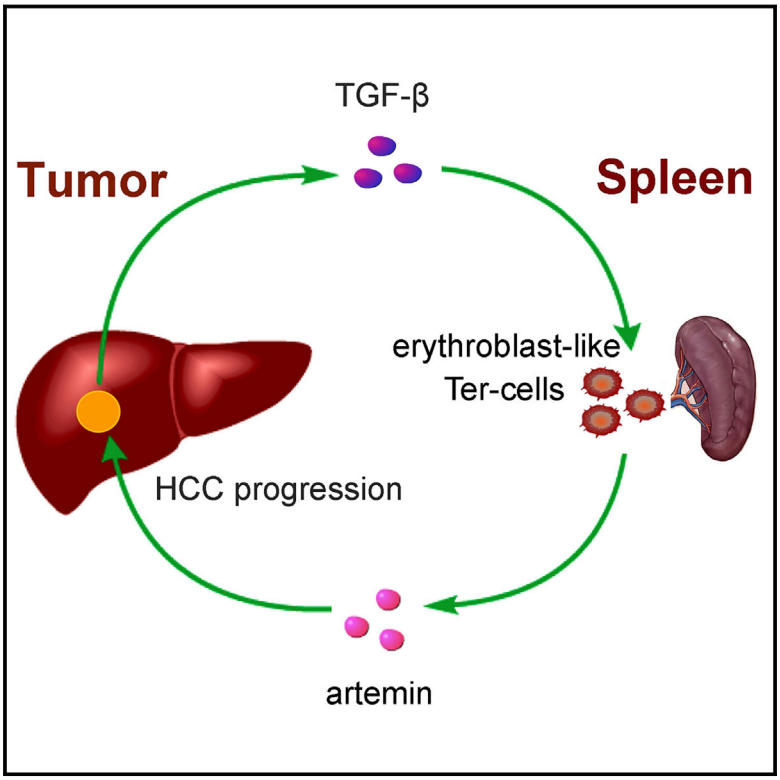
Article

Cell

Tumor-Induced Generation of Splenic Erythroblast-like Ter-Cells Promotes Tumor Progression

Graphical Abstract



Highlights

- Ter-119^{+}CD45^{-} erythroblast-like cells were induced in spleen of tumor-bearing mice
- TGF-β and Smad3 activation are important in the generation of splenic Ter-cells
- Splenic Ter-cells produce artemin, and high serum artemin predicts poor prognosis
- Blockade of artemin or its receptor GFRα3 signaling inhibits tumor progression

Authors

Yanmei Han, Qiuyan Liu, Jin Hou, ..., Yizhi Yu, Nan Li, Xuetao Cao

Correspondence

caoxt@immunol.org

In Brief

A population of immune cells in the erythroid lineage are induced in a mouse model of hepatocellular carcinoma, which promotes tumor progression through artemin production.

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Tumor-Induced Generation of Splenic Erythroblast-like Ter-Cells Promotes Tumor Progression

Yanmei Han,[1,9] Qiuyan Liu,[1,9] Jin Hou,[1,9] Yan Gu,[1] Yi Zhang,[1] Zhubo Chen,[2] Jia Fan,[3] Weiping Zhou,[4] Shuangjian Qiu,[3] Yonghong Zhang,[2,5] Tao Dong,[2,5] Ning Li,[2,5] Zhengping Jiang,[1] Ha Zhu,[1] Qian Zhang,[1] Yuanwu Ma,[6] Lianfeng Zhang,[6] Qingqing Wang,[7] Yizhi Yu,[1] Nan Li,[1] and Xuetao Cao[1,2,8,10,*]

[1]National Key Laboratory of Medical Immunology & Institute of Immunology, Second Military Medical University, Shanghai 200433, China
[2]CAMS-Oxford Joint Center for Translational Immunology, Department of Immunology & Center for Immunotherapy, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing 100005, China
[3]Liver Cancer Institute, Zhongshan Hospital, Institutes of Biomedical Science, Fudan University, Shanghai 200032, China
[4]Third Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Shanghai 200438, China
[5]Beijing Youan Hospital, Capital Medical University, Beijing 100069, China
[6]Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences, Beijing 100021, China
[7]Institute of Immunology, Zhejiang University School of Medicine, Hangzhou 310058, China
[8]School of Medicine, Nankai University, Tianjin 300071, China
[9]These authors contributed equally
[10]Lead Contact
*Correspondence: caoxt@immunol.org
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SUMMARY

Identifying tumor-induced leukocyte subsets and their derived circulating factors has been instrumental in understanding cancer as a systemic disease. Nevertheless, how primary tumor-induced non-leukocyte populations in distal organs contribute to systemic spread remains poorly defined. Here, we report one population of tumor-inducible, erythroblast-like cells (Ter-cells) deriving from megakaryocyte-erythroid progenitor cells with a unique Ter-119^{+}CD45^{-}CD71^{+} phenotype. Ter-cells are enriched in the enlarged spleen of hosts bearing advanced tumors and facilitate tumor progression by secreting neurotrophic factor artemin into the blood. Transforming growth factor β (TGF-β) and Smad3 activation are important in Ter-cell generation. *In vivo* blockade of Ter-cell-derived artemin inhibits hepatocellular carcinoma (HCC) growth, and artemin deficiency abolishes Ter-cells' tumor-promoting ability. We confirm the presence of splenic artemin-positive Ter-cells in human HCC patients and show that significantly elevated serum artemin correlates with poor prognosis. We propose that Ter-cells and the secreted artemin play important roles in cancer progression with prognostic and therapeutic implications.

INTRODUCTION

Non-neoplastic cell populations in the tumor microenvironment have been reported to not only play critical roles in cancer progression but also be educated or reprogrammed by the microenvironment itself. Targeting the tumor microenvironment is increasingly considered as a promising approach for cancer intervention (Shalapour et al., 2015; Peng et al., 2015). For example, some of these tumor-educated cell populations, such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T (Treg) cells are being explored as potential drug targets (Hanahan and Coussens, 2012; Elinav et al., 2013; Finn, 2012). Interestingly, most of the tumor-promoting cell populations educated in the tumor microenvironment that have been identified to date are leukocyte subsets originated from myeloid cells.

Primary tumors can actively induce inflammatory, immunosuppressive changes and other tumor-promoting consequences in distant organs, facilitating tumor progression and metastasis. Identifying tumor-induced or expanded cell populations outside of the tumor microenvironment and their derived circulating factors thus become increasingly critical in understanding cancer as a systemic disease and exploring more effective prognosis and treatment strategies. For example, primary tumor-induced recruitment of neutrophils to distant organs can facilitate metastasis formation (Coffelt et al., 2015; Liu et al., 2016). Furthermore, platelets can protect tumor cells from immune elimination in the circulatory system and support their establishment in secondary lesions (Gay and Felding-Habermann, 2011; Labelle et al., 2011), further suggesting an important role of non-leukocyte cell populations outside of the tumor microenvironment in promoting tumor metastasis. Nevertheless, the full spectrum of non-leukocyte cell populations involved in different stages of tumor progression and their functional roles are still poorly defined.

The spleen of tumor-bearing hosts is usually enlarged, especially at later or more advanced stages (Miluzio et al., 2011). Splenectomy has been proposed to be a clinical option for treating massive splenomegaly in advanced cancer patients with