Stromal cells and myeloid leukemic cells: Are they friends? Or foes?

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An important question when designing targeted therapy by modulation of stromal cells in the leukemic microenvironment is whether the stromal-derived support of tumor cell growth can be halted by drugs including originally tumor supportive agents. We recently used an in vitro system to show that either bone marrow stromal cells as a feeder layer or lipopolysaccharides (LPS) in culture medium is required for the proliferation of murine myeloid tumor cells. However, the stromal-derived support of leukemic growth is strongly suppressed when LPS is coupled in the same culture. This opposing effect of stromal cells or LPS on the myeloid leukemic growth is due, at least in part, to the rapid secretion of interleukin 12, Fas ligand and tissue inhibitor of metalloproteinases-2 from stromal cells upon LPS stimulation. These results provide a proof of principle that stromal cells can be “re-educated” by therapeutic drugs to attenuate tumor cell proliferation through re-wiring the cytokine network in the tumor microenvironment, thus diverting the disease course of myeloid leukemia in the opposite direction.

Keywords: myeloid leukemia; lipopolysaccharides; stromal cells; endothelial cells; cytokines; tumor microenvironment

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Introduction

The leukemic microenvironment in bone marrow (BM) is composed of a large numbers of cells and soluble factors released from different cell types including stromal cells. It is generally accepted that BM stromal cells play a critical role in the initiation, survival, proliferation and drug resistance of myeloid leukemia. But have you ever wondered whether stromal-derived support of leukemic growth could be stopped by modifying the stromal cells using another tumor supportive signal? This turns out to be especially true for murine myeloid leukemic cells. In our recent work published in Experimental Cell Research (ECR) [¹], we find that bone marrow stromal cells alone strongly support the proliferation of murine myeloid leukemic cells in vitro. In this study, we also demonstrate that lipopolysaccharides (LPS) alone presents a strong proliferation effect on murine myeloid tumor cells. Surprisingly, when stromal cells and LPS are
both available in the same compartment, the pro-tumorigenic activities of stromal cells and LPS are completely reversed. This is due, at least in part, to the rapid secretion of tumor suppressive soluble mediators interleukin 12 (IL-12), Fas L and TIMP-2 to reverse the pro-proliferative activities of stromal cells. Re-illustrated with permission [1].

Another finding in our study is that the re-wiring of the cytokine network in the microenvironment that reprograms the function of stromal cells and LPS. In this case, IL-12, Fas L and TIMP-2 are actively involved. Aberrant cytokine signals in the tumor microenvironments are widely recognized to be crucial for the facilitation of tumor growth; therefore, cytokines themselves or the molecular pathways controlled by these cytokines represent legitimate perturbation targets. For example, TGF-β plays a predominant role in tumorigenesis when its production in certain tumors or their microenvironments is overproduced, thereby making it a very druggable target [4]. However, all strategies are faced with limitations since all classes of drugs

Designing targeted therapy using modulation of stromal cells is difficult, simply because of the extremely complicated crosstalk between tumor cells and the tumor niche as well as the molecular signals from outside the microenvironment. One of the fundamental yet puzzling questions is whether a single molecule or therapeutic agent can present an opposing effect on the same tumor cells by manipulating the cellular and molecular components in tumors. It has been reported that a single molecule or its transduced signaling pathway could have opposite functions under different conditions. Krause et al. have reported that osteoblastic cell-specific activation of the parathyroid hormone (PTH) receptor attenuates BCR-ABL1-induced chronic myelogenous leukemia (CML)-like myeloproliferative neoplasia, but enhances MLL-AF9-induced acute myeloid leukemia (AML) in mouse transplantation models [2]. Transforming growth factor beta (TGF-β) also exhibits paradoxical implications for cancer, depending on the context. In some cases, TGF-β suppresses cancer growth and progression; in other instances, it promotes tumor growth through the induction of epithelial-mesenchymal cell transition [3]. However, both PTH receptor and TGF-β present opposing effects on the tumor cells simply because the tumor cells are of different origins. This indicates that the effect of PTH receptor and TGF-β are of cell or tissue specificity. In our case, bacterial endotoxin LPS, usually available under pathological conditions, targets exactly the same leukemic cells through stimulation of BM stromal cells (either established cell lines or primary stromal cells isolated from BM), thus reversing the pro-proliferative function of both stromal cells and LPS itself.

Figure 1. Model for the function of bone marrow stromal cells and LPS in murine myeloid leukemic proliferation. LPS (top panel) or stromal cells (middle panel) strongly support the growth of murine myeloid leukemic cells in vitro. However, when both LPS and stromal cells are in the same culture, LPS stimulates stromal cells to rapidly secrete tumor suppressive cytokine IL-12, Fas L and TIMP-2 to reverse the pro-proliferative activities of stromal cells (bottom panel). Re-illustrated with permission [1].
have potentially highly pleiotropic activities, including the tumor suppressive effect of TGF-β on some other potentially transformed cells. Therefore, thorough understanding of cytokine dynamics in the tumor microenvironment is critical for targeted cytokine therapies. Our findings reported in ECR add further complexity in understanding the crosstalk between myeloid leukemic blasts and their microenvironment, and an additional layer of difficulty to the targeted therapy strategy.

Another area of immense interest has been the disruption of the positive crosstalk between leukemic cells and stromal cells. This strategy includes the interference with homing, and subsequent retention of leukemic cells in a tumor supportive microenvironment. A novel approach is to mobilize leukemic cells away from their tumor-supportive niche, thereby reducing their viability and increasing their susceptibility to other therapies [5]. Our study places a spotlight on the importance of modulating the tumor-supportive stromal cells themselves for treating myeloid leukemias.

Numerous aberrations in the cellular or molecular compartments in primary tumors affect the interaction between malignant cells and their surrounding environment. LPS can generate complex network signals not just locally but also systemically and can be sensed by leukemic blasts. Moreover, stromal cells can help LPS with stimulating other cells to produce interleukin-10 for improving organ functions [6]. The more considerable challenges will then be to use relevant animal model systems to unravel the net effects of LPS and its regulated mediator IL-12, Fas L and TIMP-2 on the suppression of myeloid leukemias in vivo, although our in vitro system is useful for dissecting the function of each individual cellular or molecular event. Another limitation of our study is the lack of the study on clinical relevance. We cannot use LPS to produce a cure for leukemia patients, but we provide a proof of principle that pro-tumor stromal cells could be the foes of blood malignancies if we can deliver the right targeted agents.

Collectively, our findings reported in ECR demonstrate that even a pro-tumorigenic signal can re-educate tumor-supportive stromal cells in the tumor microenvironment to suppress the growth of neoplastic myeloid cells. This discovery will broaden our repertoire of potential options for therapeutic agents and help us to assess the therapeutic effects that certain drugs or other systemic disease conditions may have through facilitating or ameliorating stromal cells’ functions.

**Conflicting interests**

The authors have declared that no conflict of interests exist.

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**Abbreviations**

AML: acute myeloid leukemia; BM: bone marrow; CML: chronic myelogenous leukemia; Fas L: Fas ligand; LPS: lipopolysaccharides; IL-12: interleukin 12; PTH: parathyroid hormone; TGF-β: transforming growth factor beta; TIMP-2: tissue inhibitor of metalloproteinases-2.

**Author contributions**

L.Y., Y.Z. and D.Y. designed the study, L.Y., Y.Z. and J.W. conducted the experiment, L.Y., Y.Z., J.W. and D.Y. analyzed the data, D.Y. wrote the manuscript.

**References**