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Spotlight

Tumor Cell Dormancy—Triggered by the Niche

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Dormant cancer cells often survive treatment and increase the risk for tumor relapse, associated with dismal prognosis. Two recent papers describe mechanisms used by the bone marrow niche to regulate leukemia dormancy. The findings provide a molecular basis for niche-targeting therapies that may enable elimination of dormant tumor cells.

Anti-cancer treatment has improved dramatically in recent years, greatly increasing cure rates, especially among young patients. However, dormant tumor cells remain a major current challenge as they resist treatment, survive over prolonged periods of time, and can induce relapse. Dormancy refers to a reversible state of cellular quiescence that persists over prolonged periods of time (Aguirre-Ghiso and Sosa, 2018). Dormancy of tumor stem cells is especially undesirable; if they exit dormancy, they can repopulate the tumor, analogous to the way normal adult stem cells can activate and regenerate tissue (Aguirre-Ghiso and Sosa, 2018; Goddard et al., 2018; Recasens and Munoz, 2019).

Both cell intrinsic characteristics and extrinsic influences from surrounding normal cells determine tumor cell dormancy. Extrinsic factors include mesenchymal stem cells (MSCs), endothelial cells (ECs), and immune cells that form the tumor's niche (Aguirre-Ghiso and Sosa, 2018; Goddard et al., 2018). Indeed, tumor cells and their niche engage in multifaceted, bidirectional crosstalk that relies on soluble factors and cell-cell contacts. Dormant tumor cells are resistant to most anti-cancer therapies because cytotoxic drugs generally target proliferation-associated processes. Several therapeutic concepts to target dormancy have been suggested, among which is the disruption of the tumor-niche interaction in order to recruit dormant cells into the cell cycle and sensitize them to treatment (Ebinger et al., 2016; Recasens and Munoz, 2019). However, the complexity of combinatorial intrinsic and extrinsic regulatory cues makes it difficult to identify individual factors to target.

Two recent papers advance our knowledge of the mechanisms driving chronic myeloid leukemia (CML) cell dormancy. Zhang et al. (2018) and Agarwal et al. (2019) employ elegant conditional tissue-specific knockout mouse models and combine them with bone transplantation approaches to separate the roles of intrinsic and extrinsic influences on tumor cell dormancy. Genetically manipulating tumor and niche cells separately allowed the authors to functionally define individual factors and carefully analyze the interaction between niche and tumor cells (Figure 1).

Leukemia models have been at the forefront of the efforts to decipher general aspects of tumor biology, including cancer stem cell biology and dormancy (Greaves, 2016). As a model disease, leukemia harbors several advantages; first, the tumors are soluble, allowing for repeated sampling from patients and easy modeling in mice. Second, leukemia cells reside in the bone marrow niche, which has been well characterized in studies on normal hematopoietic stem cells (HSCs). Third, leukemias display the lowest mutational burden; CML, for example, is driven by a single oncogene, the BCR-ABL fusion. As a prototype targeted therapy, tyrosine kinase inhibitors (TKIs) induce long-lasting CML remissions by targeting the hyper-activated ABL kinase. Nevertheless, life-long dependency on TKIs remains a challenge for CML patients, as dormant CML leukemia stem cells (CML LSCs) can persist and induce relapse when TKIs are suspended.

Agarwal et al. examine one mechanism that contributes to dormancy in this context (Agarwal et al., 2019). The authors report an important role of the chemokine CXCL12 (C-X-C motif chemokine ligand 12) and its receptor CXCR4 (C-X-C chemokine receptor type 4) in CML LSC dormancy. The authors found that CXCL12 deletion in MSC increased proliferation of LSCs, rendering them sensitive to TKI treatment, and decreasing long-term engraftment in secondary recipient mice. Thus, in the absence of CXCL12, TKI was able to increase removal of CML LSCs, supporting the idea that CXCL12-targeted therapies may promote CML LSC exit from dormancy to enable their therapeutic targeting. However, the effect of CXCL12 is complex and cell type specific; in contrast to MSC, deletion of CXCL12 from EC decreased LSC proliferation. Furthermore, MSC-specific CXCL12 deletion decreased HSC numbers significantly, suggesting that CXCL12-directed therapy could display hematotoxicity.

Zhang et al. approached the regulation of CML LSCs from another angle, examining the role of microRNA-126-3p (miR-126) (Zhang et al., 2018). miR-126 is a known cell-intrinsic regulator of stem cell dormancy, yet, with opposite functions in non-transformed HSC and acute myeloid leukemia (AML) LSC. In AML LSCs, miR-126 knockdown results in LSC proliferation and exhaustion, while in HSCs, knockdown of the miRNA does not affect self-renewal capacity (Lechman et al., 2016). These observations have fueled hopes that inhibition of miR-126 could specifically target LSCs while sparing HSCs.

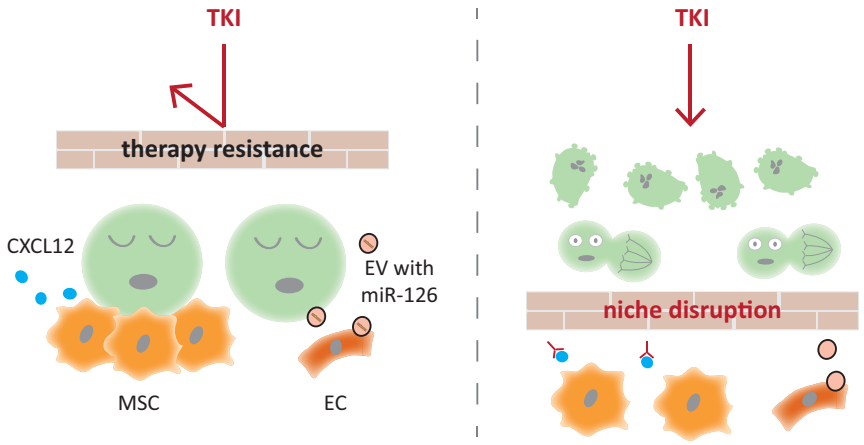

Figure 1. Niche Influences on Tumor Cell Dormancy and Treatment Resistance
Tumor cell dormancy can be induced by protective factors from the niche, which, for example, protect chronic myeloid leukemia stem cells (green) from treatment with tyrosine kinase inhibitors (TKIs). Disrupting the tumor-niche interaction by inhibiting mesenchymal stem cell (MSC)-derived CXCL12 (blue dots) or extracellular vesicle (EV)-mediated miR-126 transfer enables proliferation and sensitizes tumor cells toward treatment.

Zhang et al. now report the surprising finding that miR-126 levels are in fact consistently lower in LSCs compared to their corresponding non-transformed HSC counterparts, allowing LSC expansion (Zhang et al., 2018). These lower levels are due to the activity of the BCR-ABL fusion protein. Indeed, BCR-ABL decreased cytoplasmic miR-126 levels via effects on miRNA precursor shuttling and maturation. TKI treatment reversed these effects, leading to increased miR-126 levels, which increased CML LSC quiescence and therapy resistance. Thus, TKI treatment may have a previously unrecognized harmful effect by promoting LSC persistence.

What is the source of the miR126 that promotes CML LSC dormancy? Using smart *in vitro* and *in vivo* models, the authors demonstrate that neighboring ECs, which line the arterioles in the endosteal bone marrow, provide miR-126 to CML LSCs. This exogenous source of miR-126 prevents stem cell exhaustion of both human and murine LSCs. In transplantation models, lack of miR-126 in CML LSCs only slightly reduced CML engraftment, whereas lack of miR-126 in ECs drastically inhibited LSC long-term engraftment capacity. Most important from a therapeutic perspective, combined knockout of miR-126 in transplanted LSCs and recipient ECs had the strongest effect, with the majority of recipient mice still alive as the control group succumbed to disease. These promising results prompted the authors to design therapeutic oligonucleotides capable of inhibiting miR-126 in ECs and LSCs *in vivo* following systemic administration. Mice bearing human CML cells that received a combination of miR-126 inhibitor with TKI survived longer and, importantly, showed the least persistence of CML LSCs in limiting dilution re-transplantation assays.

Together, the two studies highlight the importance of non-transformed niche cells in the regulation of tumor cell dormancy. Cells like EC or MSC, and likely many others, secrete supportive signals, and these represent potential therapeutic targets for inhibition. The exchange of cellular material also plays an important role, in the case discussed here occurring via extracellular vesicles (Figure 1), but also by other mechanisms, such as exchange of mitochondria via heterocellular transfer (Moschoi et al., 2016). Other examples involve sympathetic nerves and the vasculature, which have been shown to influence bone marrow LSCs and their dormancy (Medyouf, 2017). Although the studies highlighted here focused on CML, similar mechanisms may apply more broadly, including in the context of bone marrow metastases of solid tumors.

In conclusion, disrupting the tumor-niche interactions represents an attractive therapeutic option for pushing dormant tumor stem cells back into proliferation and sensitizing them to treatment. The enhanced mechanistic understanding provided by these and other papers brings us one step closer to the overall goal of targeting dormant tumor cells and preventing disease relapse, for the benefit of cancer patients.

REFERENCES

Agarwal, P., Isringhausen, S., Li, H., Paterson, A.J., He, J., Gomariz, Á., Nagasawa, T., Nombela-Arrieta, C., and Bhatia, R. (2019). Mesenchymal niche-specific expression of cxcl12 controls quiescence of treatment-resistant leukemia stem cells. Cell Stem Cell. https://doi.org/10.1016/j.stem.2019.02.018.

Aguirre-Ghiso, J.A., and Sosa, M.S. (2018). Emerging topics on disseminated cancer cell dormancy and the paradigm of metastasis. Annu. Rev. Cancer Biol. *2*, 377–393.

Ebinger, S., Özdemir, E.Z., Ziegenhain, C., Tiedt, S., Castro Alves, C., Grunert, M., Dworzak, M., Lutz, C., Turati, V.A., Enver, T., et al. (2016). Characterization of rare, dormant, and therapy-resistant cells in acute lymphoblastic leukemia. Cancer Cell *30*, 849–862.

Goddard, E.T., Bozic, I., Riddell, S.R., and Ghajar, C.M. (2018). Dormant tumour cells, their niches and the influence of immunity. Nat. Cell Biol. *20*, 1240–1249.

Greaves, M. (2016). Leukaemia 'firsts' in cancer research and treatment. Nat. Rev. Cancer *16*, 163–172.

Lechman, E.R., Gentner, B., Ng, S.W., Schoof, E.M., van Galen, P., Kennedy, J.A., Nucera, S., Ciceri, F., Kaufmann, K.B., Takayama, N., et al. (2016). miR-126 regulates distinct self-renewal outcomes in normal and malignant hematopoietic stem cells. Cancer Cell *29*, 214–228.

Medyouf, H. (2017). The microenvironment in human myeloid malignancies: emerging concepts and therapeutic implications. Blood *129*, 1617–1626.

Moschoi, R., Imbert, V., Nebout, M., Chiche, J., Mary, D., Prebet, T., Saland, E., Castellano, R., Pouyet, L., Collette, Y., et al. (2016). Protective mitochondrial transfer from bone marrow stromal cells to acute myeloid leukemic cells during chemotherapy. Blood *128*, 253–264.

Recasens, A., and Munoz, L. (2019). Targeting cancer cell dormancy. Trends Pharmacol. Sci. *40*, 128–141.

Zhang, B., Nguyen, L.X.T., Li, L., Zhao, D., Kumar, B., Wu, H., Lin, A., Pellicano, F., Hopcroft, L., Su, Y.L., et al. (2018). Bone marrow niche trafficking of miR-126 controls the self-renewal of leukemia stem cells in chronic myelogenous leukemia. Nat. Med. *24*, 450–462.