REVIEW

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Understanding and targeting erythroid progenitor cells for effective cancer therapy

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Purpose of review
It is well described that tumor-directed aberrant myelopoiesis contributes to the generation of various myeloid populations with tumor-promoting properties. A growing number of recent studies have revealed the importance of the previously unappreciated roles of erythroid progenitor cells (EPCs) in the context of cancer, bringing the updated concept that altered erythropoiesis also facilitates tumor growth and progression. Better characterization of EPCs may provide attractive therapeutic opportunities.

Recent findings
EPCs represent a heterogeneous population. They exhibit crucial pro-tumor activities by secreting growth factors and modulating the immune response. Cancers induce potent EPC expansion and suppress their differentiation. Recent single-cell transcriptome and lineage tracking analyses have provided novel insight that tumor-induced EPCs are able to be transdifferentiated into immunosuppressive myeloid cells to limit T-cell function and immunotherapy. Therapeutic strategies targeting key factors of EPC-driven immunosuppression, reducing the amount of EPCs, and promoting EPC differentiation and maturation have been extensively investigated.

Summary
This review summarizes the current state of knowledge as to the fascinating biology of EPCs, highlights mechanisms by which they exert the tumor promoting activities, as well as the perspectives on future directions and strategies to target these cells for potential therapeutic benefit.

Keywords
cancer, erythroid progenitor cells, erythropoiesis, immunotherapy

INTRODUCTION

Tumor is a heterogeneous and complex ecosystem. The tumor microenvironment contains myriads of stromal cells of hematopoietic and nonhematopoietic developmental origin, such as myeloid cells, T-cells, B cells, natural killer (NK) cells, fibroblasts, pericytes, adipocytes, endothelial cells, and neural cells, which collectively shape the course of the disease and affect therapeutic efficacy of various treatment regimens. Over the past few decades, remarkable progress has been made in understanding the roles of regulatory T-cells (Tregs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), and cancer-associated fibroblasts (CAFs) in cancer progression and response to therapies. Recent studies revealed the importance of the previously unappreciated cell population, erythroid progenitor cells (EPCs), as a negative regulator of antitumor immunity.

Erythropoiesis is a well orchestrated and strictly regulated process for maintaining a stable number of red blood cells (RBCs), which is necessary for adequate oxygen transport. Classically, the commitment of hematopoietic stem cells (HSCs) to erythroid cells starts with the differentiation to a multipotent megakaryocyte-erythroid progenitor (MEP) in the bone marrow, followed by a burst-forming erythroid (BFU-E) and colony-forming erythroid (CFU-E) progenitors. Subsequent maturation of CFU-E gives

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KEY POINTS

- Cancers induce EPC expansion and alter their differentiation.
- EPCs possess potent immunosuppressive properties, which promote tumor progression and diminish therapeutic efficacy.
- EPC-focused therapeutics are under development, and better understanding the biology of EPCs may offer more effective cancer treatment.

rise to a cascade of morphologically distinguishable erythroid precursors, including proerythroblasts, basophilic erythroblasts, polychromatophilic erythroblasts, and orthochromatic erythroblasts that extrude their nuclei to generate reticulocytes. Reticulocytes then enter the peripheral blood wherein they fully mature to functional RBCs in a few days. Noteworthy, findings from recent single-cell genomic studies have advanced our view on erythropoiesis, which suggest a continuum of cell states during EPCs differentiation into mature erythrocytes [1].

MAIN PHENOTYPIC AND EXPANSION OF ERYTHROID PROGENITOR CELLS IN CANCER

EPCs represent a heterogeneous population, predominantly composed of erythroblasts and reticulocytes, based on the classical view of erythropoiesis. These immature erythroid cells are characterized by the expression of transferrin receptor 1 (CD71) and erythroid lineage markers, glycophorin A (CD235a) in humans and glycophorin A-associated protein (TER119) in mice. Therefore, these cells also have been defined as 'CD71' erythroid cells (CEC). Moreover, studies have shown that a subpopulation of $CD71^{+}$ erythroid cells also express pan-leukocyte marker CD45, which is lost during late-stage erythroid differentiation. Thus, CD45 is also used as a marker of early-stage nucleated erythroid cells [2].

In healthy adults, EPCs are mainly in bone marrow with relatively low frequency. However, they are physiologically enriched in extramedullary sites (including spleen, liver, and peripheral blood) in neonates and during pregnancy of murine models and humans [3,4], which enables the production of sufficient erythrocytes in these special stages. The expansion of EPCs is also observed as a response to anemia, thus enhancing erythropoiesis. Clinically, it has been demonstrated that EPC abundance generally correlates with the severity of anemia in patients [5]. Intriguingly, the percentage of EPCs in peripheral blood is significantly increased in patients with lymphocytic leukemia [6] and solid tumors [5,7]. Moreover, the substantial expansion of EPCs in cancer patients having bone marrow metastases leads to leucoerythroblastosis [7]. These erythroid progenitors also expand rapidly at extramedullary sites, predominantly in the spleen [5,8], and subsequently infiltrate into the tumor, such as in hepatocellular carcinoma [9▪▪] and glioblastoma [10▪]. In tumor-bearing mice, EPCs expand during tumor progression in the bone marrow, spleen, liver, peripheral blood, and in the tumor microenvironment [5,8,9▪▪,11▪]. Furthermore, their abundance in the tumor microenvironment is reported to be higher than that of MDSCs and Tregs. Notably, immune regulatory molecule programmed death ligand-1 (PD-L1) and CD244 (2B4) are shown to be highly expressed on tumor-infiltrating EPCs, which represent promising targets for cancer immunotherapy [11▪].

MECHANISMS OF CANCER-INDUCED DYSREGULATION OF ERYTHROPOIESIS

As to the main cause of EPC expansion, one of the prevailing views is the increase of erythropoietin (EPO), a kidney-derived hormone secreted in response to anemia. Experimental data have shown that EPO blockade reduces tumor-induced immature erythroid cells and slows down tumor growth [11▪]. This observation suggests that tumors trigger renal EPO production and EPO-dependent expansion of immature erythroid cells to enhance tumor progression. Moreover, studies have found that various tumor and niche-derived growth factors and pro-inflammatory cytokines are remarkable regulators of ineffective erythropoiesis. It has been proposed that tumor-secreted transforming growth factor (TGF)-β contributes to the expansion of EPCs in the spleen via SMAD signaling [8]. In acute myeloid leukemia [12] and myeloma [13], CCL3 inhibits erythroid differentiation by activation of CCR1-p38 and subsequent downregulation of GATA1, a key transcription factor for erythroid lineage commitment and differentiation [1]. Moreover, in squamous cell carcinoma, tumor cells leverage IL-33-TGF-β niche signaling loop via NF-κB pathway to promote malignant progression. Given the findings that IL-33 suppressed differentiation of erythroid progenitors by activation of NF-κB and inhibition of signaling events downstream of the EPO receptor during chronic inflammatory spondylarthritis [14], it is possible that cancer-related inflammation might induce the maturation arrest of EPCs through similar mechanisms. Collectively, these findings suggest that cancers not only induce

potent EPC expansion, but also arrest their development at early stages of differentiation. However, the mechanisms of cancer-induced dysregulation of erythropoiesis are complex and yet to be fully delineated.

IMMUNE-INDEPENDENT TUMOR PROMOTING ACTIVITIES OF ERYTHROID PROGENITOR CELLS

It has been reported that bone marrow EPCs may contribute to tumor angiogenesis [15] by secreting vascular endothelial growth factor A (VEGF-A) and placenta growth factor (PIGF). On the contrary, a recent study found a dramatic increase of CD45 negative ($CD45^-$) late-stage EPCs (termed Ter-cells in the study) in the spleen of hepatocellular carcinoma (HCC)-bearing mice [8], but not in bone marrow or tumor tissue. During tumor progression, the accumulation of splenic $CD45^-$ EPCs is dependent on TGF-β and SMAD3 signaling [8]. Although these $CD45^-$ EPCs lack immunosuppressive capacities, they promote tumor growth and metastasis of HCC via secretion of a neurotrophic factor, artemin, which in turn interacts with its receptor, GFRα3, on tumor cells (Fig. 1). In accordance, levels of splenic $CD45^-$ EPCs have been found to correlate with poor prognosis in pancreatic ductal adenocarcinoma patients [16▪]. Artemin secreted by $CD45^-$ EPCs has also been demonstrated to promote growth of Lewis lung carcinoma, B16-F10 melanoma, and MC38 colon adenocarcinoma [17▪▪]. These findings reveal EPCs as novel players in tumor-directed hematopoiesis and demonstrate that EPCs could be a potential therapeutic target. Indeed, targeting EPCs-artemin axis leads to the inhibition of tumor growth and enhances therapeutic efficacy of radiotherapy, immunotherapy, or the combination in murine models [8,17▪▪]. Further studies are warranted to understand the ontogenesis of $CD45^-$ EPCs and the molecular mechanisms of their interactions with tumors and other cells.

IMMUNOMODULATORY FUNCTIONAL CHARACTERISTICS OF ERYTHROID PROGENITOR CELLS

The immunomodulatory properties of EPCs were first observed in neonates, wherein EPCs were found to prevent excessive activation of immune cells in response to infection. Previous studies found that neonatal EPCs induce temporal immunosuppression by arginase-2 (ARG2), L-arginine degrading enzyme, and TGF-β, resulting in downregulation of cytokine production by myeloid cells [18] and promotion of $CD4^+$ T-cell differentiation toward Tregs [19,20]. In recent years, a growing number of studies have revealed that cancer-induced EPCs possess a series of immunosuppressive properties to promote tumor progression [21].

EPCs isolated from peripheral blood of cancer patients suppress $CD4^+$ T-cell proliferation and differentiation as well as inhibit $CD8^+$ T-cell proliferation and cytotoxicity, via a reactive oxygen species (ROS) dependent mechanism [5,9▪▪,22▪▪]. Moreover, tumor microenvironment infiltrating EPCs were demonstrated to suppress IFN-γ secretion and proliferation of intratumoral $CD4^+$ and $CD8^+$ T-cells isolated from human liver tumors through IL-10 signaling [9▪▪]. Noticeably, the suppressive properties of EPCs were found to be transient and gradually lost during erythroid differentiation, as late-stage EPCs (such as splenic $CD45^-$ EPCs [8]) and mature erythrocytes lack significant immunoregulatory function [22▪▪]. Strikingly, the immunosuppressive potential of EPCs from tumor-bearing mice was observed to be in between that of Tregs and MDSCs [5], while human EPCs appear to possess more substantial immunosuppressive activities than Tregs or MDSCs [5,9▪▪]. In addition, in hepatocellular carcinoma tissue, the $CD45^+$ EPCs were much more abundant compared to Tregs, MDSCs, and $CD45^-$ EPCs [5,9▪▪]. Thus, the immunomodulatory properties of EPCs may depend on their location, developmental stage, and there can be significant differences between humans and mice. More importantly, considering the higher frequency and immunosuppressive capacity of EPCs, targeting EPCs is an appealing strategy and may offer superior therapeutic advantages in certain types of cancer. Further investigations are needed to dissect the biology and the mechanisms controlling immunomodulatory roles of these cells in the context of cancer progression.

Intriguingly, a recent study revealed a previously unappreciated mechanism that promotes immunosuppression, tumor progression, and drug resistance mediated by erythroid progenitors [23▪▪]. Through innovative single-cell transcriptome and lineage tracking analyses, the study shows that tumors can induce a subset of $CD45^+$ EPCs to differentiate into an 'erythroid-myeloid hybrid' cell population, referred to as erythroid-differentiated myeloid cells (EDMCs). $CD45^+$ EPC to EDMC transdifferentiation is promoted by tumor-derived GM-CSF (Fig. 1). The study also observed that erythroid-derived myeloid cells ($Ter119^+CD71^+$) exhibit elevated capacity to inhibit T-cell proliferation and decrease IFN-γ production as compared to myeloid-originated MDSCs ($Ter119^-CD71^-$), which correlated with higher expression of immune inhibitory molecules, including PD-L1, PD-L2, Nox2, and Arg1

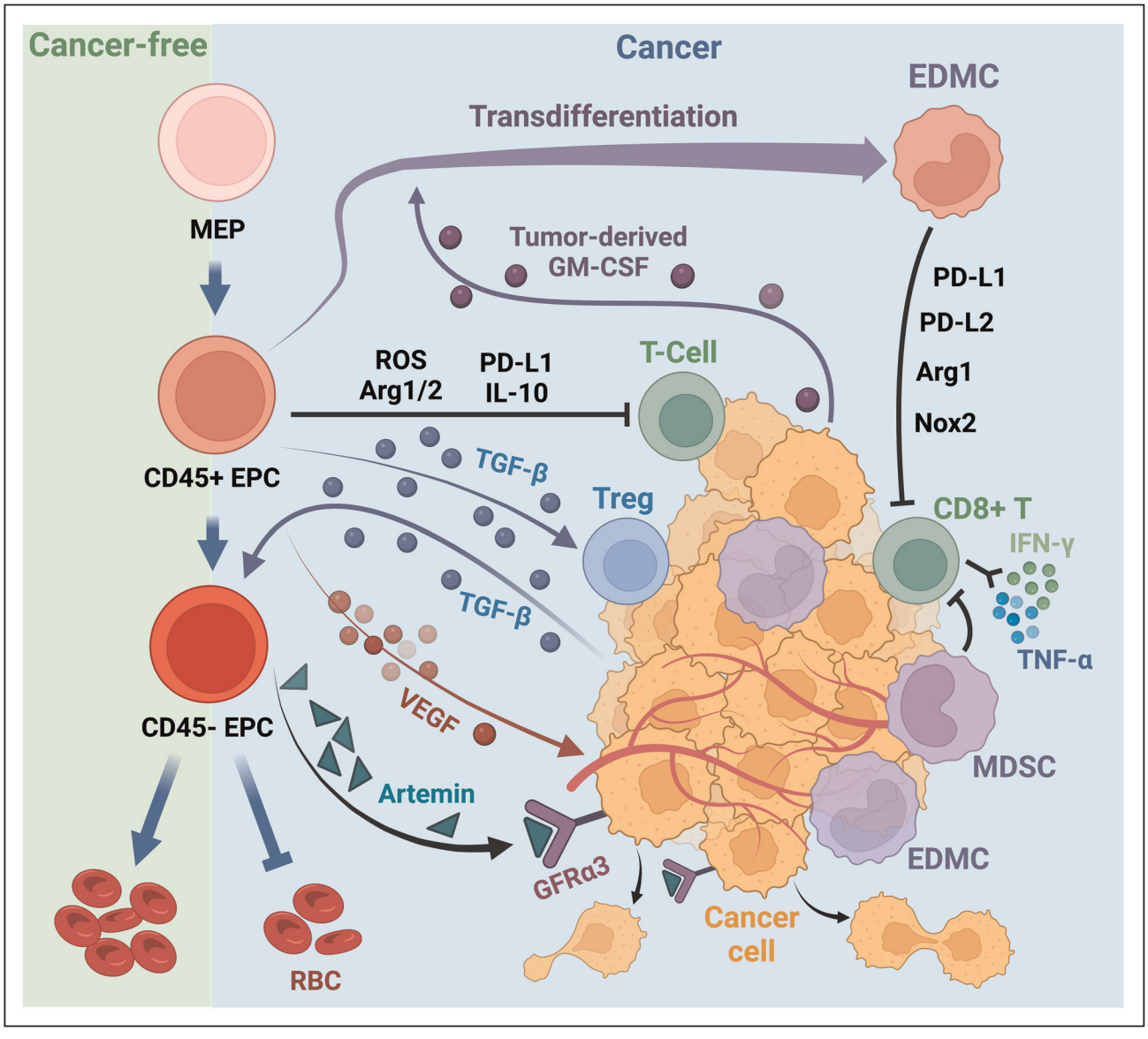

FIGURE 1. Dysregulation of erythropoiesis in cancer and tumor-promoting activities of erythroid progenitor cells. Cancer-induced dysregulation of erythropoiesis results in decreased production of red blood cells. EPCs contribute to tumor angiogenesis by secreting VEGF. Tumor-derived TGF-β induces expansion of late-stage $CD45^-$ EPCs. $CD45^-$ EPCs promote tumor growth and metastasis via secretion of artemin, and interaction with GFRα3 on tumor cells. Moreover, $CD45^+$ EPCs secreted TGF-β promotes $CD4^+$ T-cell differentiation toward Tregs. $CD45^+$ EPCs suppress proliferation and function of $CD4^+$ and $CD8^+$ T-cells through ROS, arginase, PD-L1, and IL-10 signaling. In addition, a subset of $CD45^+$ EPCs can switch their erythroid lineage to myeloid cells, named erythroid-differentiated myeloid cells (EDMCs). This EPC to EDMC transdifferentiation is promoted by tumor-derived GM-CSF. EDMCs highly express immune inhibitory molecules, including PD-L1, PD-L2, Arg1, and Nox2. They inhibit $CD8^+$ T-cell proliferation, and decrease production of IFN-γ and TNF-α, thus, accelerate tumor progression. EDMCs, erythroid-differentiated myeloid cells; EPCs, erythroid progenitor cells; GFRα3, glial-derived neurotrophic factor (GDNF) family receptor alpha-3; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon γ; IL-10, interleukin-10; MDSCs, myeloid-derived suppressor cells; MEP, megakaryocyte-erythroid progenitor; PD-L1, programmed death ligand-1; ROS, reactive oxygen species; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; Tregs, regulatory T-cells; VEGF, vascular endothelial growth factor.

in those $Ter119^+CD71^+$ cells (Fig. 1). Moreover, adoptive transfer of erythroid-derived myeloid cells into mice bearing established melanoma accelerated tumor progression, shortened survival, enhanced metastases formation, and reduced responses to anti-PD-L1 therapy, compared with mice receiving myeloid-originated MDSCs. Anemia is frequently observed in patients with advanced cancer and in

tumor-bearing mice, and in this study, patients with moderate to severe anemia exhibited EDMC expansion and lower response rates to immune checkpoint inhibitor (ICI) treatment. These results indicate that in patients with advanced cancer, anemia-associated induction of EDMCs could represent an additional mechanism for immunosuppression and limit response to ICIs. Further studies are needed to answer the question of whether this erythroid-to-myeloid transdifferentiation process generally occurs in other types of tumors and its association with clinical outcome of the patients. Nonetheless, on the basis of these novel findings and concept, it will be important to elucidate whether therapeutic elimination of EDMCs or inhibition of $CD45^+$ EPC reprogramming could restore protective T-cell immunity and synergize with ICIs in cancer patients. This will be of great clinical interest given that immunosuppressive myeloid cells are a major hurdle for current immunotherapies.

THERAPEUTIC TARGETING OF ERYTHROID PROGENITOR CELLS

With increasing research that advances our understanding of the tumor-promoting and immunosuppressive properties of EPCs (Fig. 1), targeting mechanisms of EPCs-driven immunosuppression, reducing the number of EPCs, and promoting their differentiation and maturation may be promising cancer treatment strategies. Extensive efforts are under way to develop EPC-focused therapies.

Inhibiting mediators of erythroid progenitor cell driven immunosuppressive function

EPCs use multiple mechanisms to regulate the immune response [21], including, but not limited to, depletion of L-arginine by arginase, robust production of ROS, secretion of immunomodulatory cytokines (such as TGF-β, IL-10), and immune checkpoint molecules. Therapeutics modulating these factors and their downstream signaling have been developed and are under investigation, as highlighted elsewhere [21]. Of note, it is likely that therapeutic approaches targeting a single mediator will be insufficient to overcome multiple redundant immune-suppressive mechanisms.

Depletion of erythroid progenitor cells

It is also reasonable to develop therapies that deplete tumor promoting EPCs. A recent study demonstrated that local radiotherapy or anti-PD-L1 treatment decreases tumor-induced late-stage $CD45^-$ EPCs in the mouse spleen and overall artemin level outside the irradiation field [17▪▪]. Both strategies induced activation of adaptive immunity, which led to EPC apoptosis mediated by $CD8^+$ T-cell secreted interferons. Therefore, the elimination of EPCs by radiotherapy and immunotherapy may improve the therapeutic outcomes in cancer patients. In addition, the above findings encourage further studies to determine if pathological EPCs can be eliminated by using certain chemotherapeutic reagents or targeted therapies. Further work to unveil unique vulnerable features of EPCs might identify targets for novel therapeutics.

Inhibition of erythroid progenitor cells expansion

Anemia is a common, expected complication among cancer patients and is negatively associated with prognosis and therapeutic outcomes. Regardless of the cause, cancer-associated anemia remains an underestimated and inadequately treated chronic condition. The correction of anemia in cancer patients might be a clinically applicable strategy to prevent and/or mitigate EPCs expansion. Iron is an essential functional component of erythrocyte hemoglobin and is a crucial regulator of erythropoiesis. Epidemiological studies show a high prevalence of iron deficiency anemia in cancer patients [24,25]; thus, evaluation of iron status is recommended, and iron should be supplemented for patients with low ferritin levels (absolute iron deficiency) [26]. Baseline hepcidin levels seem to strongly correlate with response to intravenous iron, but long-term studies are required to determine the impact of iron therapy on survival in cancer-associated anemia [26]. On the other side, for anemic patients with normal ferritin levels (functional iron deficiency), modulation of iron metabolism with hepcidin antagonists is under clinical investigation [26]. Further investigation into mechanisms of expansion and differentiation blockade of EPCs would provide a better understanding of cancer-EPCs interaction and potentially identify novel targets to counteract the detrimental effects on cancer progression and response to treatments.

Promoting terminal differentiation of erythroid progenitor cells

The immunosuppressive properties of EPCs are implicated to be lost during their maturation. It has been demonstrated that late-stage $CD45^-$ EPCs fail to inhibit T-cell proliferation and dendritic cell activation compared with early-stage $CD45^+$ EPCs

[5,8,9▪▪], probably due to low expression of IL-4, IL-6, IL-10, and TGF-β in CD45⁻ EPCs [8]. In line with these findings, another recent study demonstrated that EPCs possess potent, but transient suppressive properties that disappear during erythroid differentiation [22▪▪]. Therefore, promoting EPCs differentiation into mature erythroid cells to diminish immunosuppression may be a favorable therapeutic strategy. A recent study revealed that vitamin C (ascorbic acid) is able to rescue terminal erythroid differentiation under conditions of oxidative stress [27▪], highlighting the therapeutic potential of vitamin C for ineffective erythropoiesis. Another study showed that inhibition of aryl hydrocarbon receptor signaling promotes the terminal differentiation of human erythroblasts [28▪], which provides a possible way to enhance the terminal differentiation of EPCs. Furthermore, Luspatercept (ACE-536), a TGF-β ligand-trapping fusion protein and the first approved therapeutic for β-thalassemia [29], can selectively promote erythroid differentiation under maturation arrest, which may merit further investigation for treating cancer-associated anemia.

CONCLUSION

Over the recent years, the experimental and clinical findings accumulated have profoundly expanded our knowledge regarding the crosstalk between tumor and erythro-myelopoiesis. Tumors induce expansion and maturation arrest of EPCs, while EPCs in turn promote tumor progression either by secreting inflammatory factors or suppressing antitumor immune response, depending on the development stage [2,5,8,9▪▪] and cell fate [23▪▪]. It may be necessary to target EPCs or modulate their function to interfere with the symbiotic nature of EPCs with cancer in order to achieve better and longer lasting responses to treatments. However, targeting EPCs specifically seems to be particularly challenging, as they are heterogeneous and dynamically changing cells. Hence, comprehensive and discovery-driven characterization is needed to thoroughly understand the regulation of the expansion, differentiation, and reprogramming of suppressive EPCs, which may yield more fruitful biological mechanisms for targeting therapeutically.

There are several outstanding questions that need to be addressed. First, what factors drive the expansion of EPCs at extramedullary sites and how these cells are recruited to TME. Second, what mechanisms orchestrate the fate of EPCs. Third, whether and how EPCs interact with other tumor-infiltrating immunosuppressive cells, including MDSCs, macrophages, and Tregs, to facilitate immunosuppression and tumor progression. Another important goal for future studies is to develop consensus definitions, identify specific markers of EPCs, and devise feasible methods to detect these cells in clinical samples. This would empower us to comprehensively investigate the impact of EPCs on cancer progression and/or response to therapies. Continued advances of cellular barcoding, single-cell and spatial transcriptomics techniques [30,31] will provide deeper insights into lineage commitment, intercellular communication, regulatory networks, and clinical prognosis, which will help to answer these questions and uncover potential biomarkers and druggable targets.

Given the versatility of EPCs' immunosuppressive machinery, targeting of a single mediator will most likely be insufficient, and effective pharmacologic agents promoting the terminal differentiation of these cells offers a distinct advantage. In view of the unique differentiation mechanism of EDMCs, it is possible to speculate that methods to enforce EPC differentiation will diminish their generation and immunosuppressive function as well. Accordingly, application of existing or novel anemia therapies, which will promote EPC differentiation, may provide a potential combinational strategy to improve efficacy of immunotherapy in patients with cancer-associated anemia, which warrants further investigation. Uncovering more detailed molecular mechanisms governing the biology of EPCs in cancer will open the doors for more effective and precise targeted therapies that will deliver better clinical outcomes.

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Conflicts of interest

M.O. has research support from Eli Lilly and Bayer, and serves on advisory boards at Pfizer, AstraZeneca and Novartis. The rest of the authors declare no conflict of interest.

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