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The (miR)e of CTCL

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In this issue of *Blood*, Ito et al demonstrate pathogenic implications of microRNA-150 (miR-150) repression in an aggressive form of cutaneous T-cell lymphoma (CTCL).[1] Noncoding RNAs, such as microRNA, profoundly influence gene transcription and protein translation machinery to change hematopoietic cell fate in physiologic and pathologic conditions.

Among the hematopoietic cells, miR-150 is predominantly expressed in B, T, and natural killer cells through their development and maturation, except during the differentiation of naïve T cells into the effector Th1 and Th2 cells.[2-4] Importantly, miR-150–deficient mice lack lymphoid cell maturation and effector functions.[2,4] In nonlymphoid lineages, miR-150 favors differentiation of megakaryocyte-erythrocyte progenitors to megakaryocytes at the expense of erythrocytes.[5] In determining cell fate, miR-150 targets multiple downstream targets, including *MYB*, *FLT3*, *CBL*, *EGR2*, *DKC1*, *AKT2*, *Myb* and *Notch3*.[6]

While miR-150 functions as a tumor suppressor in acute leukemia and lymphoma, its role in altering the behavior of the malignant CTCL cells is largely unknown.[6] Similar to data previously published by other groups,[7,8] data in this study showed that miR-150 was significantly reduced in patients with advanced-stage CTCL who exhibited extensive nodal or visceral involvement. Ito et al[1] report an interesting series of events initiated by miR-150 repression in $CD4^+$ CTCL cells. By using CTCL cell lines, Ito et al identify chemokine receptor 6 (CCR6) as a novel target for miR-150, as evidenced by direct binding of miR-150 within the CCR6 regulatory region. Of note, $CCR6^+$ cells migrate toward a chemokine ligand 20 (CCL20) gradient, and their activation by interleukin-22 (IL-22) causes cell proliferation and migration. Through comprehensive gain- and loss-of-function approaches, Ito et al show that miR-150 negatively regulates an IL-22-CCL20-CCR6 autocrine pathway in CTCL cells. These findings uncover a previously unknown miR-150-chemokine receptor pathway that may act widely to control metastatic potential of CTCL.

What determines whether malignant cells migrate to the skin is a riddle that has baffled scientists for long time. Since skin produces CCL20 during inflammation,[9] these novel observations fit well in a model in which the cutaneous tissue provides chemotactic signals for migrating cells as well as a fertile niche in which the neoplastic cells can grow and survive. Previous studies have linked both chemokines and chemokine receptors in the migration of malignant T cells to epidermal keratinocytes.[10] Although the mechanisms controlling cell migration to the skin are poorly understood, the study by Ito et al hints at the possibility that they may be due to intrinsic defects in T cells, specifically from diminished expression of noncoding RNA such as miR-150. Since an increase in tumor cell migration is not enough to fuel metastasis, induction of IL-22 for cell proliferation represents a significant step in dissemination of lymphoma in vivo. Further work is required to resolve how miR-150 is regulated in malignant T cells in CTCL.

Overall, Ito et al present a compelling study of the importance of miR-150 in CTCL metastasis. Their work also paves the way for the therapeutic strategies that can be used to restore miR-150 levels in malignant cells by either pharmacologic inhibitors that target miR-150 repression or by miR replacement therapy for CTCL treatment. Undertaking the challenges of dissecting signaling mechanisms upstream of miR-150 provides an invaluable insight on pathogenic signals and furthers our understanding of complex oncogenic pathways in T cells that can be extrapolated beyond CTCL. ■

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Comment on Rumi et al, page 1544, and on Rotunno et al, page 1552

Two faces of ET: *CALR* and *JAK2*

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In this issue of *Blood*, Rumi et al and Rotunno et al demonstrate that essential thrombocythemia (ET) patients with *calreticulin* mutations exhibit lower leukocyte and hemoglobin values, higher platelet counts, and a lower thrombosis risk vs *JAK2*-mutated ET. *Calreticulin*-mutated ET appears to be a distinct entity with a more indolent course.[1,2]