receptor type 5 (CXCR5) [196]. CXCR5 is necessary for migration into the germinal center and is also expressed by naïve and differentiating B cells [197–199]. In CRC, Tfh cells correlate negatively with tumor progression and are associated with better prognosis (Fig. 2) [200–203]. Another subpopulation of Tfh cells are considered follicular regulatory T cells (Tfr) because they additionally express FoxP3 [204]. Tfr cells exhibit tumor-promoting capabilities and can inhibit the formation of tertiary lymphoid structures [204,205], which can lead to a pro-tumor immune shift in CRC (Fig. 2) [206].

The functional diversity and overlap among different Th subtypes suggests that Th subtypes may be accurately displayed by a spectrum model rather than a sharp separation of Th subtypes. Future studies may use an identification strategy for Th cells that simultaneously incorporates lineage markers and functional markers to examine whether the subtype or the functional state contributes to CRC prognosis.

Natural Killer T cells

Natural Killer T (NKT) cells combine features of NK cells and T cells [207], expressing markers like CD56 (NK cell-associated) and CD3 (T

cell-associated, Table 2) [207]. These cells possess an invariant $\alpha\beta$TCR and an MHC I-like receptor called CD1d, which can recognize lipid antigens such as sphingolipids and microbial lipid-like antigens [208]. Unlike conventional T cells, NKT cells—like innate lymphocytes—can rapidly release cytokines upon antigen recognition, which quickly eliminates pathogens and attacks altered cells. NKT cells have also demonstrated cytotoxicity against human CRC cell lines [209].

Few studies have explored the prognostic role of NKT cells in CRC patients. Gharagozloo et al. (2018) found reduced abundance of circulating NKG2D$^+$CD56$^+$ NKT cells in metastatic CRC [210]. Another study linked circulating CD16$^+$ NKT cells to shorter disease-free survival [211]. In contrast, Tachibana et al. (2005) investigated tumor-infiltrating NKT cells in CRC [212], revealing that a specific Vα24$^+$ NKT subtype is associated with reduced lymph-node invasion and prolonged overall survival [212]. Recent research also correlated PD-1 expression on tumor-infiltrating NK and NKT cells with prolonged survival in CRC patients [213]. These findings suggest diverse prognostic roles for NKT cells in CRC (Fig. 2) that are largely influenced by co-expressed markers. Future studies must identify distinct NKT subtypes and differentiate between marker-related and NKT cell-specific prognostic impacts in CRC.

TCR$\gamma\delta^+$ T cells

A subset of T cells, known as $\gamma\delta$T cells, possesses a TCR with a γ and a δ chain. This oligoclonal receptor allows $\gamma\delta$T cells to detect minimal mutational and metabolic changes in cancer cells independently of MHC. De Vries et al. (2023) confirmed that $\gamma\delta$T cells are highly reactive against human CRC cells that contain a β2-microglobulin (B2M) mutation, which leads to MHC-I loss [214]. They also showed that MMR-deficient B2M-mutated CRC tumors with high $\gamma\delta$T cell infiltration respond to anti-PD-1 therapy [214].

While $\gamma\delta$T cell infiltration correlates with a good prognosis in many tumors [22], the prognostic role in CRC remains uncertain (Fig. 2) [215]. This variability likely stems from the diverse functionality and phenotypes of $\gamma\delta$T cells. Researchers categorize $\gamma\delta$T cells based on different δ-chains into Vδ1, Vδ2, and a very small group of Vδ1$^-$Vδ2$^-$ cells (Table 2). Further distinctions within these subtypes arise from the γ-chain. In CRC, Vδ1 cells with a diverse gamma chain repertoire [216] and Vδ2 cells with γ chain 9 (Vγ9Vδ2) are most common [217].

Earlier studies primarily linked the prognostic role of $\gamma\delta$T cells to δ-chain subtypes: Vδ1 subtypes are often immuno-suppressive and tumorigenic, while Vδ2 subtypes are cytolytic and anti-tumor [218]. In particular, Vγ9Vδ2 cell infiltration has been associated with favorable CRC prognosis [219,220]. However, recent studies challenge this view as more $\gamma\delta$T subtypes emerge that do not fit into this pattern. For example, Mikulak et al. (2019) reported that Vδ1 cells expressing NKp46 exhibit cytotoxic activity and correlate with reduced risk of metastasis in tumor-free CRC patients [221]. Reis et al. (2022) demonstrated in a murine model that the anti-tumor and pro-tumor capabilities of $\gamma\delta$T cells depend on the γ-chain, not the δ-chain [222]. They found that early stage human CRC is infiltrated by anti-tumor $\gamma\delta$T cells, whereas late stage CRC is dominated by tumor-promoting $\gamma\delta$T cells [222]. These findings suggests that the TME influences $\gamma\delta$T cell functionality, pushing them toward a pro-tumor phenotype as the tumor progresses [215,216,223]. Meraviglia et al. (2017) confirmed that both Vδ1 and Vδ2 exhibit more tumor-promoting properties in CRC compared to healthy tissues [216]. Potential underlying subtypes include IL-17-secreting and CD39-expressing $\gamma\delta$T cells, both linked to cancer progression in CRC [216,224,225]. These findings highlight that $\gamma\delta$T cells exhibit diverse tumor-effective properties, which are dependent upon the combination of γ-chains with co-expressing markers. By incorporating chain subtypes, functional states, and biomarker expression into a spectrum model, researchers may refine the prognostic role of $\gamma\delta$T subtypes in CRC.

B-lymphocytes

B-lymphocytes, or B cells, are adaptive immune cells that develop in the bone marrow (Fig. 1). After a rigorous maturation process, naïve B cells move to peripheral lymphoid organs, where they bind to foreign antigens or neoantigens. When co-stimulated by other immune cells, B cells activate, proliferate, undergo somatic hypermutation and affinity maturation, class switch, and differentiate into plasmablasts or longer-lived memory B cells or plasma cells to produce high-affinity antibodies that trigger antigen-specific humoral and cellular immune responses. B cells also perform antigen presentation, secrete cytokines, and form antigen-specific memory.

B cell subsets are categorized based on their development and differentiation stages, and each have unique phenotypic markers and functions (Table 2) [226]. Common subtypes include naïve B cells, non-switched memory B cells, switched memory B cells, germinal center B cells, regulatory B cells, plasmablasts, and plasma cells [226]. These subtypes are often found in tumors with their frequency and function closely linked to the presence and maturation of peritumoral tertiary lymphoid structures as well as favorable outcomes in various malignancies [226,227].

A meta-analysis on tumor-infiltrating B cells in solid malignancies found that B cells are associated with reduced cancer progression and favorable prognosis in CRC (Fig. 2) [227]. However, many studies use CD20 as a surface marker to study B cell infiltration [227], which does not differentiate between B cell subsets [226]. Moreover, CD20 is not expressed on plasma cells [228], which underlines that B cell studies need to use either CD19 (Table 2) or multiple biomarkers to also include plasma cells in their analyses.

The distribution of B cell subtypes can change in the tumor environment, and some can even exhibit pro-tumor properties. A recent study using single-cell RNA sequencing identified five distinct CRC-infiltrating B cell subsets (naive B cells, germinal center B cells, memory B cells, immunoglobulin A (IgA) plasma cells and immunoglobulin G (IgG) plasma cells) and observed a shift from IgA to IgG plasma cells within tumors compared to healthy tissues [229]. A subset of activated IgG plasma cells, called the immature plasma cell population alpha, exhibits an incomplete IgG and correlates with CRC-related liver metastasis [230]. Additionally, exhaustion gene-expressing B cells are associated with poor CRC prognosis [231]. These studies show that gene expression analysis can help identifying novel B cell subtypes and biomarkers that correlate with CRC prognosis.

Another subset of B cells, called regulatory B cells, are recognized for their ability to secrete immunosuppressive cytokines [232]. The most common cytokine secreted by these regulatory B cells is IL-10, which exerts suppressive effects on T cells [232]. Regulatory B cells represent a functional group of B cells rather than a lineage phenotype due to overlapping surface markers with different B cell lineages [233], such as memory B cells, immature B cells, and plasmablasts [232]. To define regulatory B cells more precisely, one study analyzed whole-genome datasets and isolated IL-10-secreting regulatory B cells using the marker profile CD19$^+$CD73$^-$CD25$^+$CD71$^+$ (Table 2) [234]. Shankar and colleagues confirmed that this regulatory B cell phenotype suppressed CD4$^+$ T cells [235]. This study also demonstrated that the suppressive property of this regulatory B cell was not dependent on IL-10 secretion but the expression of TIM-1 and CD154 [235]. In CRC, Wang et al. (2022) identified a regulatory B cell subtype that expresses leucine-tRNA-synthetase-2, a mitochondrial enzyme sensitive to the amino acid leucine [236]. This regulatory B cell subtype exhibited TGF-β1-regulatory properties and correlated with tumor growth as well as reduced survival in CRC. The same study also showed that a leucine-rich diet, often suggested for cancer patients, increases the activity of leucine-tRNA synthetase-2 in these cells [236]. This highlights a potential clinical translation of immune-linked enzymatic mechanisms to improve treatment approaches for CRC patients.

Immunotherapy Response and Resistance in CRC

The functional diversity of adaptive immune cells drives tumor defense and tumor progression, and only functional T cells with competent anti-tumor properties can prevent tumor growth. Metabolic changes, stroma, and cancer cells within the TME affect T cell differentiation and function. Under the influence of the TME and with advancing tumor stage, T cells increasingly develop a dysfunctional state leading to exhaustion [151,237], which disables them from attacking cancer cells properly. Under physiological conditions, immune cells and healthy tissue regulate T cell responses by targeting specific surface proteins called immune checkpoint proteins (ICPs), which either enhance immune activation or trigger cell inhibition and exhaustion [238].

Cancer cells exploit these key immunoregulatory mechanisms and target ICPs as an adaptation to evade immune surveillance and attack [239,240], which led researchers to group these as 'adaptive immune resistance' (AIR) mechanisms [21]. The most well-known AIR mechanism is the PD-1/PD-1-ligand (PD-L1) pathway, where tumor cells express PD-L1 in order to escape T cell surveillance. Since PD-L1 is uniquely found in tumor tissue following the infiltration of activated T cells [21,241], specifically targeting this pathway for treatment (anti-PD therapy) can modify the immune surveillance within tumors without altering the systemic immune response [21]. Although clinically implemented anti-PD therapy shows sufficient and curative response in a subset of patients with advanced solid tumors [21], only 5% of patients with advanced CRC benefit from anti-PD therapy [242].

In 2012, Taube et al. demonstrated that metastatic melanoma patients showed prolonged overall survival when PD-L1 expression was present in tumors with lymphocyte infiltration [241]. They proposed that inflamed tumors must simultaneously express PD-L1 in order to respond to immune checkpoint inhibition sufficiently [241] and eventually developed the Tumor Immunity in the MicroEnvironment (TIME) classification to categorize cancers by tumor-infiltrating lymphocytes (TILs) and PD-L1 expression [243]. They identified four subtypes, which were designated as TIME I (PD-L1$^-$, TILs$^-$), TIME II (PD-L1$^+$, TILs$^+$), TIME III (PD-L1$^-$, TILs$^+$), and TIME IV (PD-L1$^+$, TILs$^-$) [243] to describe distinct anti-PD therapy responses and resistance mechanisms [21]. As an example of classification, TIL-infiltrated PD-L1-expressing tumors are defined as TIME II tumors and should theoretically respond to anti-PD therapy. The other subtypes would be unlikely to respond to anti-PD therapy due to the lack of either one or both anti-PD targets, which is termed target-missing resistance.

In CRC, 14% of the tumors exhibit a TIME II subtype, while the remaining 86% of CRC tumors lack at least one target [21]. Hamada et al. used a Cox proportional hazards model to assess the predictive value of TIME in 812 CRC tumors by comparing them with clinical outcomes [244]. They found that TIME subtypes could not predict survival rates but demonstrated that lymphocyte-infiltrated subtypes (TIME II and III) correlated with prognostic factors such as MSI status [244]. These findings were consistent with the first clinical trial, showing that MSI colorectal tumors sufficiently responded to the PD-1 inhibitor pembrolizumab [4]. An immunohistochemical examination of untreated specimens of this trial showed that tumor-infiltrating CD8$^+$ lymphocytes were associated with MSI status and a favorable treatment response [4]. A further study confirmed that PD-1$^+$ CD8$^+$ lymphocytes in the tumor may predict anti-PD-1 therapy response in CRC, whereas PD-L1 expression did not significantly correlate with treatment response [14].

Although PD-L1 expression could not be identified as a sole predictor for anti-PD-1 therapy response, it may play a significant role in combination with other predictors [21]. Two independent case studies analyzed untreated tumor tissue of anti-PD therapy responders and found that both tumor microenvironments expressed PD-L1 before therapy induction [154,245]. The tumor of the first case, a patient with MSI CRC, expressed PD-L1 on lymphocytes, tumor-infiltrating macrophages, and rare tumor cells that were closely related to PD-1$^+$ CD3$^+$ T cells [245]. In contrast, the second patient had an MSS CRC tumor bearing a POLE mutation, which expressed PD-L1 mainly on non-tumor cells that were in proximity to PD-1$^+$ CD8$^+$ T cells [154]. Together, these studies suggest that a combined analysis of TIL infiltration *and* PD-L1 expression can enhance our understanding of anti-PD therapy response in CRC.

In recent years, numerous prognostic ICPs have been discovered and novel immunotherapeutic agents target these ICPs in Phase I and II clinical trials for CRC (summarized in Table 3). Therefore, physicians need to select from an increasing number of immunotherapeutic options over the next decade to optimally treat an individual CRC patient [21]. Clinical decision-making can potentially be improved by incorporating the overall picture of AIR pathways within an individual tumor because several distinct AIR mechanisms can contribute to tumor progression and therapeutic response [17,21]. By enhancing our understanding of AIR mechanisms, we can expand our repertoire of AIR pathways while investigating and creating CRC tumor-specific AIR profiles. These AIR profiles can lead to both the identification of novel clinically relevant ICPs as potential therapeutic targets and the improvement of predictive classification systems (e.g. TIME) for CRC patients.

Conclusion

Tumor-infiltrating immune cells contribute distinctly to CRC progression and prognosis. Lymphoid cells often support effective immune surveillance and are associated with favorable prognosis while available immunotherapies target the PD-1/PD-L1 pathway in MSI CRC tumors. This contrasts with recent findings on myeloid cells, which often promote tumor growth and lymphocyte exclusion, especially in tumors that have innate immune infiltration, such as MSS tumors. To develop effective immunotherapy for MSS CRC tumors, researchers need to further understand molecular mechanisms of cancer-myeloid interactions and myeloid-related immune resistance.

In order to characterize intercellular tumor mechanisms more precisely, studies need to create extensive multi-cellular and functional CRC tumor profiles from which immune phenotypes and adaptive immune resistance profiles can be derived. Although previous studies have identified core immune cell subtypes and biomarkers, ongoing research must revise traditional cell definitions to capture dynamic surface marker expression. The study of multi-cellular functional CRC profiles requires comprehensive biomarker panels that enable the differentiation of numerous cell subtypes and their functional states. In this review, we analyzed protein biomarkers for the myeloid and lymphoid lineages to enable the differentiation of immune cells in the tumor microenvironment of CRC. Ultimately, we envision the application of these panels to single-cell technologies for identification of key prognostic cell types, creation of CRC-specific immune profiles, and refinement of clinical staging systems.

Cutting-edge multi-omics technologies with single-cell resolution have revolutionized tumor immunology by creating holistic multicellular tumor profiles [246]. These technologies combine genetic, epigenetic, transcriptomic, proteomic, and/or metabolomic data to establish novel and more precise cell definitions. Spatial multi-omics can additionally visualize cellular proximities to characterize cellular interactions within an intact tumor tissue [246]. Using these technologies to generate CRC-specific tumor profiles, our studies aim to identify novel prognostic immune cells, intercellular mechanisms, and immunotherapy targets. Integrating artificial intelligence to analyze these profiles will aid in identification of predictive patterns that can be translated into widely accessible diagnostic tools to enhance staging accuracy and guide next-generation precision therapies. Given the rising global incidence of CRC, we are working to develop novel immunotherapies for MSS CRC tumors and improve tumor staging systems to support precision therapy.

CRediT authorship contribution statement

Sonia A.M. Ferkel: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Elizabeth A. Holman:** Writing – review & editing. **Raoul S. Sojwal:** Writing – review & editing. **Samuel J.S. Rubin:** Supervision, Writing – review & editing. **Stephan Rogalla:** Conceptualization, Project administration, Resources, Supervision, Visualization, Writing – review & editing.

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