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REVIEW

Cancer Focus

Myeloid diversity in tumors: Shaped by genes, location, and time

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Myeloid cells are present in neoplastic tissues from the earliest stages of transformation through to fully developed tumors. However, their intrinsic dynamism and plasticity make them difficult to target therapeutically. Emerging technologies are uncovering previously unrecognized cellular states and functions, thus reshaping our understanding of myeloid cell biology beyond their traditional inflammatory roles. This review discusses recent advances in identifying tumor-specific cues, tissue structural components, and the temporal modulation of neutrophil and macrophage programs in tumors, which are influenced by both cell-intrinsic and systemic signals. By integrating molecular, environmental, and time-dependent aspects of myeloid biology, we discuss here our understanding of their functional diversity and inform the development of future cancer therapy strategies.

Introduction

A marked enrichment of myeloid cells characterizes solid tumors. Mainly produced in the bone marrow (BM), their accumulation of myeloid leukocytes at the tumor site is the result of the abnormal and enhanced production of recruiting cytokines and chemokines by tumoral and stromal cells. The most abundant myeloid populations in tumors are neutrophils, monocytes, macrophages, and various precursors expressing low to intermediate levels of lineage-defining markers. Among these, polymorphonuclear myeloid-derived suppressor cells (MDSCs) and monocytic MDSCs—which display immunosuppressive functions—fall within this category (Veglia et al., 2021). However, this classification does not capture the full spectrum of states and functional phenotypes observed in tumors.

As early responders to tumor-induced damage, myeloid cells can be rapidly reprogrammed by signals from the tumor and its microenvironment (TME), redirecting their normal homeostatic immune functions toward tumor-promoting activities. Among these, pro-tumoral neutrophils exhibit increased formation of neutrophil extracellular traps (NETs), elevated production of ROS, and enhanced angiogenic potential (Ng et al., 2025b). In contrast, pro-tumoral macrophages are often metabolically reprogrammed toward highly glycolytic states, displaying reduced antigen-presenting and phagocytic capacities, while activating tissue-remodeling programs that facilitate tumor progression (Kloosterman and Akkari, 2023). Notably, mutation-driven specificity further refines these functional adaptations, a topic we discuss in detail within the context of the spatial organization of myeloid cells in tumors. Finally, we emphasize how circadian biology emerges as a critical determinant of functional heterogeneity in myeloid cells, offering new perspectives on how these programs can be therapeutically modulated. By integrating recent discoveries in myeloid tumor immunology with insights into mutation-driven adaptations, tumor spatial architecture, and circadian regulation, we frame a model whereby understanding the molecular, cellular, and temporal dimensions of myeloid biology will be essential for designing personalized therapeutic strategies aimed at controlling—and ultimately curing—cancer.

Mutational drivers of myeloid heterogeneity in tumors

The TME is a dynamic ecosystem composed of cancer cells and various nonmalignant components that collectively influence tumor growth and progression. Immune and stromal cells, including fibroblasts, endothelial cells, adipocytes, and neurons, interact with the extracellular matrix (ECM) to create a supportive niche for tumor development. Soluble cytokines/chemokines and growth factors released by tumors—including G-CSF, GM-CSF, M-CSF, TNF-α, and VEGF—modulate immune activity by promoting the expansion, recruitment, and activation of myeloid cells within the TME. Additional cytokines and chemokines—such as

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CCL2, CXCL1, CXCL2, IL-6, IL-1β, and CXCL8—facilitate the mobilization of neutrophils and macrophages into the TME of solid tumors. Despite strong preclinical rationale targeting recruitment axis for myeloid cells (Lin et al., 2001; Tap et al., 2022), clinical trials targeting these pathways have shown limited success (Sandhu et al., 2013; Tap et al., 2022). This underscores the limitations of targeting solely recruitment-based mechanisms to revert pro-tumoral myeloid functions. As a result, more nuanced strategies are emerging. A notable example includes blockade of TREM2, which, when combined with anti–PD-1 therapy, has shown promising results across several cancer models (Molgora et al., 2020). Nevertheless, in human hepatocellular carcinoma (HCC), TREM2^{HI} tumor-associated macrophages (TAMs) are linked to both good prognosis and enhanced response to anti–PD-1 therapy (Pauline et al., 2025, *Preprint*), highlighting the difficulty in applying a one-size-fits-all treatment approach across different cancers. The next section discusses how the mutational landscape of solid tumors influences not only the recruitment but also the phenotype and functional diversity of tumor-infiltrating neutrophils and macrophages (summarized in Fig. 1 A and Table 1).

Loss of *TP53* is one of the most frequent events in cancer (Serrano and Blasco, 2007). The most common *TP53* mutation in humans, which is *R175H* (*R172H* in mice), promotes the upregulation of the chemokines CXCL1, CXCL5, and CCL2 in pancreatic ductal adenocarcinoma (PDAC), facilitating neutrophil and monocyte recruitment by activating NF-κB target genes (Mahat et al., 2025). *Trp53*$^{R172H/-}$-mutated PDAC tumors exhibit increased infiltration of heterogeneous Gr-1$^+$ arginase (Arg-1)$^+$ myeloid cells, which correlated with greater tumor burden (Mahat et al., 2025). Additionally, p53 deficiency in KRAS-driven lung and pancreatic tumors enhanced macrophage recruitment through elevated expression of CCL2, CSF-1, and CXCR3 (Blagih et al., 2020). In breast cancer, genetic loss of *Trp53* increased the number of circulating neutrophils (CD11b$^+$Ly6G$^+$Ly6C$^+$) via enhanced expression of CCL2, IL-1, IL-17A, and G-CSF across 16 different breast cancer genetically engineered mouse models (GEMM) (Wellenstein et al., 2019). These neutrophils were mostly immature (expressing cKIT$^+$ or CD117) in all *Trp53*-deficient models, but especially abundant in those harboring mutations for *Met*, estrogen receptor 1 (*Esr1*), and *Brca1*. Mechanistically, the authors demonstrated that *Cdh1*, *Trp53*-deficient, and *Akt*-mutated cancer cells secreted WNT (wingless-related integration site) ligands that stimulated TAMs to produce IL-1β, ultimately driving neutrophil expansion in BM and blood and infiltration at metastatic sites (Wellenstein et al., 2019). Given the impact of mutations on the secretory profile of tumor cells and the local and peripheral modulation that these cytokines/chemokines and growth factors can have on myeloid differentiation pathways in the BM (as exemplified by IL-1β modulation), it is critical to understand how mutations affect neutrophil and macrophage maturation, trafficking, or terminal effector profiles in tumors, which underscore the notion that myeloid cell biology cannot be comprehensively integrated without analyzing their ontogeny, trafficking, and target organ/tumor. Generally, TP53 loss and mutations across multiple cancer types reshape tumor secretory programs to drive neutrophil and macrophage recruitment, expansion, and functional polarization with local (tumor) effects and systemic changes affecting BM hematopoiesis.

The PI3K pathway regulates cell proliferation, survival, migration, and stem cell self-renewal, and it is frequently dysregulated in cancer. *PIK3CA*^{H1047R} is found in hormone receptor (HR)$^+$ HER2$^+$ breast cancer, head and neck carcinomas, pancreas, and melanoma, and gain-of-function (GOF) mutations are associated with poor prognosis (Wang et al., 2025). Studies using the murine MC38 colon carcinoma cell line have shown that tumors expressing *PIK3CA*^{H1047R} are frequently associated with an enrichment of myeloid cells (neutrophils and monocytes) expressing CCR2, Arg1+, and IL-1β, as well as cancer cells overexpressing myeloid recruitment cytokine genes, such as *Csf1*, *Ccl2*, and *Ccl7* (Collins et al., 2022). PI3K activation through PIK3CA GOF mutations promotes cytokine-driven recruitment and immunosuppressive polarization of neutrophils and monocytes across tumor types. This positions oncogenic PI3K signaling as a direct regulator of tumor-associated myeloid remodeling and clinical progression.

PTEN—a key regulator of PI3K activity—is frequently inactivated in human malignancies (Milella et al., 2015) and plays a crucial role in tumor growth, invasion, and stem cell plasticity. In prostate cancer (PCa), *Pten* loss in basal cells enhances NF-κB inflammatory signaling, increasing the recruitment of Ly6G$^+$ myeloid cells and promoting tumor proliferation (Jiang et al., 2025a). This loss upregulates *Il1a* and *Il1r1*, triggering an IL-1/IL-1R autocrine loop that sustains basal stem cell plasticity and tumor initiation, while also inducing inflammatory and chemokine genes (*Ifit1, Tnfaip2, Cxcl2, Cxcl13,* and *Cxcl15*) that favor the recruitment of neutrophils, monocytes, and macrophages (Jiang et al., 2025a). Club cells adopt a senescent-associated secretory phenotype profile in PCa, recruiting myeloid cells via CXCR2-CXCL1–8, which are predictive of limited survival in metastatic castration-resistant PCa (CRPC) (Kiviaho et al., 2024). Interestingly, PCa cells can induce neutrophil senescence through APOE, promoting an immunosuppressive phenotype that can be reversed with histone deacetylase inhibitors (Bancaro et al., 2023). PTEN loss has been associated with the presence of SPP1-expressing macrophages, which contribute to therapy resistance in metastatic CRPC. In preclinical mouse models of PCa, SPP1^{HI} TAMs reduced the efficacy of anti-PD1 and anti-CTLA4 immunotherapy, as they expressed enriched A2A receptor signaling. A phase I trial revealed improved outcomes with the A2AR antagonist ciforadenant, particularly in patients with high baseline SPP1^{HI} TAM levels, suggesting its potential as a biomarker to select patients responsive to combination therapy (Lyu et al., 2025). Collectively, PTEN deficiency sustains inflammatory, stemness—supporting niches that reinforce myeloid recruitment, immune suppression, and therapy resistance in PCa. Specialized macrophage states such as SPP1^{HI} TAMs further identify the myeloid compartment as a key therapeutic vulnerability.

KRAS, a small GTPase that cycles between active (GTP-bound) and inactive (GDP-bound) states, is one of the most frequently mutated oncogenes in cancer. It is particularly associated with highly fatal cancers like PDAC, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC) (Isermann et al., 2025). Oncogenic mutations in KRAS disrupt the nucleotide exchange cycle, leading to persistent activation of downstream signaling pathways that drive cell proliferation, survival, migration, and

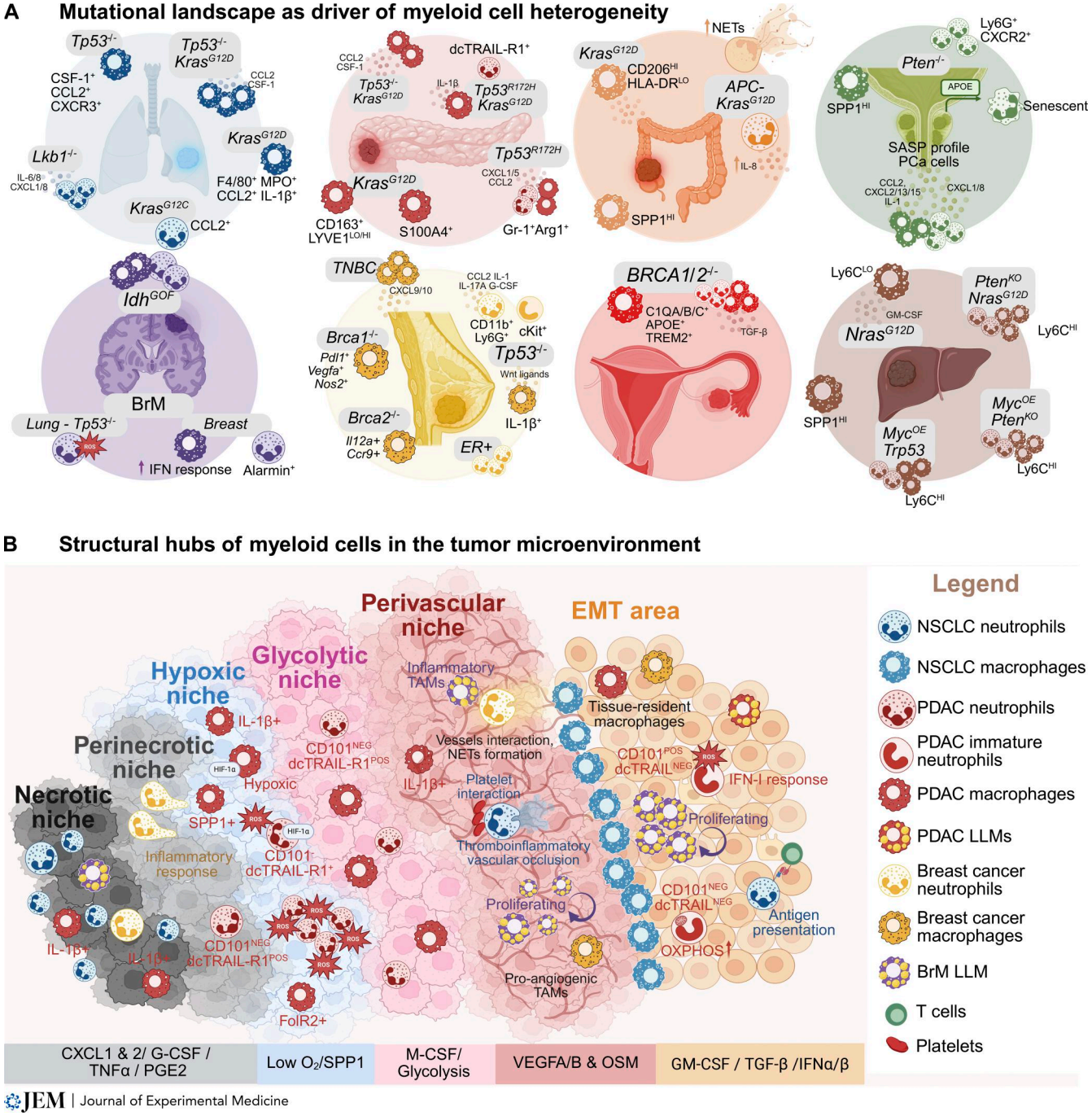

Figure 1. **Genetic and spatial determinants of myeloid heterogeneity. (A)** Tumor mutations drive distinct myeloid phenotypic profiles across different tumors. **(B)** Myeloid cells can be compartmentalized within specific tumor regions (PDAC, NSCLC, breast cancer and brain metastasis are shown as examples), reflecting local microenvironmental cues. LOF, loss-of-function; OXPHOS, oxidative phosphorylation; SASP, senescence-associated secretory phenotype.

tumor progression across multiple cancer types. One of the key effects of KRAS mutations is the shaping of the immune microenvironment, primarily through the activation of NF-κB, which promotes the expression of pro-inflammatory mediators like IL-1α/β, IL-6, TNF-α, CXCL1/2/5/8, CCL2, and inducible nitric oxide synthase. Additionally, KRAS signaling activates downstream pathways like MAPK and PI3K, which induce expression of IL-10, TGF-β, and GM-CSF, thereby fostering an immunosuppressive TME (Hamarsheh et al., 2020). In lung cancer, KRAS mutations occur in over 30% of cases, particularly in NSCLC (with $KRAS^{G12C}$ and $KRAS^{G12V}$ mutations being associated with smoking, and $KRAS^{G12D}$ with nonsmokers) (Pereira et al., 2022). Studies on $KRAS^{G12C}$-mutant lung cancer models showed that treatment with KRAS inhibitor MRTX1257 reduced CCL2 and neutrophil chemokines, limiting monocyte and neutrophil recruitment and partially reversing myeloid-driven immunosuppression (Mugarza et al., 2022). $Kras^{G12D}$ mutations drive an immunosuppressive macrophage phenotype, characterized by

Table 1. **Major drivers of myeloid recruitment and heterogeneity in solid tumors**

	Mutation	Cancer cell secretory/ gene expression profile	Tumor	Myeloid response	Reference
TP53	*TP53*^{R175H}	↑ CXCL1, CXCL5, and CCL2	PDAC	Activation NF-κB pathway Neutrophil and monocyte recruitment	Mahat et al. (2025)
	Trp53$^{-/-}$	↑ CCL2 and CSF-1	NSCLC and PDAC	Macrophage recruitment via CXCR3	Blagih et al. (2020)
	Trp53$^{-/-}$	↑ CCL2, IL-1, IL-17A, and G-CSF	Breast tumors	Recruitment of immNeus	Wellenstein et al. (2019)
PI3K	*PI3KCA*^{H1047R}	↑ *Csf1*, *Ccl2*, and *Ccl7*	CRC	Enhanced recruitment of immunosuppressive myeloid cells. ↑ CCR2, arginase, and IL-1β expression	Collins et al. (2022)
PTEN	*Pten*$^{-/-}$	↑ *Il1a* and *Il1r1* ↑ *Ifit1, Tnfaip2, Cxcl2, Cxcl13,* and *Cxcl15*	PCa	Activation NF-κB pathway. Recruitment of neutrophils, monocytes, and macrophages	Jiang et al. (2025a)
KRAS	*KRAS*^{G12D}/ *KRAS*^{G12C}	↑ IL-1α/β, IL-6, TNFα, CXCL1/2/5/8, and CCL2	PDAC, CRC, and NSCLC	NF-κB activation	Hamarsheh et al. (2020)
	Kras^{G12D}	↓ TGFA, TGFB, CXCL1, and CXCL2	NSCLC	Increased infiltration of F4/80 MPO$^+$, complement genes, *Mrc1,* and *Csf1r* ↑ CCL2, IL-1β, and CCL4	Lasse-Opsahl et al. (2025)
		GM-CSF and lactate	CRC	Reprogrammed TAMs IL-10$^+$, TGF-β$^+$, and CCL17$^+$	Liu et al. (2021)
LK1B	*LKB1* loss	↑ IL-6, IL-8, and CXCL1/8	NSCLC	↑ Neutrophil recruitment ↓ Type II–IFN signaling	Skoulidis and Heymach (2019), Li et al. (2021), Compton et al. (2023), and Koyama et al. (2016)

increased infiltration of F4/80$^+$ MPO$^+$ macrophages and the upregulation of complement-related genes like *C1qa, C1qb, C1qc, Mrc1,* and *Csf1r*. These macrophages also express CCL2, IL-1β, CCL4, S100a9, and CX3CR1, further reinforcing their pro-tumoral profile (Lasse-Opsahl et al., 2025). KRAS-mutant lung cancer is strongly associated with an immune-evasive phenotype, in which KRAS signaling plays a critical role by orchestrating this immunosuppressive environment through cytokine and chemokine expression (Drizyte-Miller et al., 2025).

PDAC tumors are driven by KRAS mutations in 90% of cases, and macrophages critically regulate almost all stages of tumor development (Bleriot et al., 2024; Dunsmore et al., 2024). CD163$^+$ LYVE1$^+$ tissue-resident macrophages (TRMs) expand during acute pancreatitis and PDAC, with embryonic and adult-derived subsets showing distinct functions: embryonic LYVE1^{HI} TRMs promote tissue repair and fibrosis, while monocyte-derived LYVE1^{LO} cells are more inflammatory. In PDAC models, TRM depletion reduces fibrosis and slows tumor progression, underscoring their dual role in both normal repair and in fostering a pro-fibrotic, tumor-promoting microenvironment (Ying et al., 2025; Baer et al., 2023). KRAS^{G12D} inhibitor MRTX1133 reshapes the PDAC TME by reducing granulocytic MDSCs and dendritic cells (DCs) while increasing macrophage infiltration, and its efficacy improves when combined with anti-CXCR2, anti-LAG3, or anti–4-1BB therapies (Kemp et al., 2023; Liu et al., 2025). However, pairing MRTX1133 with anti-PD1 instead promotes an immunosuppressive macrophage state and upregulates CXCL3 and CCL5, showing that KRAS-targeted inhibition can trigger myeloid cell reprogramming depending on the immunotherapeutic context. In chronic pancreatitis, elevated TGF-β drives KRAS therapy resistance by activating epithelial–mesenchymal transition (EMT) and recruiting S100A4$^+$ TAMs via SMAD3/4–NFAT5 signaling. Suppressing NFAT5 reduced S100A4 in tumor cells, but not in TAMs, which remained abundant near cancer cells, maintaining resistance despite NFAT5 inhibition (Deng et al., 2024). In a *Kras*^{G12D}; *Trp53*$^{R172H/+}$ experimental PDAC model, both immature and mature neutrophils infiltrate tumors and undergo irreversible reprogramming into a dcTRAIL-R1$^+$ pro-angiogenic state, localizing to hypoxic and glycolytic tumor niches. Interestingly, co-occurrence of *KRAS* and *TP53* mutations in PDAC stratifies patients at high risk, showing a myeloid landscape dominated by inflammatory macrophages and neutrophils, with reduced T cell infiltration (Ng et al., 2024; Jiang et al., 2025b). KRAS-mutant CRC cells enhanced lactate secretion and GM-CSF reprogrammed TAMs to a phenotype that secretes IL-10, TGF-β, and CCL17, promoting tumor migration, invasion, and immune evasion (Liu et al., 2021). Additionally, in APC-KRAS^{G12D}–driven preclinical models of CRC, increased neutrophil infiltration, NET formation, and elevated IL-8 expression collectively contribute to tumor progression (Shang et al., 2020). Overall, KRAS mutations not only drive tumor progression but also profoundly shape the myeloid landscape in the TME, fostering both immune evasion and tumor promotion. Targeting KRAS directly or through immune modulation presents a promising strategy to reprogram the myeloid compartment and improve therapeutic outcomes. Oncogenic KRAS signaling reshapes the TME by coordinating inflammatory cytokine production, metabolic remodeling, and suppressive myeloid differentiation. The context-dependent myeloid reprogramming observed after KRAS inhibition supports combined strategies targeting both KRAS and tumor-associated myeloid cells.

Liver kinase B1 (LKB1) is an upstream activator of AMPK and several kinases that play a key role in cell growth, metabolism, and polarity (Shackelford and Shaw, 2009). Inactivating mutations in LKB1 are found in 20% of NSCLC patients (Skoulidis and Heymach, 2019), and its loss induces proliferative advantage to cancer cells, as well as enhanced production of IL-6, IL-8, CXCL1, and CXCL8, which are associated with an increased neutrophil recruitment and a reduction of type II IFN signaling (Li et al., 2021; Compton et al., 2023; Koyama et al., 2016). These alterations highlight LKB1 inactivation as a key regulator of myeloid recruitment and immune evasion.

BRCA1/2 mutations shape tumor immunity by modulating TAM and neutrophil populations, with BRCA1-deficient tumors showing STING-driven macrophage recruitment and BRCA2-null tumors harboring mixed pro- and anti-inflammatory TAMs. These myeloid alterations contribute to variable immune checkpoint responses and may be exploited to optimize targeted immunotherapies. BRCA1 and BRCA2 are tumor suppressors involved in homologous recombination repair of DNA double-strand breaks, safeguarding genomic stability. Germline or somatic loss-of-function mutations in these genes significantly increase susceptibility to breast and high-grade serous ovarian cancer (OC) (Li et al., 2022). In breast tumors, TAMs are a major component of the immune milieu (Mehta et al., 2021b). While estrogen receptor–positive (ER^+) breast tumors show reduced TAM numbers, triple-negative breast cancer (TNBC) exhibits increased TAM diversity. Interestingly, ER^+ breast cancers, once classified as "cold" or poorly infiltrated by immune cells, are now known to be heavily infiltrated by neutrophils, with estrogen signaling driving their recruitment and immunosuppressive functions. A population of neutrophil progenitors in ER^+ tumors has been recently linked to higher tumor grades (Mukherjee et al., 2025). Mechanistically, succinate secreted by neutrophil progenitors disrupts homologous recombination and sensitizes tumors to PARP inhibitors (Mukherjee et al., 2025), revealing a potential immunomodulatory role for immature neutrophils (immNeus). In BRCA1-mutant TNBC, TAMs increase about 10-fold compared with WT, driven by cytosolic DNA accumulation that activates the STING pathway, leading to CXCL9/10 secretion and macrophage recruitment (Mehta et al., 2021a). HR-deficient tumors, such as those with BRCA1/2 mutations, often present complex immune landscapes but tend to have lower clinical responses to immune checkpoint blockade (ICB). *Brca2* null tumors show TAMs co-expressing both pro-inflammatory and immunosuppressive markers, while *Brca1*-deficient tumors exhibit a distinct TAM profile (Samstein et al., 2021). These differences in TAM subsets may influence ICB responsiveness, warranting further investigation into their contribution to tumor immunity in BRCA-mutant tumors. In OC, *Brca1*-mutant tumors exhibit increased infiltration of $CD8^+$ T cells and conventional DCs (cDCs), enhancing immune responses via the CXCL9/10–CXCR3 axis (Ghisoni et al., 2025). In contrast, HR-proficient tumors have an immunosuppressive TME, with higher numbers of exhausted $CD8^+$ T cells and TAMs. HR-deficient tumors with mutant *Brca1* are characterized by an immune-inactive TME with increased TAM infiltration and elevated cytokine levels (MIP-3β and TGF-β1/2), which promote T cell suppression (Iyer et al., 2021). Furthermore, TAMs expressing C1QA/B/C, APOE, and TREM2 are enriched in benign fallopian tubes in BRCA1/2 mutation carriers, when compared with HR-proficient cases (Brand et al., 2024; Launonen et al., 2022), which might contribute to the different clinical outcomes in OC. These studies underscore the critical role of BRCA mutations in shaping the immune landscape of tumors, with distinct TAM and neutrophil populations influencing therapeutic responses. Further exploration of the immune microenvironment of BRCA-mutant tumors is essential for developing targeted immunotherapies, potentially enhancing the effectiveness of immune checkpoint inhibitors and other treatments in OC.

The constitutive activation of the MAPK pathway (e.g., $Nras^{G12D}$ mutation) in HCC alters the TME by promoting the infiltration of immunosuppressive monocyte-derived $Ly6C^{LO}$ cells. Mechanistically, $NRAS^{G12D}$ activates the MEK–ERK1/2–SP1 axis, leading to increased GM-CSF production, which drives myeloid cell accumulation. Blocking GM-CSF reduced inflammation, enhanced tumor cell death, and improved survival—particularly when combined with VEGF inhibition—suggesting a myeloid-targeted treatment strategy for genetically defined HCC subgroups (Ramirez et al., 2024). Abnormal activation of the MAPK pathway in melanoma disrupts the role of inflammatory monocytes in stimulating T cells, limiting immune response in the TME (Elewaut et al., 2025). These monocytes, which normally present tumor antigens to T cells, are suppressed by decreased type I IFN (IFN-I) and increased prostaglandin E2 (PGE2) due to MAPK activation. The study suggests that restoring IFN-I or blocking PGE2 can reverse this immunosuppression, potentially improving responses to immunotherapy in resistant tumors. Constitutive MAPK activation drives immunosuppressive myeloid accumulation, including $Ly6C^{LO}$ monocytes in HCC and dysfunctional inflammatory monocytes in melanoma. Targeting MAPK-dependent cytokines or prostaglandin pathways can reverse this suppression and improve immunotherapy responsiveness.

In glioblastoma (GBM), isocitrate dehydrogenase (IDH) mutations are linked to a more aggressive phenotype, with increased infiltration of monocyte-derived macrophages (MDMs) (Karimi et al., 2023) and neutrophils (Maas et al., 2023) compared with *IDH* WT tumors. The myeloid TME also differs between primary and metastatic brain tumors. In brain metastases (BrM), neutrophils show stronger inflammatory and immune-activating profiles than those in primary GBM, particularly in BrM from lung cancer (Maas et al., 2023). The immune landscape of BrM further varies with the genetics of the primary tumor. For example, *Trp53*-mutant lung BrM show immunosuppressive macrophages/microglia and pro-angiogenic, ROS-producing neutrophils, while breast cancer BrM arising from hypermutated tumors exhibit a pro-inflammatory environment with IFN-driven macrophage activation and alarmin-expressing neutrophils (Alvarez-Prado et al., 2023). Interestingly, neutrophils derived from the skull (but not from peripheral blood) upregulate MHC II and can present local antigens to CD4 T cells in GBM, ultimately driving CD8 cytotoxicity and CD4 T cell memory (Lad et al., 2024), suggesting that the skull BM rather than long-BM might preferentially give rise to antigen-presenting neutrophils.

While much of cancer research has focused on classical mutations in genes such as TP53 and KRAS, recent studies are uncovering a broader spectrum of somatic mutations—including those in DNMT3A, TET2, and among others—that shape the myeloid cell landscape in the TME. Clonal hematopoiesis of indeterminate potential (CHIP)—primarily associated with aging—drives mutations in epigenetic and DNA repair regulators, leading to the clonal expansion of hematopoietic stem cells (HSCs) with altered immune function, ultimately impacting disease progression (Cai et al., 2025). CHIP mutations promote myeloid-biased differentiation, increasing neutrophil and macrophage output, which can release pro-inflammatory cytokines and influence tumor biology (Park et al., 2024). Recent studies have shown that TET2-and DNMT3A-mutant macrophages enhance tumor growth in NSCLC and GBM (Pich et al., 2025; Park et al., 2024; Buttigieg et al., 2025) and can also contribute to BRAF/MEK inhibitor resistance (Tiedje et al., 2024, *Preprint*). In humans and mice, *Tet2* deletion leads to the production of immNeus with reduced phagocytic capacity, enhanced ROS production (Huerga Encabo et al., 2023), and defective NET formation (Huerga Encabo et al., 2023; Quin et al., 2024a). Conversely, *PPM1D*-mutant neutrophils enhance co-stimulatory $CD8^+$ T cell activity, and *Tet2*-mutant macrophages exhibit enhanced pro-inflammatory and antigen-presenting programs in response to IFNγ (Herbrich et al., 2025). Interestingly, CHIP can also modulate ICB response in models of melanoma and pancreatic cancer (Herbrich et al., 2025) and enhance survival in NSCLC (Pich et al., 2025), showing the role of CHIP as an immunomodulatory program enhancer in myeloid cells. With its prominent role in shaping the TME by influencing myeloid secretory and functional phenotypes, the impact of CHIP mutations on stromal-tumor interactions is an emerging field that will present novel paradigms in tumor evolution. Collectively, oncogenic mutations and tumor suppressor losses -including PI3K, PTEN, KRAS, LKB1, BRCA1/2, MAPK, IDH, and CHIP-associated alterations- converge on common myeloid-modulatory programs. These genetic events orchestrate cytokine and chemokine networks that recruit, expand, and functionally polarize neutrophils and macrophages, shaping immunosuppressive TMEs and influencing therapeutic responsiveness across cancer types. Earlier studies focused on quantitatively measuring the myeloid cells recruited into tumors, yet how individual mutations affect myeloid cell function has only recently begun to be investigated. We propose that a deeper understanding of each tumor's genetic landscape will illuminate tumor-specific myeloid phenotypes that can inform the development of targeted immunotherapies. In the next section, we will examine how specific chemokines, cytokines, and survival signals orchestrate myeloid cell infiltration, and how factors such as vascular access and fibroblast-driven barriers further shape and establish spatially restricted niches for myeloid cell behavior within the tumor.

Niche-organizing hubs of myeloid-tumor communication

Follow the call: Key guiding factors orchestrating myeloid recruitment

The TME relies on soluble signaling molecules to orchestrate the recruitment, differentiation, and functional reprogramming of myeloid cells. Among these, chemokines and cytokines serve as central hubs, shaping both local immunity and tumor behavior. For instance, chemokines such as CCL2 and CCL5 play central roles in the recruitment of monocytes and macrophages. CCL2, also known as MCP-1, is overexpressed in multiple cancers, including breast, lung, and ovarian tumors (Yoshimura et al., 2023; Arenberg et al., 2000; Negus et al., 1995), where it promotes infiltration of TAMs and natural killer (NK) cells and contributes to cachexia and immune evasion (Liu et al., 2024a; Kadomoto et al., 2021). Cancer-associated fibroblasts (CAFs) are a source of CCL2 in gastric cancer, enhancing TAM accumulation in a JAK-STAT–dependent mechanism (Lee et al., 2025). CCL5 (RANTES), secreted by the tumor, CAFs, and myeloid cells (Thomas et al., 2019; Schlecker et al., 2012) interact with CCR5 and other receptors to promote both pro- and anti-tumor activities (Schlechter and Stebbing, 2024). Elevated CCL5 enhances EMT via Wnt/β-catenin and NF-κB signaling (Singh et al., 2020), and its expression correlates with increased infiltration of NK cells, cytotoxic T cells, and immune-suppressive TAMs (Yang et al., 2020; Datar et al., 2016). In CRC, high CCL5 expression is linked to increased expression of immune checkpoint regulators such as PD-1, PD-L1, and CTLA-4, facilitating transition to an immune cold TME (Schlechter and Stebbing, 2024).

CXC chemokines, like CXCL1 and CXCL2, primarily attract neutrophils through the CXCR2 receptor, which is highly expressed on this cell type (Hughes and Nibbs, 2018). Neutrophils can also secrete CXCL1, amplifying their own recruitment in a feedforward loop (Korbecki et al., 2023). In tumors like HCC and PCa, $CXCR2^+$ neutrophils drive resistance to immunotherapy and androgen receptor blockade, and CXCR2 inhibitors have shown potential in preclinical mouse models and early clinical studies (Guo et al., 2023; Calcinotto et al., 2018). CXCL8 (also known as IL-8) is a key human neutrophil-attracting chemokine, crucial in infection and tissue injury response, and is highly upregulated in tumors via HIF-1α and NF-κB signaling (Korbecki et al., 2021), while endothelial and myeloid cells can also produce it (Waugh and Wilson, 2008), amplifying and fueling a pro-angiogenic and immunosuppressive loop. In breast cancer, IL-8 drives EMT and invasion and facilitates the differentiation of immunosuppressive $CD206^+$ TAMs, associated with poor prognosis (Qin et al., 2023; Haque et al., 2019). GM-CSF is produced by immune and tumor cells under stress, drives myelopoiesis, and enhances macrophage activation via JAK-STAT pathways (Zhan et al., 2019; Guthridge et al., 2006). Mobilization and activation of neutrophils is driven by G-CSF (CSF3) that stimulates granulopoiesis and leads to proliferation, maturation, and BM mobilization of neutrophils, promoting malignancy progression, metastasis, poor prognosis, and decreased overall cancer patient survival (Karagiannidis et al., 2021). M-CSF (CSF1) is a cytokine essential for the survival, proliferation, and differentiation of mononuclear phagocytes. Beyond its normal physiological role, the CSF1/CSF1R axis is often overexpressed in many tumors and is associated with poor prognosis (Lin et al., 2001). IL-1β is largely secreted by TAMs and neutrophils and induces expression of IL-6, IL-10, CSF1/2, and chemokines like CCL2 and CXCL1/2/3, sustaining inflammatory and immunosuppressive programs (Caronni et al., 2023). In advanced PDAC, inflammatory IL-1β+ TAMs are

significantly enriched in patients due to local PGE2 expression by cancer cells, which perpetuate an inflammatory environment via TNFα that sustains IL-1β TAM, favoring PDAC progression and aggressiveness (Caronni et al., 2023). Its blockade via anakinra suppresses tumor progression and myeloid infiltration in models of prostate, lung, and breast cancer (Jiang et al., 2025a; Park et al., 2024; Garner et al., 2025). TGF-β, primarily secreted by TAMs in hypoxic tumor zones, drives immune suppression and metastasis (Adrover et al., 2025). TGF-β modulates CXCR4 expression in monocytes, facilitating their recruitment and differentiation into perivascular macrophages (Arwert et al., 2018). Oncostatin M (OSM), a macrophage-derived IL-6 family cytokine, enhances proliferation, angiogenesis, and immune cell recruitment (Richards, 2013; Hoagland et al., 2025). In tumor preclinical models, OSM signaling between myeloid cells and fibroblasts triggers the secretion of CXCL10, CXCL12, and CCL2, reinforcing myeloid infiltration and immune evasion (Araujo et al., 2022). Lastly, osteopontin (SPP1 or OPN) has emerged as a hallmark of immunosuppressive TAMs across tumors in prostate, liver, colorectal, and head and neck squamous carcinoma (Lyu et al., 2025; Sheban et al., 2025; Bill et al., 2023) and is often associated with hypoxia and fibrosis (Gao et al., 2024; Bill et al., 2023). Interestingly, SPP1$^+$ TAMs are associated with poorer clinical outcomes, whereas patients with higher levels of CXCL9-expressing TAMs had better outcomes, defining a probably oversimplified, but prognostically relevant framework for TAM phenotypes across cancers (Bill et al., 2023). SPP1$^+$ TAM abundance correlates with poor prognosis, although in specific contexts like metabolic dysfunction-associated steatohepatitis, SPP1$^+$ macrophages may exert protective metabolic effects (Han et al., 2023). In a recent landmark study, TGF-β, IFN-β, and GM-CSF were identified as critical modulators of neutrophil phenotypic and functional activity in tissues and tumors (Cerezo-Wallis et al., 2025), highlighting how these cytokines can orchestrate context-dependent transcriptional programs that shape neutrophil effector functions. Together, these findings underscore the plasticity of neutrophils and reveal potential therapeutic avenues for modulating their function in inflammatory disorders and cancer.

Altogether, chemokines and cytokines form a signaling network that governs the behavior of myeloid cells in tumors. Their multifaceted roles not only support tumor progression and immune evasion but also present promising therapeutic targets, particularly for combination strategies involving immune modulation and myeloid-directed interventions.

While most of these cytokines and chemokines play critical roles in myeloid cell survival and in orchestrating inflammatory, healing, and tissue regeneration processes, it remains unclear which of them, beyond CCL2 (Qian et al., 2011) and CSF1 (Lin et al., 2001), are essential for driving cancer progression. It also remains unresolved why tumors co-opt fundamental survival and recruitment factors, such as GM-CSF or M-CSF, and what advantages they gain in return from the organism-wide responses that these factors provoke (from local tumor recruitment to BM enhanced myelopoiesis). We speculate that these essential immunomodulatory cytokines fuel systemic responses that, in turn, drive systemic disease and prime tissues beyond the local TME, potentially establishing pre-disease niches conducive to metastatic spread. In this scenario, tumor and TME-signaling levels may surpass normal homeostatic or even inflammatory ranges due to an expansion of the cell populations that produce them to affect the whole body systemically. It is also tempting to speculate that cytokines and chemokines are at the forefront of both cancer and regeneration programs and might bridge the immune system's reparative functions within this paradigm.

Identifying their niche: Myeloid organization hubs within tumors

Spatial analysis of the TME has revealed the diverse localization and functional specialization of myeloid cells (Casanova-Acebes et al., 2021). This has been appreciated in early-stage tumors in which anti-tumoral ICAM-1 CD95$^+$ stroma-associated neutrophils observed in human CRC (Vadillo et al., 2023) and in NSCLC (Peng et al., 2023) were enriched in genes associated with antigen presentation and IFN-stimulated pathways. High densities of clustered HLA-DRA$^+$ neutrophils in the tumor core and margin are linked to better outcomes—especially in early-stage disease—while their specific spatial localization, including opposite effects at the margin, appears critical for tumor control and may influence therapeutic response, supporting their potential targeting in neoadjuvant immunotherapy treatment settings (Marteau et al., 2026). By contrast, late-stage tumors display a core enriched with neutrophils with mostly pro-angiogenic and lymphangiogenic phenotypes (Ng et al., 2024; Bui et al., 2024; Wang et al., 2023b; Peng et al., 2023; Enfield et al., 2024). In human TNBC, necrotic tumor areas are densely infiltrated by neutrophils (Adrover et al., 2025). These necrotic zones create a hypoxic environment that induces tumor cells to express genes such as *Hif1a, Vegfa, Cxcl1*, and *Ddit4*, boosting metastatic programs. Within this context, a distinct subset of neutrophils with low Ly6C expression accumulates near necrotic areas, characterized by expression of genes involved in inflammatory responses and motility (e.g., *Cyria, Dok1, Icam1, Itgax*, and *Itga4*), but with downregulated innate immune and extravasation pathways. Mechanistically, these Ly6C^{LO} neutrophils interact with tumor vessels through adhesion to fibrin and basal membrane components, engage platelets, and form NETs, causing thromboinflammatory vascular occlusion that perpetuates necrosis in tumor cores. Importantly, tumor-derived CXCL1 orchestrates recruitment and production of these neutrophils, linking their infiltration to tumor necrosis (Adrover et al., 2025). These examples suggest a mechanism by which tumors may co-opt anti-tumoral neutrophil programs as the disease progresses: early-stage tumors may contain anti-tumoral neutrophils with antigen-presenting capacity driven by IFN-I signaling, whereas overt metastatic tumors instead harbor highly motile neutrophils primed to enhance platelet interaction and promote vascular damage within hypoxic regions (Adrover et al., 2025). These highly motile neutrophils may, in turn, promote dissemination from core tumor regions, as opposed to dissemination from peritumoral areas, a process controlled by resident macrophages (Casanova-Acebes et al., 2021). We hypothesize that this shift is driven by peripheral, tumor-induced co-option of homeostatic granulopoietic programs in the BM.

In PDAC, neutrophils within tumors segregate into three main subsets with distinct markers and functional programs (Ng et al., 2024). Immature T1 (Ly6G$^+$CD101$^-$dcTRAIL-R1$^-$) neutrophils

exhibit high transcriptional and metabolic activity, including oxidative phosphorylation, while activated T2 (Ly6G$^+$CD101$^+$dcTRAIL-R1$^-$) neutrophil subset expresses ROS and IFN-I–related genes. The most tumor-adapted subset, T3 (Ly6G$^+$CD101$^-$/$^+$dcTRAIL-R1$^+$), displays transcriptional signatures linked to hypoxia, angiogenesis, and glycolysis, highlighting their pro-tumoral phenotype. Spatial mapping showed T3 neutrophils concentrate near necrotic, hypoxic, and glycolytic tumor regions, whereas T1 and T2 neutrophils are distributed more peripherally within tumor stroma and peritumoral areas. This spatial arrangement reflects the dynamic migration and metabolic adaptation of neutrophils as they infiltrate specialized tumor niches and undergo functional reprogramming in response to local microenvironmental cues (Ng et al., 2024). Similar to the PDAC neutrophil T3 subset, observations from the Pittet laboratory indicate that CCL3^{HI} tumor-associated neutrophils accumulate in hypoxic tumor niches, where hypoxia induces CCL3 expression and sustains neutrophil survival through a CCL3-CCR1 feedforward autocrine loop that promotes terminal differentiation, senescence-like features, pro-tumor activity, and resistance to anti–PD-1 therapy, identifying this population as a conserved and clinically relevant pro-tumor TAN subset across human and murine solid tumors (Bolli et al., 2026) Together, these studies emphasize the critical role of neutrophil heterogeneity and spatial organization within tumors, showing how distinct subsets respond and adapt to microenvironmental factors such as hypoxia, necrosis, and chemokine gradients–particularly those involving CXCL1/2–to promote tumor progression and immune modulation.

Neutrophils have emerged as candidates for cell-based therapeutic delivery owing to their exceptional motility and innate capacity to infiltrate necrotic or highly inflamed tumor regions. This tropism is driven by chemotactic cues present within hypoxic tumor cores, allowing neutrophils to access sites that are often poorly reached by conventional therapeutics. Conceptually, harnessing these cells as carriers for anti-tumor agents could enable more precise deposition of therapies deep within solid tumors, potentially disrupting pro-metastatic signaling niches and modifying the local TME in ways that limit disease progression. Although still at an early exploratory stage, this strategy highlights a broader trend toward leveraging the functional plasticity and navigational capabilities of myeloid cells for targeted intervention in otherwise inaccessible tumor compartments.

Neutrophils and macrophages exhibit a striking division of labor in PDAC that reflects their distinct developmental origins, spatial niches, and microenvironmental cues. CD163$^+$LYVE1$^+$ TRMs expand substantially during pancreatitis and PDAC, with embryonic-derived LYVE1^{HI} TRMs driving fibrosis and tissue remodeling, while monocyte-derived LYVE1^{LO} macrophages adopt more inflammatory and antigen-presenting functions (Baer et al., 2023). Importantly, IL-1β expressing TAMs locate in highly vascularized inflamed and hypoxic regions in PDAC tumors (Caronni et al., 2023); hypoxic PDAC TAMs expressing *Cxcl2, Slc2a1, Ero1l,* and *Bnip3* are enriched near necrotic tumor cores, while lipid-laden macrophages (LLMs) expressing *Itgax, Cd36, Trem2,* and *Gpnmb* are preferentially found in the periphery (Dunsmore et al., 2024). In contrast, neutrophils segregate into T1–T3 subsets with metabolic and transcriptional specialization (Ng et al., 2024). Together, these findings reinforce the concept that PDAC relies on a coordinated myeloid division of labor: TRM compartments sculpt fibrotic and immunosuppressive architecture, whereas neutrophil subsets dynamically infiltrate and respond to metabolic and inflammatory gradients, amplifying tumor-promoting inflammation, immune exclusion, and metastatic potential.

In NSCLC, TAMs spatially redistribute during tumor progression (Casanova-Acebes et al., 2021). In early-stage tumors, cancer cells are found close to TRMs expressing CD206 and CD169. However, in later stages, these TAMs relocate to the tumor periphery, forming granuloma-like structures. Similar redistributions of CD206$^+$-resident macrophages have been observed in breast cancer (Linde et al., 2018; Laviron et al., 2022), melanoma (Ray et al., 2025), and PDAC (Dunsmore et al., 2024). Analogously, in tumor models as the MMTV-PyMT breast cancer model, TAMs (F4/80$^+$ CD11c$^+$) localize near tumor nests, whereas MDMs (F4/80$^+$ CD206$^+$ CD169$^+$) primarily surround the tumor margins (Saglimbeni et al., 2025). However, other areas can be found in the breast TME, showing LYVE1$^+$ TAMs positioned adjacent to blood vessels, supporting angiogenesis, and LYVE1$^+$ MDMs located near vessels and ECM-rich regions. In contrast, LYVE1$^-$ MDMs formed clusters around mammary ducts in naive tissue and, under tumoral conditions, localized predominantly in peritumoral regions (Saglimbeni et al., 2025).

In GBM, up to eight TAM states are localized in distinct anatomical niches: microglia populate leading-edge areas (with also a microglia subset expressing glycoprotein non-metastatic melanoma protein B [GPNMB] localized in necrotic areas), while MDMs are phenotypically stratified into CCR2$^+$ and Ki67$^+$ MDMs close to the vasculature, while EB1$^+$ and Ki67$^+$ located in the leading edge (Kloosterman et al., 2024). GBM TAMs—also named LLMs to reflect their lipid accumulation—are epigenetically rewired, display immunosuppressive features, and are enriched in the aggressive mesenchymal GBM subtype (Kloosterman et al., 2024). These TAM subsets include pre-activated microglia (P2RY12$^+$) and MDMs (CCR2$^+$), inflammatory TAMs expressing TNF-α and CD74, metabolically activated TAMs expressing GPNMB, and proliferating TAMs characterized by Ki67 expression. Interestingly, a recent study identified four distinct myeloid immunomodulatory programs within the brain TME by integrating single-cell and spatial transcriptomics with chromatin accessibility profiling (Miller et al., 2025). Notably, these functional states were not dictated by the type or origin of myeloid cells, nor by the tumor's genetic landscape, but rather by local microenvironmental cues shaped by their spatial location within the tumor niche. In CRC, KRAS polarization of neutrophils occurs at the tumor site, where IL1β-expressing neutrophils are found in clusters in close contact to IL1R1 fibroblasts expressing CXCL5, CXCL3, and CXCL1, promoting neutrophil recruitment via CXCR1/R2 (Marteau et al., 2026). Importantly, a phase I clinical trial with anakinra (inhibitor of IL-1RA) in combination with chemotherapy in CRC patients has recently been completed (Fleischmann et al., 2022), suggesting that targeting this pathway could dismantle these immunosuppressive hubs.

Using imaging mass cytometry to classify NSCLC tumors according to their histological subtypes—lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC)—a recent

study mapped the complete immune infiltrate of these tumors. The study demonstrated that LUAD is more enriched in TAMs compared with LUSC, with CD163^{-} macrophages showing a higher propensity to interact with regulatory T cells (Tregs) (Desharnais et al., 2025). In contrast, LUSC tumors were heavily infiltrated by neutrophils expressing the NET-associated marker cleaved histone H3. Given the recently described neutrophil functional heterogeneity in tumors (Ng et al., 2025b), it is plausible that specific neutrophil phenotypes or their spatial localization within the TME contribute to the therapeutic responses observed in different histological NSCLC. It is tempting to speculate whether neutrophil–macrophage interaction networks might control tumor fate transitions between LUAD and LUSC, for example, in NSCLC, and if such interactions can influence treatment outcomes.

While evident in the current state of the art, it is still intriguing to understand why so many immune cells—particularly those originating from the myeloid compartment—accumulate within solid tumors. A plausible explanation is that tumor cells undergo dynamic phenotypic shifts, which are mostly sensed by innate immune cells, ultimately generating microenvironmental TME-myeloid "pocked" niches. In this scenario, tumors may exploit innate immunity to establish spatially distinct signaling ecosystems: some of these niches may attempt to initiate repair-like responses, whereas others may instead favor tumor growth, metabolic rewiring, or immune evasion (Fig. 1 B). Speculatively, tumor-derived factors (GM-CSF, M-CSF, IL-6, IL-1β, VEGF-A, and TGF-β) or fibroblasts (Marteau et al., 2026) could drive the recruitment, expansion, and reprogramming of myeloid cells. Chemokines such as CCL2, CCL5, CXCL8, CXCL12, and CXCL1 likely generate chemotactic gradients that continuously recruit monocytes, neutrophils, and myeloid precursors into the tumor bed, while therapeutic interventions (chemotherapy, radiotherapy, and immunotherapy) may further amplify or constrain these remodeling programs. In glycolytic tumor regions, lactate accumulation can function as an immunomodulatory metabolite that skews myeloid cells toward tolerogenic, tumor-supportive phenotypes through metabolic and epigenetic reprogramming. TRMs may partially recapitulate developmental-like energetic programs—characterized by high glycolytic demand and lipid accumulation—linked to regenerative and wound-healing functions within a forming organ or tumor context.

Altogether, these signaling landscapes suggest that tumors do not passively attract myeloid cells but instead orchestrate a dynamic, spatially heterogeneous dialogue with the innate immune system that resembles concurrent processes of growth, wound healing, unresolved inflammation, and organ-level remodeling. Distinct microenvironmental niches—such as hypoxic, glycolytic, invasive-front, and perivascular regions—may therefore select for specialized myeloid phenotypes (Fig. 1 B), including suppressive macrophages near T cell infiltration zones, pro-angiogenic neutrophils in hypoxic areas, and TRMs at invasive fronts, collectively shaping tumor progression, immune evasion, and therapeutic response.

We anticipate that within the coming years, studies leveraging CRISPR-based functional genomics screening methods combined with single-cell spatial transcriptomics—such as Perturb-seq (Dixit et al., 2016)—hold great promise. These technologies may enable a mechanistic blueprint of how tumor and stroma–myeloid interactions drive immune resistance (such as IL-10 signaling, PD-L1 upregulation, metabolic rewiring, or myeloid-mediated T cell exclusion) *in situ*, and uncover regulators of anti-tumoral myeloid phenotypes, including pathways associated with IFN-I responses, as well as transcriptional regulators such as STAT3, NF-κB, HIF-1α, and others that may operate in a context-dependent manner. Additionally, perturbation-based single-cell profiling can reveal temporal programs controlling transitions between inflammatory, tissue-repair, immunomodulatory, and immunosuppressive states—programs that are otherwise difficult to infer from static single-cell datasets—paving the way for more precise and durable immunotherapeutic strategies (Liu et al., 2024b; Yeh et al., 2024).

Tumor-tailored myelopoiesis: New roads for myeloid cell education in cancer

Hematopoiesis is a dynamic and tightly regulated process that sustains the lifelong production of blood and immune cells. In adult mammals, HSCs reside in BM niches alongside multipotent and lineage-committed progenitors, where they respond to both homeostatic needs and stress signals. HSCs are functionally heterogeneous: long-term HSCs (LT-HSCs) maintain self-renewal and multipotency, while short-term HSCs (ST-HSCs) are multipotent but with limited self-renewal.

Upon activation, they give rise to multipotent progenitors (MPPs), which lack self-renewal but differentiate into all blood lineages. MPP subsets, defined by surface markers and lineage bias, include MPP2 (lymphoid-biased), MPP3 (myeloid-biased), and MPP4 (megakaryocyte-erythroid–biased) (Swann et al., 2024). All these clonal populations can exhibit preferential expansion in pathological contexts, such as cancer, and could acquire monoclonal or polyclonal developmental trajectories to give rise to tumor-infiltrating neutrophils, monocytes, and, eventually, macrophages.

Neutrophil ontogeny

Neutrophil ontogeny in the BM proceeds through two major phases: specification and determination (Aroca-Crevillen et al., 2024). During specification, granulocyte–monocyte progenitors (MPs) generate early proNeus, guided by transcription factors such as C/EBPα and GFI-1, which initiate primary granule formation and nuclear remodeling necessary for later lobulation (Evrard et al., 2018; Aroca-Crevillen et al., 2024; Qu et al., 2023). ProNeu1 cells exhibit high proliferative capacity but limited effector function, whereas proNeu2 cells represent a transitional population toward preNeus. Under inflammatory conditions, proNeu1 can partially divert toward monocytic trajectories, reflecting their ontogenic proximity to Ly6C^{-} GMPs (Fig. 2). The transition to preNeus marks full commitment to the neutrophil lineage and depends on C/EBPε and GFI-1. At this stage, genes associated with effector functions (ROS production, phagocytosis, and chemotaxis) begin to be expressed, and secondary granules are formed. Neutrophils also initiate a metabolic shift toward increasing reliance on glycolysis, although significant metabolic plasticity persists (Kwok et al., 2020; Evrard et al.,

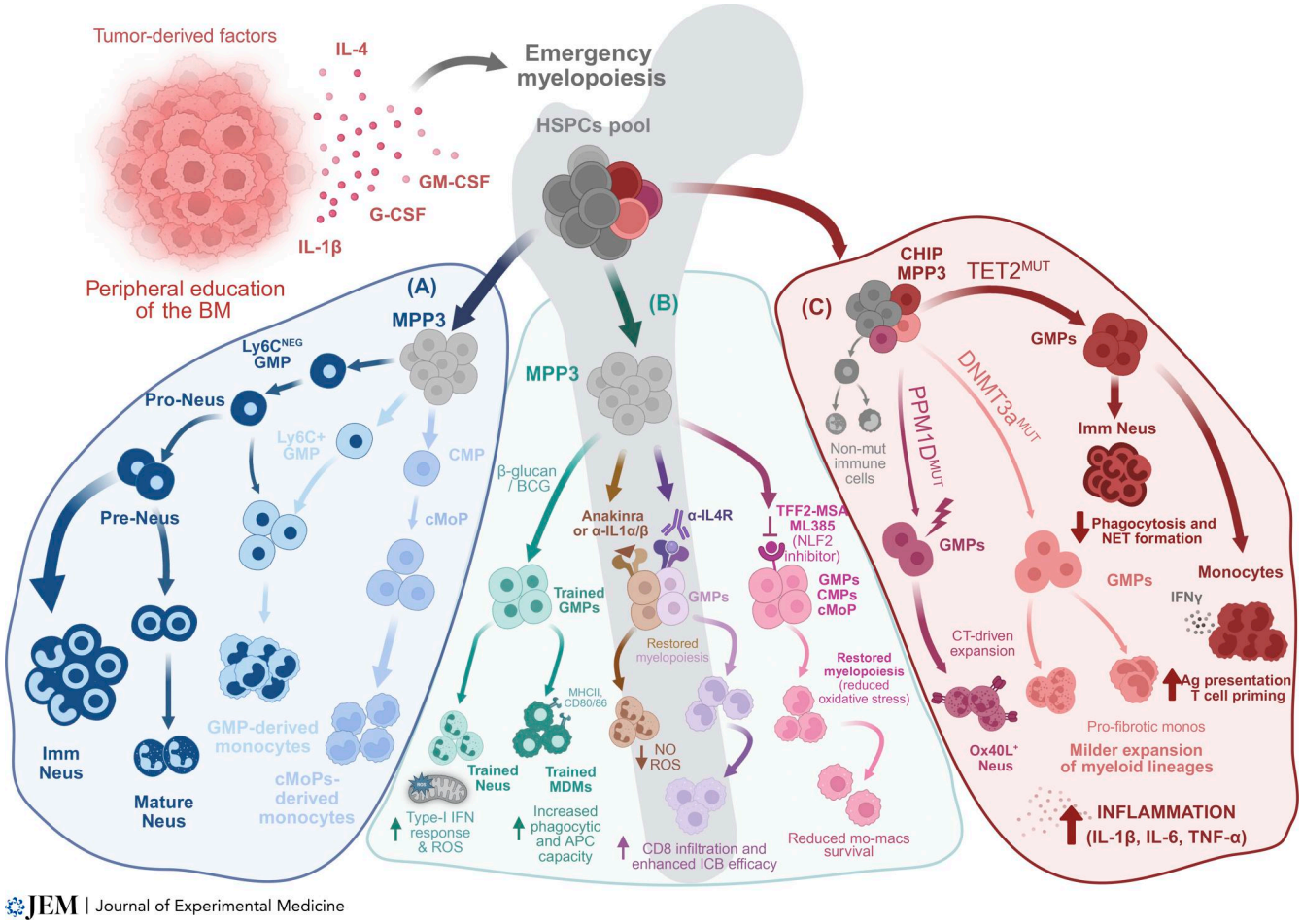

Figure 2. **Emerging developmental trajectories for myeloid cells in cancer. (A)** The first trajectory describes an increase in myeloid cell production (immNeus and monocytes) arising from GMPs, CMPs, and cMoPs. **(B)** In the myeloid trajectories shown in B, HSPC reprogramming occurs upon TI (BCG and β-glucan) and upon blockade of IL4R, IL1R, and with anakinra, giving rise to reprogrammed anti-tumoral myeloid cells. **(C)** In C, CHIP-mutated HSPCs can outcompete WT HSPCs (as in TET2 LOF) and rapidly generate myeloid cells. Other CHIP mutations (DNMT3A and PPM1D) coexist with WT cells and require either time (aging) or cytotoxic damage (chemotherapy) to facilitate expansion. HSPC differentiation trajectories driven by CHIP mutations, as well as the functions of myeloid cells harboring CHIP mutations, are only beginning to be appreciated. GMPs, granulocyte-MPs; NRF2, nuclear factor erythroid 2–related factor 2; Ag, antigen; LOF, loss-of-function.

2018; Karsunky et al., 2002). PreNeus differentiate into immNeus, characterized by a banded nucleus and open chromatin that supports high transcriptional activity. Notably, in tumor-bearing mice and cancer patients, CD117⁺ immNeus adapt metabolically to maintain ROS production and T cell suppression despite glucose restriction, supporting the notion that oxidative neutrophils contribute to tumor progression (Hageb et al., 2025).

Final maturation into mature neutrophils is driven by C/EBPδ and SPI-1, accompanied by formation of tertiary granules, full acquisition of antimicrobial and inflammatory effector programs, and regulation of CXCR4/CXCR2 expression that controls BM retention and release into circulation via the CXCL12 axis (Ganesh and Joshi, 2023). Mature neutrophils rely predominantly on glycolysis and display the complete functional repertoire required for innate immune defense.

Monocyte ontogeny

MPP3s give rise to the common myeloid progenitor (CMP), which generates the myeloid lineage. Monocyte differentiation follows two independent pathways (Yanez et al., 2017). The first involves CMP differentiation into GMPs (CD34⁺ CD16/32HI FLT3⁻ CX3CR1⁻) regulated by C/EBPα in response to GM-CSF. GMPs lose granulocyte potential and give rise to MPs, with IRF8 and PU.1 driving monocyte-specific gene expression in response to M-CSF (Rosenbauer and Tenen, 2007). The second pathway involves CMP differentiation into monocyte DC progenitors (MDPs; CD34⁺ CD16/32⁺ FLT3⁺ CX3CR1⁺), generating both DCs and monocytes via the common monocyte rogenitor (cMoP) (Ng et al., 2023). Both pathways produce Ly6C⁺ monocytes, with functional differences depending on their ontogeny (Yanez et al., 2017). These pathways expand in response to different stimuli, such as LPS (bacterial infection) and IFNγ/CpG (viral infection) (Trzebanski et al., 2024). Notably, GMP-derived monocytes infiltrate the brain, while MDP-derived monocytes are enriched in the lung (Trzebanski et al., 2024). Classical monocytes (Ly6C^{HI}/CD16⁺) differentiate into macrophages or DCs, while non-classical monocytes (Ly6C^{LO}/CD16⁻) are involved in homeostasis and tissue repair, arising from classical monocytes via

C/EBPβ (Yanez et al., 2017). Understanding these pathways and their reprogramming in pathological contexts, incorporating tumor genetics, requires advanced tools like fate-mapping, immunophenotyping and single-cell transcriptomics. Elucidating how developmental myeloid pathways in the BM occur can inform anti-tumoral developmental strategies worth exploring in cancer therapy.

Differentiated macrophage's ontogeny

Differentiated macrophages found in tissues arise from two different origins. In steady-state conditions, TRMs derive from embryonic progenitors that colonize developing tissues and establish a long-lasting population of resident macrophages, whereas MDMs arise from circulating monocytes that differentiate upon entry into tissues. Only recently has ontogeny been recognized as a driver of distinct functional specialization of macrophages within tissues, particularly in response to injury and disease (Park et al., 2022; Hochstadt et al., 2025; Bleriot et al., 2024).

In cancer, these origin-dependent differences have been reported in GBM, where authors identified LLMs originating from both embryonic microglia and MDMs. Although both subsets adopt immunosuppressive phenotypes, MDMs undergo more pronounced chromatin-accessibility rewiring, highlighting their greater plasticity compared with developmentally imprinted embryonic macrophages (Kloosterman et al., 2024). Similarly, in PDAC, $LYVE^{HI}$ TRMs display homeostatic functions more closely related to ECM remodeling associated with tissue repair, whereas $LYVE^{LO}$ MDMs preferentially activate inflammatory transcriptional programs. Interestingly, the tissue-maintenance and repair functions intrinsic to TRMs can be co-opted by tumor cells to promote tumor progression and aggressiveness (Zlotoff et al., 2011). Another key example of this co-option is observed in NSCLC, where TRMs establish a supportive niche for tumor cells by inducing EMT and Treg expansion (Kloosterman et al., 2024) and dormancy (Dalla et al., 2024).

Together, these findings highlight the role of ontogeny in shaping tumor progression through multiple mechanisms. However, understanding the role of resident macrophages across early tumor development, dissemination, dormancy, and relapse remains an evolving research area. Conceptually, a comprehensive view of the mechanisms that drive TRM survival, disappearance, and response to damage to different cancer therapies within tumors is still lacking.

Emergency myelopoiesis in cancer

Hematopoiesis is a highly dynamic process that can adapt immune cell production in response to peripheral demands. During acute inflammation, such as that caused by infection or cancer, this process is reprogrammed to meet the increased need for myeloid cells, a response known as emergency myelopoiesis (EM). Transcriptional, epigenetic, and metabolic programs that are inactive under homeostatic conditions are activated during EM to rapidly produce myeloid cells at the expense of other lineages (Swann et al., 2024). EM increased demand for innate immune cells in the TME is triggered by a range of activating signals. Among these, pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α play a key role in promoting HSC differentiation into MPP2 and MPP3 progenitors. Expansion of myeloid-biased MPP3 is enhanced by tumor-secreted factors, including G-CSF, WNT, and β-catenin (Aliazis et al., 2024). Several preclinical mouse tumor models, including PDAC (Bayne et al., 2012), HCC (Ramirez et al., 2024), and breast cancer (Yonemitsu et al., 2022), demonstrated that elevated tumor-derived GM-CSF promotes enhanced myeloid cell production. Likewise, tumor-secreted G-CSF activates STAT3 signaling and enhances myeloid cell survival, contributing to lung metastasis by upregulating pro-metastatic factors such as S100A8 and S100A9, as well as expanding GMP-lineage populations (Kowanetz et al., 2010). G-CSF and C/EBPβ are crucial regulators of granulopoiesis, and mice deficient in either factor show impaired granulocyte production under homeostatic conditions (Aliazis et al., 2024). Clinically, G-CSF is frequently administered to chemotherapy-treated patients experiencing neutropenia, highlighting its essential role in restoring neutrophil levels (Ng et al., 2025b). In response to myeloid demand after depletion of a given population (neutrophils), MPP3s expand at the expense of the HSC pool, suggesting that HSCs can be activated to generate an overproduction of myeloid-biased MPP3 populations (Kang et al., 2020). Another potential mechanism promoting EM involves the reprogramming of lymphoid-biased MPP4s toward the myeloid lineage, a shift enhanced by IL-6 in the context of myeloid malignancies (Reynaud et al., 2011). Cell-extrinsic regulation of EM has also been observed. A secretory MPP3 subset biased toward GMP differentiation, producing IL-1α, TNFα, GM-CSF, and M-CSF, and activating PU.1, established a feedforward loop that accelerates myeloid lineage expansion (Kang et al., 2023). Interestingly, local IL-1α produced in lung tumor niches enhances myelopoiesis in the BM, leading to accumulation of immunosuppressive myeloid progenitors (Park et al., 2024). A similar mechanism is observed in breast cancer, where tumor-derived IL-1β promotes granulopoiesis via increased C/EBPα activity (Garner et al., 2025). In both cases, disrupting the IL-1 signaling axis normalizes aberrant myelopoiesis (Fig. 2).

IL-4 produced in murine lung tumors drives additional mechanisms that act on BM GMPs to preferentially promote monocytic over granulocytic differentiation (LaMarche et al., 2024). This remodeling of hematopoiesis is essential for tumor progression, as blocking IL-4 signaling in early MDM progenitors markedly reduces lung tumor burden. These findings show that IL-4 from BM basophils and eosinophils programs myeloid progenitors toward immunosuppressive, tumor-promoting MDMs in NSCLC. Accordingly, deleting IL-4Rα in GMPs or depleting basophils diminishes tumor burden and restores myelopoiesis, while combining IL-4Rα blockade (dupilumab) with immune checkpoint inhibitors provides clinical benefit in resistant NSCLC patients.

EM can occur early during tumor progression. In MMTV-PyMT breast cancer mouse models, non-metastatic tumors drive myelopoiesis by expanding $Lin^{-}Sca\text{-}1^{+}c\text{-}Kit^{+}$ HSC populations, particularly MPP3 MPPs, while displacing LT- and ST-HSCs. This reprogramming is sustained, with HSCs from tumor-bearing mice upregulating myeloid genes such as *Mpo*, *Cebpb*, *Elane*, and *Ctsg* (Gerber-Ferder et al., 2023). Single-cell RNA sequencing (scRNA-seq) and ATAC-seq studies confirmed increased

chromatin accessibility for transcription factors like NFE2L2, STAT3, C/EBPβ, and C/EBPα in several tumor types, including NSCLC and HCC (Aliazis et al., 2024; Park et al., 2024; Hegde et al., 2024, *Preprint*).

Using a transgenic KEP (*K14^{Cre}; Cdh1$^{fl/fl}$; Trp53$^{fl/fl}$*) mouse model of spontaneous invasive breast lobular carcinoma an expansion of GMPs, pre-Neus, pro-Neus, and cMoPs, arising from an increased MPP3 pool was reported, providing evidence for tumor-driven myeloid skewing at the expense of the lymphoid and erythroid progenitor pool (Garner et al., 2025). Chromatin accessibility analysis of KEP BM showed enhanced activity of C/EBP and GATA family transcription factors, with a notable increase in *Cebpa* expression in GMPs, reinforcing myeloid lineage commitment. This myeloid bias is driven in part by IL-1β produced by TAMs, which activates a downstream pro-inflammatory and immunosuppressive signaling cascade (Wellenstein et al., 2019; Park et al., 2024). Hematopoietic stem and progenitor cells (HSPCs), which express the IL-1R1 receptor, respond to IL-1β by upregulating genes such as *Cebpa*, *Saa3*, and *Wfdc17*, further promoting myeloid skewing. Notably, this bias is reversible, as anti-IL-1β treatment reduces chromatin accessibility in GMPs, restores neutrophil maturation, and shifts their phenotype toward a less immunosuppressive state, characterized by increased CD101 expression and decreased expression of cKIT on circulating neutrophils (Garner et al., 2025).

Further exploration in BM reprogramming recently showed how lung tumors promote EM by activating *Nfe2l2* (NRF2) in myeloid progenitors, thereby enhancing their resistance to oxidative stress while suppressing IFN response and promoting the generation of immunosuppressive MDMs. Genetic deletion or pharmacological inhibition of NRF2 in tumor-bearing mice reduced MDMs survival, restored NK and T cell–mediated antitumor immunity, and improved the effectiveness of ICB therapy (Hegde et al., 2025).

While all these studies clearly demonstrate a shift in hematopoiesis toward myeloid overproduction in solid tumors, the underlying mechanism driving this expansion—whether through hyperactivation of homeostatic developmental myelopoiesis or through alternative, tumor-induced differentiation pathways—has not been fully elucidated.

Modulation of EM, including therapeutic targeting of IL-1β signaling, has emerged as a potential strategy in inflammation-driven hematologic states, particularly in clonal hematopoiesis (Hosseini and Chan, 2025). Inflammatory cues are central regulators of HSC activation, lineage bias, and mutant-clone fitness, and their dysregulation contributes to sustained myeloid skewing and expansion of inflammation-adapted clones (Swann et al., 2024). Interventions directed at these pathways may therefore attenuate downstream consequences of inflammatory clonal expansion. However, prolonged suppression of inflammatory signaling also carries biological risks, as chronic perturbation of cytokine-mediated stress responses can promote functional exhaustion within HSC-derived compartments and accelerate progenitor attrition (Wadley et al., 2025; Cervantes-Silva et al., 2022). In addition, systemic blockade of key inflammatory cytokines may impair the physiological maturation and antimicrobial competence of myeloid lineages, potentially increasing susceptibility to infection during treatment. Accordingly, these biological considerations must be carefully integrated across oncological patients from different age groups, given the central role of the myeloid compartment in organismal aging and the recognition of hematopoietic tissue as a key target for rejuvenation strategies (Andersson et al., 2025).

Epigenetic and metabolic reprogramming of the BM: Trained immunity

The traditional view that memory is exclusively a feature of adaptive immunity has been expanded to include the innate immune compartment, a phenomenon known as trained immunity (TI). TI refers to the long-term functional reprogramming of innate immune cells that enhances their response to subsequent challenges. Conceptualized by Netea et al. (2011) and refined in 2016 (Netea et al., 2016), TI is driven by transcriptional, epigenetic and metabolic changes that occur after an initial exposure to a stimulus, preparing the immune system for a more robust secondary response (Dominguez-Andres and Netea, 2019). In TI, innate immune cells undergo significant reprogramming, often switching toward glycolysis, and enhancing cytokine production and heightened effector functions.

Bacillus Calmette-Guérin (BCG) and β-glucan are frequently used in TI studies. BCG, an attenuated *Mycobacterium bovis* vaccine used against tuberculosis, has recently shown therapeutic benefits in cancer treatment and has been successfully used in the management of non-muscle invasive bladder cancer (Miyake et al., 2022; Morales et al., 1976). Additionally, intradermal and subcutaneous BCG administration enhanced local anti-tumor T cell responses in melanoma (Nishida et al., 2019; Kremenovic et al., 2020), CRC (Nishida et al., 2019), and NSCLC (Nishida et al., 2019). In these studies, myeloid cells showed increased production of pro-inflammatory cytokines, such as TNF-α, IL-6, IL-12, and IL-1β, together with enhanced pathogen killing capacity and ROS production.

β-glucan, a yeast-derived polysaccharide (Khan et al., 2025; Moorlag et al., 2020), is another powerful inducer of TI and shows promise as an anti-tumoral therapy. Several studies demonstrated that β-glucan induces epigenetic modifications in human monocytes, such as increased histone acetylation (H3K27ac mark), which facilitates chromatin remodeling and activation of anti-tumoral and antibacterial pathways (Tarancon et al., 2020). These changes result in heightened pro-inflammatory cytokine production (e.g., IL-6 and TNF-α) and a shift toward glycolytic metabolism, with decreased oxygen consumption and extracellular acidification (Moorlag et al., 2020).

The long-term memory ascribed to the impact of TI reprogramming in HSCs and myeloid progenitors not only ensures transmissible trained progeny but also influences myeloid differentiation pathways in the BM (Fig. 2), directly shaping the immune response in cancer. Concrete examples of how TI affects myeloid progeny can be found in both neutrophils and macrophages. As such, TI-GMP reprogramming was first demonstrated in melanoma models, where long-lived BM progenitors generate IFN-I–trained neutrophils with enhanced IFN-I response, degranulation, and ROS production, producing a transmissible anti-tumor phenotype that contributes to tumor growth

suppression independent of B and T cell immunity (Kalafati et al., 2020). A similar phenotype for trained neutrophils has recently been reported in a study that explored whether the adjuvant β-glucan can reprogram innate immunity to protect against influenza A virus (IAV) infection (Khan et al., 2025). This protection relies on a population of immNeus recruited to the lungs via RORγ⁺ T cells. β-glucan induced systemic reprogramming of HSPCs via IFN-I–signaling, generating regulatory neutrophils with enhanced mitochondrial oxidative metabolism and IL-10 production. The protective effect of trained macrophages derived from CCR2⁺ interstitial macrophages (IMs) has also been explored. Trained BM-derived IMs were enriched in phagocytic genes (such as *Rap1* and *Sirpa*), as well as exhibiting increased mitochondrial ROS production. This reprogramming enabled IMs to gain enhanced phagocytic, cytotoxic, and enhanced expression of co-stimulatory molecules (CD80 and CD86) and antigen presentation, reinforcing anti-tumoral effects (Ding et al., 2023). The authors also reported similar results in preclinical mouse models of breast cancer development. Whole glucan particle–treatment in adjuvancy (posttumor resection) showed improved survival outcomes and reduced metastasis in orthotopic and *K-ras*^{LA1} GEMM model. Trained BM-derived monocytes and macrophages also infiltrate efficiently in dense stromal TME—as seen in PDAC—and directly kill tumor cells alone or combined with anti-PD1 ICB (Woeste et al., 2023; Geller et al., 2022).

Local TI can also be acquired by resident cells, as exemplified by trained alveolar macrophages following viral infection. IAV-exposed resident alveolar macrophages (Wang et al., 2023c) showed enhanced phagocytic and tumor cytotoxic functions in B16 and 4T1 preclinical mouse models of lung metastasis. These trained anti-tumoral functions seen in alveolar macrophages are dependent on IFNγ and NK cells. Similarly, β-glucan and IFNγ-stimulated macrophages and neutrophils induce regression of metastatic OC through an IL-27–dependent mechanism, enhancing CD8⁺ T cell activation and supporting myeloid-centric immunotherapy (Murphy et al., 2024).

Interestingly, the role of influenza or other viral infections, such as SARS-CoV-2, has gained attention because of recent findings showing IL-6–dependent exit from dormancy in disseminated tumor cells in breast cancer models (Chia et al., 2025). The authors analyzed clinical data to determine whether cancer survivors had a higher risk of cancer-related death after SARS-CoV-2 infection. Patients who tested positive nearly doubled their risk, highlighting the potential detrimental impact that previous inflammatory challenges can impose on organs and predisposition to lung metastasis. How this initial viral challenge might have impacted long-term reprogramming of HSPC and its causative effects on long-term immunity remains to be determined.

Epigenetic and metabolic reprogramming represent a new frontier in innate immune memory, demonstrating how myeloid cells can be reprogrammed to boost anti-tumoral responses. Combining TI inducers with ICB has been shown to induce potent anti-tumor immunity and reduce tumor burden, including in models of ICB-resistant tumors (Geller et al., 2022; Priem et al., 2020) Despite significant progress in TI and cancer immunotherapy, important questions remain, for example, the intensity and durability of TI, how different routes of administration (e.g., intravenous versus intradermal/subcutaneous) alter the magnitude and quality of training, and the optimal timing/sequence for inducing TI relative to time-dependent responses to ICB (as discussed below).

CHIP reprogramming of hematopoiesis

Understanding how clonal expansion alters hematopoiesis is key to elucidating the role of CHIP in disease and tissue dysfunction. Competitive HSC transplantation studies showed that *TET2* and *DNMT3A* mutations confer increased self-renewal (Ostrander et al., 2020), and aging hematopoiesis becomes increasingly reliant on dominant clones, often carrying these mutations (Rodrigues et al., 2021; Mitchell et al., 2022; Spencer Chapman et al., 2024). *DNMT3A* mutations tend to arise early and expand gradually, while *TET2* mutations can occur later and continuously generate altered immune cells (Fabre et al., 2022), potentially shaping long-lived lineages and reducing immune non-mutated diversity. A hallmark of CHIP is its promotion of a chronic inflammatory state (Fig. 2).

Mutant HSCs and their progeny activate inflammatory signaling (Jakobsen et al., 2024; Heimlich et al., 2024) and secrete cytokines like IL-1β, TNF-α, and IL-6 (Belizaire et al., 2023), which enhance the expansion of myeloid-biased progenitors (e.g., GMPs) and reinforce the pro-inflammatory loop (Balandran et al., 2023). This environment facilitates further clonal expansion: TNF-α boosts *Tet2*- and *Dnmt3a*-mutant HSCs (Abegunde et al., 2018; SanMiguel et al., 2022; Quin et al., 2024b), IL-6 promotes *DNMT3A*-mutant HSC growth (Zioni et al., 2023), and IL-1α drives proliferation in *Tet2*-deficient cells (Caiado et al., 2023). IL-1α secretion after DNMT3A inhibition also enhances myelopoiesis and aging features (Park et al., 2024). These findings suggest that aging selects for clones with enhanced fitness under inflammatory stress (Schleicher et al., 2024). Indeed, in humans, DNMT3A- and TET2-mutant HSCs exhibit a reduced inflammatory response compared with WT HSCs within the same sample, which might indicate that fitness is gained through desensitization of mutated cells to a harsh inflammatory environment (Jakobsen et al., 2024).

Rather than passive bystanders, CHIP-mutant clones actively reshape the BM niche to support their survival. Beyond self-renewal, CHIP skews lineage output—particularly *TET2* mutations, which drive a myeloid bias at the expense of lymphoid lineages (Fabre et al., 2022; Jakobsen et al., 2024)—reducing immune competence.

While similar mechanisms are well established in acute myeloid leukemia (Miraki-Moud et al., 2013; Jager et al., 2021), CHIP may also impair erythropoiesis (Vlasschaert et al., 2022). Age-related immune decline features increased myelopoiesis and reduced lymphoid output (Rodrigues et al., 2021). Mouse models show that depleting myeloid-biased HSCs restores antiviral immunity (Ross et al., 2024), suggesting that competition between lineages may drive immune dysfunction in CHIP carriers. Moreover, CHIP-associated lymphoid progenitor loss may limit thymic regeneration after irradiation (Zlotoff et al., 2011), potentially accelerating thymic involution and adaptive immune decline.

In summary, CHIP-associated mutations foster a pro-inflammatory BM environment that favors mutant clone expansion, survival, and lineage bias. These changes overlap with hallmarks of immunosenescence, supporting the idea that CHIP contributes to immune aging and may promote premalignant or pre-metastatic niche formation.

Time-dependent modulation of myeloid plasticity: A matter of a day

Circadian rhythms (CRs) are 24-h biological oscillations that synchronize physiological processes with environmental cues such as light and temperature. These rhythms are governed by cell-autonomous molecular clocks, primarily through a transcriptional–translational feedback loop involving the core clock proteins BMAL1 and CLOCK, which regulate the expression of clock-controlled genes. Their activity is modulated through negative feedback by PER and CRY proteins, and further fine-tuned by nuclear receptors such as REV-ERBs and RORs, forming interconnected regulatory loops (Mackey and Golden, 2007). CRs are coordinated both centrally by the suprachiasmatic nucleus, which is entrained by light, and peripherally through clocks in tissues, including immune cells, which respond to systemic cues, such as feeding, hormone levels, and metabolism. This multilayered synchronization ensures that immune and cellular responses are temporally aligned with daily environmental changes, conferring evolutionary advantages by optimizing immune readiness and maintaining homeostasis.

Cell-intrinsic circadian programs in myeloid cells

Disruption of CRs can lead to desynchronization between systemic and cellular processes, particularly affecting immune cells such as myeloid cells (Fig. 3). This may lead to aberrant inflammation, impaired immune surveillance, and increased susceptibility to diseases, including cancer. Recent advances in circadian biology demonstrated that macrophages and neutrophils possess intrinsic molecular clocks that regulate their functions. In macrophages, BMAL1 and its repressors coordinate fundamental immune processes, including phagocytosis, cytokine production, and ROS generation. Loss of BMAL1 function impairs these responses, resulting in defective pathogen clearance, increased susceptibility to sepsis, and signs of accelerated immunosenescence (Shim et al., 2024; Early et al., 2018; Li et al., 2025).

Clock epigenetic regulators such as REV-ERBα/β modulate enhancer activity and gene expression of immune-related genes like *Saa1*, *Nrf2*, *Mmp9*, and *Cx3cr1* (Lam et al., 2013; Shim et al., 2024; Early et al., 2018), which in turn, modulate inflammasome activation and ROS production (Kou et al., 2022), among others. In cDCs, for example, cell-intrinsic clocks also play a crucial role in regulating immune activation. Recent studies highlight that BMAL1 in cDCs govern the circadian timing of co-stimulatory molecule expression (e.g., CD80), antigen processing, and, ultimately, T cell priming and anti-tumor immunity (Ince et al., 2023; Cervantes-Silva et al., 2022; Wang et al., 2024a). These findings underscore that the cDC clock is not a passive timekeeper, but an active regulator of immune competence in contexts such as vaccination and cancer immunotherapy (Wang et al., 2023a).

However, whether similar transcriptional programs are maintained in other myeloid subsets more abundant within tumors such as macrophages and neutrophils remain unclear. In neutrophils, circadian clocks orchestrate both their abundance in tissues and their functional states. PER2 (a BMAL1 repressor) is essential for ROS production and bacterial killing by promoting infection-induced expression of the alarmin *hmgb1a*. This regulation is mediated through a conserved cis-regulatory element that contains binding motifs for both BMAL1 and NF-κB, enabling *hmgb1a* expression specifically during the light phase in response to infection (Du et al., 2025). A neutrophil-clock intrinsic program enabled these cells with the ability of eliminate pathogens and counterbalance their blood vessel protection. BMAL1-regulated expression of the chemokine CXCL2 induces chemokine receptor CXCR2-dependent diurnal changes in the transcriptional and migratory properties of circulating neutrophils. These diurnal alterations, referred to as neutrophil aging, were antagonized by CXCR4 and regulated the outer topology of neutrophils to favor homeostatic egress from blood vessels at night, resulting in boosted antimicrobial activity in tissues. Mice engineered for constitutive neutrophil aging (CXCR4-deficient) became resistant to infection, but the persistence of intravascular aged neutrophils predisposed them to thromboinflammation and death. Thus, diurnal compartmentalization of neutrophils, driven by an internal timer, coordinates immune defense and vascular protection (Adrover et al., 2019).

Circadian immune checkpoints and therapeutic opportunities

Neutrophil aging, a process marked by downregulation of CD62L and upregulation of CXCR4, promotes their own clearance through homing to the BM (Casanova-Acebes et al., 2013). Neutrophils exhibit circadian alterations in granule content, nuclear morphology, and NETs formation, with peak antimicrobial activity at the mouse resting phase coinciding with daily variations in NET release (Adrover et al., 2019; Adrover et al., 2020). Because aged neutrophils can drive severe vascular inflammation (Adrover et al., 2019), accumulate in metastatic breast and melanoma mouse models, and enhance liver metastasis (Peng et al., 2021), manipulation of the circadian neutrophil timer holds clear clinical relevance. For instance, targeting receptors involved in neutrophil clearance—such as CXCR4—could offer novel therapeutic strategies for a wide range of neutrophil-driven conditions, including infections, cardiovascular diseases, inflammatory disorders, and cancer. As such, a recent study showed that CXCR4^{+} LOX1^{+}-immunosuppressive neutrophils impair the efficacy of anti–PD-1 therapy in gastric cancer (Qian et al., 2025). This study showed that a CXCR4 partial agonist (TFF2-MSA) selectively reduces CXCR4^{+}-immunosuppressive neutrophils, reprograms granulopoiesis, and restores anti-tumor immunity when combined with PD-1 blockade. These results are consistent with the work by Aroca-Crevillén et al. in which the authors showed that circadian regulation of neutrophil activity is a key determinant of inflammatory tissue injury. The authors demonstrate that periods of natural tissue protection coincide with peaks in the chemokine CXCL12, which inhibits the neutrophil-intrinsic clock via CXCR4

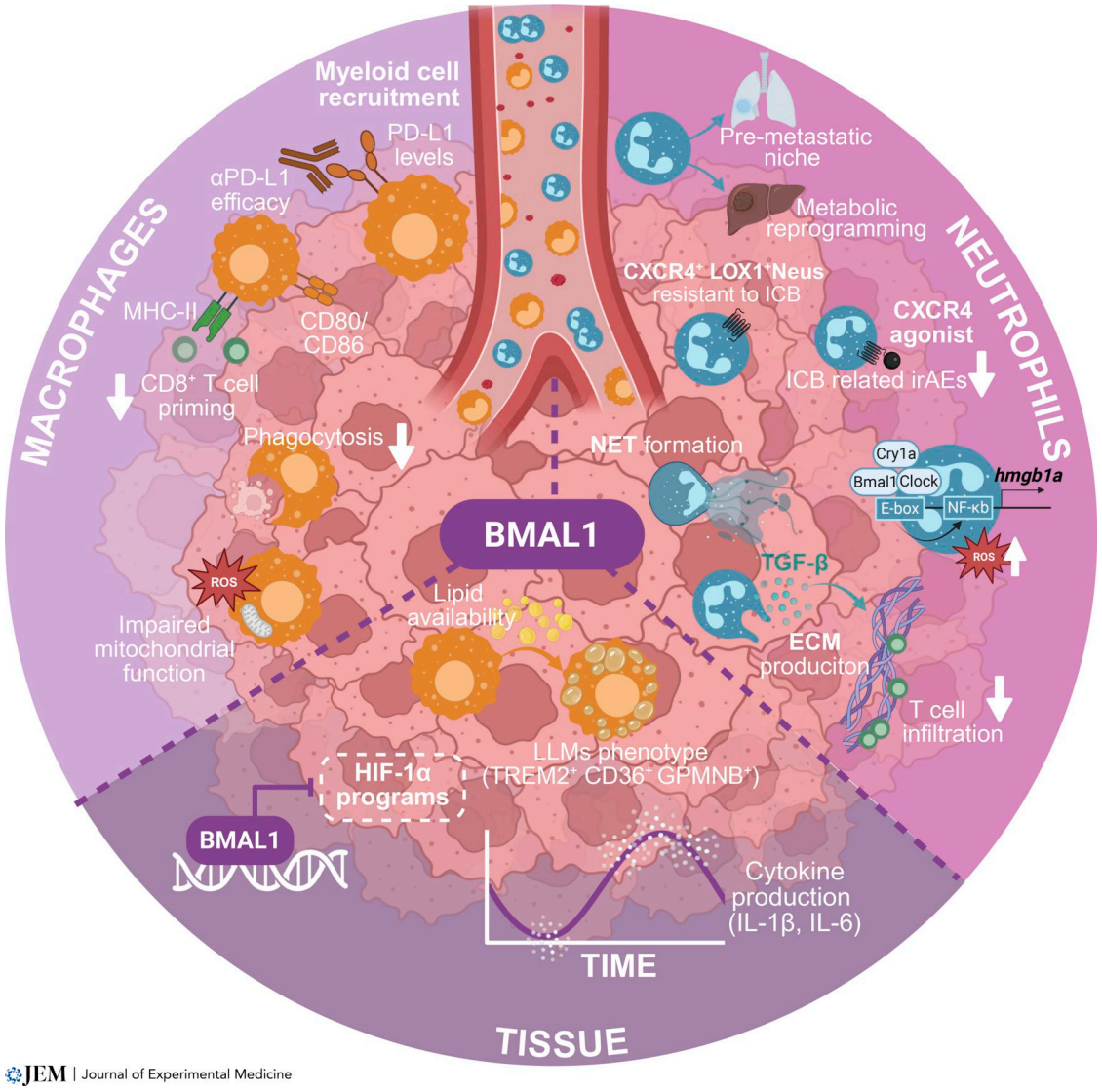

Figure 3. **BMAL1-dependent tumor programs in myeloid cells.** Loss of BMAL1 disrupts key functional programs in neutrophils and macrophages, as well as within the TME, underscoring the critical role of CRs in regulating both pro- and anti-tumoral myeloid responses. Neus, neutrophils.

signaling (Aroca-Crevillén et al., 2025). Both genetic and pharmacological activation of CXCR4 prevent harmful diurnal spikes of inflammatory injury by repositioning neutrophils away from healthy tissue, without suppressing their overall number or antimicrobial functions. Importantly, these findings identify a circadian immune checkpoint mediated by CXCR4 that can be targeted pharmacologically to protect host tissues. Based on this mechanism, pharmacological CXCR4 agonists could be explored as a strategy to prevent or reduce immune-related adverse events (irAEs) in cancer immunotherapy. By limiting the collateral damage caused by neutrophil-driven inflammation without compromising antimicrobial defense, this approach may help mitigate side effects associated with ICB and other immunotherapies, improving patient safety and therapeutic outcomes. Interestingly, neutrophil signaling can also be exploited to promote anti-tumoral phenotypes in these cells. Recent findings showed that targeted deletion (using STAT3 antisense oligonucleotide) or inhibition of STAT3 signaling in neutrophils reprograms them toward an anti-tumoral phenotype (with enhanced expression of MHCII, CD80 and CD86, and ICAM1), enhancing cytotoxic CD8⁺ T cell responses and significantly reducing tumor growth and metastasis in mouse models (Ozel et al., 2025). These findings, supported by patient-derived tumor explants, suggest that neutrophil-specific STAT3 inhibition represents a promising therapeutic strategy to improve cancer immunotherapy outcomes, which might also illuminate anti-tumoral or inflammatory programs in neutrophils controlled by BMAL1. Neutrophil trafficking follows circadian patterns, and accumulating evidence suggests they can entrain local circadian programs in peripheral tissues and possibly within tumors (Casanova-Acebes et al., 2018). For example, neutrophils regulate the rhythmic activity of the BM niche and the transcriptional profile of lung tissue, influencing HSCs egress and metastatic seeding (Casanova-Acebes et al., 2013, 2018). Neutrophil infiltration into the liver has been linked with increased expression of *Bmal1* and *Clock*, as well as enhancing hepatocyte metabolic activity (Crespo et al., 2020), suggesting that neutrophils can per se set

temporal windows in tissular activity. These data collectively highlight that cell-intrinsic clocks in myeloid cells are not only essential for innate immunity but may also influence broader aspects of tissue homeostasis and tumor progression.

Circadian clocks regulate antigen presentation in DCs and phagocytosis in macrophages under steady-state conditions (Kitchen, 2020; Cervantes-Silva et al., 2022), suggesting a temporal layer of immune regulation that can enhance T cell priming. In line with this, TAMs in the B16 melanoma model exhibit a more inflammatory phenotype during the active phase in mice (Aiello et al., 2020), accompanied by increased $CD4^+$ and $CD8^+$ T cell tumor infiltration and reduced $CD8^+$ T cell exhaustion (Wang et al., 2024b). Conversely, circadian disruption through chronic jet lag in a breast cancer GEMM (MMTV:PyMT) increases TAM abundance, reduces $CD8^+$ T cell infiltration, and promotes lung metastasis (Hadadi et al., 2020). Mechanistically, BMAL1 loss in myeloid cells impairs mitochondrial function, increases ROS production via HIF1α activation, and drives a metabolic shift toward glycolysis and amino acid catabolism. Pharmacological inhibition of mitochondrial complex II with dimethyl malonate reduces ROS and HIF1α accumulation (Alexander et al., 2020), limiting tumor growth and potentially reprogramming these macrophages. Beyond the myeloid compartment, BMAL1 depletion in transformed epithelial cells in a CRC GEMM promotes myeloid cell accumulation, impairs $CD8^+$ T cell immunity, and increases PD-$L1^+$ myeloid cells in a time-of-day–dependent manner. Notably, anti–PD-L1 blockade is more effective when administered during the active phase in CRC, lung cancer, and melanoma models (Fortin et al., 2024). Collectively, these studies position BMAL1 circadian-controlled programs as an immunometabolic checkpoint linking circadian control of mitochondrial metabolism, redox balance, and anti-tumor immunity.

Chrono-immunotherapy: Timing matters

CRs additionally shape the efficacy of cancer therapies by modulating drug metabolism, immune cell function, and tumor cell sensitivity. The timing of treatment administration affects pharmacokinetics and therapeutic outcomes due to rhythmic expression of enzymes and transporters involved in drug processing (El-Tanani et al., 2024). ICB and CAR-T cell therapies show significant time-of-day variation in both experimental models and clinical outcomes (Landre et al., 2024; Qian et al., 2021; Tsukaguchi et al., 2025; Wang et al., 2024b; Fortin et al., 2024). For a more in-depth discussion of current clinical trials evaluating the impact of administration timing in immunotherapy, readers are referred to excellent reviews (Pick et al., 2024; Karaboue et al., 2024). Notably, patients who receive immunotherapy in the morning (before 4 p.m.) exhibit longer progression-free survival (PFS) and overall survival (OS) compared with those treated later in the day (Vander Velde et al., 2020). Furthermore, in a retrospective multicenter study of unresectable NSCLC patients treated with first-line pembrolizumab, early morning administration of the first infusion (≤11 a.m.) was associated with significantly improved OS but also a higher rate of severe irAEs. The authors suggest that the timing of the initial checkpoint inhibitor dose may be a simple, clinically relevant variable that warrants prospective validation (Tsukaguchi et al., 2025). Furthermore, the first prospective randomized clinical trial evaluating the immune and clinical impact of early versus late time-of-day administration of anti–PD-1 therapy has recently been reported (Huang et al., 2026). In patients with stage III–IV NSCLC, peripheral blood immune profiles were assessed longitudinally by flow cytometry at baseline and after the second and fourth treatment cycles. Early administration was associated with increased circulating $CD8^+$ T cell levels, whereas a decline was observed in patients receiving late administration. Consistently, the ratio of activated ($CD38^+HLA\text{-}DR^+$) to exhausted ($TIM\text{-}3^+PD\text{-}1^+$) $CD8^+$ T cells was higher in the early treatment group. Importantly, these immunological changes translated into improved clinical outcomes: median PFS was 11.3 versus 5.7 mo, and median OS was 28.0 versus 16.8 mo for early versus late administration, respectively. Treatment-related adverse events were consistent with the known safety profile, with no new safety signals observed. Together, this study provides the first clinical evidence that early administration of ICB is associated with improved patient survival, likely through enhanced anti-tumor $CD8^+$ T cell immunity. These findings support consideration of time-of-day as a relevant variable in clinical practice and suggest that administering ICB during early hours may improve outcomes without compromising safety. However, several challenges may limit immediate clinical implementation. Prioritizing early-day infusions (e.g., before noon), in alignment with individual active phases, could strain hospital logistics, particularly when ICB is administered alongside other therapies requiring coordinated delivery and nursing follow-up, such as chemotherapy. In addition, understanding the "optimal" basal chronotype for patients to benefit for timed of administration of ICB should be further understood. Equally, the timing of diagnostic biopsies should be reported in publications, as immune infiltration status ("hot" versus cold tumors) varies depending on the time of sample collection and could lead to misclassification or not valid immune and effector function interpretations. Finally, there are currently no clinically accessible biomarkers to determine individual chronotypes and guide personalized treatment timing. Nevertheless, coordinated efforts combining preclinical studies—allowing deeper molecular exploration for biomarker identification—and validation in human cohorts may enable the development of clinically useful, easy-to-implement biomarkers to capture individual circadian profiles and support future time-tailored therapies.

Unexpectedly, a study described a specialized population of neutrophils in the skin that extends beyond their traditional microbicidal functions by producing ECM components, including collagen (Vicanolo et al., 2025). These neutrophils contribute to the structural reinforcement and mechanical stability of the skin barrier, protecting against bacterial invasion and foreign molecules. Upon injury, they form matrix "rings" around wounds, which act as physical shields that support healing and prevent infection. This matrix production by neutrophils is regulated by TGF-β signaling and follows a CR, with matrix deposition peaking at night, optimizing skin defense and repair functions. This work shows that certain neutrophils produce a dense ECM that can physically block T cells from entering the tumor, reducing their ability to attack cancer cells. This ECM barrier may contribute to resistance against ICB therapies. Thus, targeting pathways like TGF-β, which drive ECM production in these neutrophils at a

given time, could help improve T cell infiltration and enhance the effectiveness of ICB, particularly in skin cancers or metastases where these neutrophils are common. As shown, these effects are likely driven, at least in part, by circadian regulation of immune cell trafficking, effector function, and tissue-specific inflammation. Specifically, myeloid cell maturation, migration, and metabolic fitness may be temporally gated to enhance therapeutic efficacy when treatment aligns with periods of heightened immune activity.

Given the central role of CRs in regulating tissue metabolism, it is conceivable that these clocks orchestrate temporally dynamic transcriptional programs in tumor-associated myeloid cells. Environmental cues such as hypoxia, IL-1β, PGE2, and lipid availability shape the functional state of TREM2$^+$, GPNMB, and CD36$^+$ LLMs, which have been linked to immunosuppression and therapy resistance in HCC, PCa, and GBM (Ramirez et al., 2024; Masetti et al., 2022; Kloosterman et al., 2024). In this context, a recent study (Early et al., 2018) highlights the role of the core clock protein BMAL1 in regulating NRF2, a key anti-inflammatory transcription factor that suppresses ROS production and the pro-inflammatory cytokines IL-1β and IL-6. BMAL1 directly binds to the *Nrf2* promoter to promote its expression. Loss of BMAL1 impairs NRF2 activation in response to inflammatory stimuli (e.g., LPS), leading to reduced glutathione synthesis, increased ROS accumulation, stabilization of HIF-1α, and elevated IL-1β levels (Early et al., 2018). Notably, this pro-oxidative and pro-inflammatory phenotype can be reversed through genetic or pharmacological activation of NRF2 or via antioxidant treatment. These findings underscore a critical link between the circadian clock and inflammatory regulation in innate immune cells, with potential implications for tumor immunity and chronic inflammatory diseases. Furthermore, emerging evidence suggests that specific subsets of anti-tumoral neutrophils are essential for effective ICB therapy (Benguigui et al., 2024; Gungabeesoon et al., 2023). Given the observations of improved outcomes with time-of-day administration of ICB, together with the emerging phenotypes of anti-tumoral neutrophils, it is conceivable that circadian-controlled neutrophil mechanisms play a broader role in shaping the tumor immune microenvironment and influencing therapy responses.

The role of BMAL1 in TAMs has been further elucidated using experimental models. For instance, in a study involving co-injection of B16-F10 melanoma cells with either WT or BMAL1-deficient BM-derived macrophages, tumors receiving BMAL1-deficient macrophages displayed increased growth, reduced CD8$^+$ T cell infiltration, and diminished IFN-γ production by both CD8$^+$ T and NK cells (Alexander et al., 2020). Mechanistically, BMAL1 was shown to maintain mitochondrial function and oxidative metabolism in LPS-stimulated macrophages, with its absence resulting in elevated ROS production and reduced oxygen consumption via succinate dehydrogenase impairment. In another study using a genetic model of CRC combined with scRNA-seq, circadian disruption—either genetically or environmentally—led to accumulation of myeloid cells and a concomitant reduction in cytotoxic CD8$^+$ T cells within the TME (Fortin et al., 2024). The study identified a clock-dependent signaling axis between intestinal epithelial cells and the immune system mediated by rhythmic cytokine and chemokine release. Notably, the abundance of PD-L1–expressing myeloid cells fluctuated rhythmically in both intestinal and peripheral tissues. Furthermore, anti–PD-L1 therapy was most effective when administered during the early active phase in mice, a time when immunosuppressive myeloid cells were most abundant, reinforcing the idea that therapeutic timing can be optimized based on circadian control of immune composition and immune programs (Fig. 3).

Open questions and future directions in myeloid chronobiology

Together, these findings highlight that BMAL1 and circadian programs within myeloid cells can exert critical roles in the TME. However, it remains to be determined which are these BMAL-1–controlled programs are and whether they contribute significantly to the rhythmic regulation of either pro- and/or anti-tumor immunity. Addressing this knowledge gap may reveal new opportunities for chrono-immunotherapy strategies that align treatment schedules with peak immune responsiveness for enhanced clinical outcomes.

Concluding remarks

Modulating myeloid cells in cancer remains a complex and nuanced challenge, largely due to their intrinsic heterogeneity and essential roles in immune defense, tissue repair, and homeostasis. Broad depletion or dysfunction of these cells brings risks, compromising host immunity and increasing susceptibility to infection. Despite these challenges, recent advances in single-cell and multi-omic technologies are enhancing our spatial, temporal, and functional understanding of myeloid populations within tumors, revealing context-dependent mechanisms of response and resistance—particularly in relation to immunotherapy (Li et al., 2024).

Yet how targeting strategies functionally reprogram neutrophil and macrophage states or phenotypes in tumors—and how these interventions influence their developmental trajectories in the BM—remains largely unexplored. One potential scenario, currently being tested in clinical trials, is supported by evidence that locally identified signals can reprogram systemic responses in the BM, promoting the chronic generation of immunosuppressive myeloid cells. Targeting the IL-4R pathway (LaMarche et al., 2024) or the IL-1β–IL-1R axis (Caronni et al., 2023), alone or in combination with ICB, may enable the development of novel systemic therapies. These strategies emphasize the concept of cancer as an organism-level disease, extending therapeutic impact beyond the local TME.

One of the current limitations in cancer studies is that, while sophisticated tools are being developed to explore tumor-immune cross talk, very few investigations thoroughly characterize the functional profiles of myeloid cells in cancer patients, often restricting analyses to changes in cell numbers or broad immunosuppressive phenotypes due to limited sample availability. This underscores the persistent gap between cancer biologists (who primarily report numerical or phenotypic changes) and immunologists (who aim to uncover novel functional immune phenotypes). To overcome these challenges, the field must adopt advanced experimental systems that more accurately recapitulate

human myeloid diversity, plasticity, and TME–immune interactions. Humanized mouse models, organoid-immune co-culture platforms, and *ex vivo* myeloid differentiation systems offer promising directions, yet each capture only fragments of the complex and patient-specific cues that shape myeloid behavior *in vivo*. Integrating these models with longitudinal sampling, high-dimensional profiling, and functional perturbation technologies will be essential to uncover how therapeutic interventions remodel myeloid lineages over time. Ultimately, only by deploying more physiologically relevant and mechanistically informative models, we can design durable approaches to reprogram dysfunctional myeloid cells, restore tissue homeostasis, and improve the translational impact of immunotherapies in human cancers.

As discussed, myeloid infiltrating cells in tumors are not uniformly immunosuppressive. Increasing evidence highlights their immunomodulatory capacity, reminiscent of their multifunctional roles in homeostasis, which can be reshaped by treatment-based interventions such as ICB, chemotherapy, radiotherapy, or even BCG and COVID-19 vaccination (Grippin et al., 2025). Their localization and immediate neighbors—the so-called niche—critically determine their function, a concept that is only beginning to be fully appreciated. Importantly, accumulating evidence now indicates that BMAL1 and other core components of the circadian clock exert potent anti-tumor effects through regulation of cDCs receptors and potentially in other tumor-infiltrating myeloid subsets. These circadian programs modulate essential functions such as antigen presentation, cytokine production, metabolism, and immune cell trafficking in a time-of-day–dependent manner, thereby shaping the tumor immune landscape and influencing the efficacy of therapies such as ICB.

A major challenge ahead lies in integrating both cell-intrinsic programs (e.g., molecular clocks) and extrinsic signals (e.g., metabolic, microbial, or hormonal cues), along with broader exposome influences, into a coherent framework that enables therapeutic reprogramming of myeloid cells without compromising their homeostatic roles.

We have intentionally avoided setting a hierarchical dominance of cues (oncogenic, metabolic, and circadian) in modeling myeloid phenotypes, as these are intricately intertwined processes. The evidence suggests that these cues do not operate in isolation, but rather interact dynamically. Circadian disruption can alter cancer risk (Pariollaud, 2020), while oncogenic signals can reprogram metabolic pathways by subverting the molecular clock (Wang et al., 2024b). The specific dominance of cues likely varies by cancer type and stage, highlighting the need for nuanced and integrative context-specific investigation.

As our understanding of myeloid temporal plasticity deepens—across daily (circadian), longitudinal (developmental or disease progression), and spatial (tissue-specific) scales—we are at a pivotal moment to decipher how these dimensions intersect to influence tumor progression, immune suppression, and therapy response. This perspective also calls for a critical re-evaluation of current preclinical mouse models, which often fail to capture human circadian biology, and underscores the need for orthogonal studies in human samples—requiring coordinated efforts among researchers, clinicians, patients, and caregivers. A notable step forward has been the proposal of a modular and flexible framework to define myeloid heterogeneity, integrating developmental, spatial, and functional axes, as recently achieved for neutrophils (Ng et al., 2025a). In line with this, our definitions of myeloid cell states and subsets must remain open to incorporating novel dimensions—such as temporal factors, both longitudinal and circadian—into the evolving landscape of tumor immunology, as revealed by the modulation of mutational drivers in myeloid cells.

Doing so may uncover novel chrono-immunotherapeutic windows in which interventions are optimized not only for target specificity but also for alignment with the functional antitumoral oscillations of the immune system. In this context, time is not merely a background variable; it is an active determinant of myeloid cell identity, function, and therapeutic potential.

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