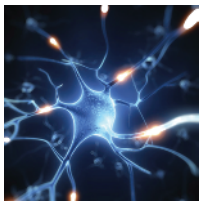
Leukemia

Major finding: AML cells generate a leukemia-supportive niche via induction of sympathetic neuropathy.

Mechanism: Sympathetic nerve disruption depletes normal HSCs and promotes expansion of osteoblast progenitors.

Impact: Modulation of adrenergic signaling may preserve HSCs and diminish LSC bone marrow infiltration.

SYMPATHETIC NEUROPATHY ENABLES NICHE REMODELING AND AML PROGRESSION



Acute myelogenous leukemia (AML) is characterized by infiltration and expansion of leukemic stem cells (LSC) in the bone marrow and disruption of normal hematopoietic stem cell (HSC) function; however, the mechanisms by which LSCs alter the bone marrow microenvironment remain unclear. Normal HSC migration and recovery after injury are regulated in part via sympathetic nervous system (SNS) innervation of the bone marrow, prompting Hanoun and colleagues to investigate the role of SNS nerves in AML. In a mouse model of AML driven by expression of the *MLL–AF9* oncogenic fusion, depletion of adrenergic nerves enhanced LSC infiltration of the bone marrow, accelerated leukemogenesis, and diminished survival. *MLL–AF9*$^+$ leukemic cell infiltration resulted in a reduction in adrenergic innervation of the bone marrow and spleen and diminished sympathetic tone, suggesting that AML-induced sympathetic neuropathy promotes leukemia development. SNS denervation in leukemic bone marrow was associated with decreased quiescence and expansion of endothelial cells and perivascular mesenchymal stem and progenitor cells (MSPC), which exhibited an increased commitment toward the osteoblast lineage but a block in differentiation to mature osteoblast cells. This accumulation of osteoblast-primed MSPCs occurred at the expense of healthy HSCs, as the expression of HSC-regulating genes was reduced and the function of HSCs in the bone marrow was impaired. The ability of SNS nerves to regulate leukemia development was mediated by the β2 adrenergic receptor (ADRβ2) expressed in the bone marrow microenvironment; inhibition of ADRβ2 signaling increased the proliferation and infiltration of LSCs in the bone marrow and reduced the survival of leukemic mice, similar to the effect of SNS denervation. These results demonstrate that *MLL–AF9*$^+$ AML cells remodel the HSC niche via induction of sympathetic neuropathy to generate a leukemia-supportive microenvironment, and suggest that modulation of adrenergic signaling may limit AML progression and protect HSCs. ■

Hanoun M, Zhang D, Mizoguchi T, Pinho S, Pierce H, Kunisaki Y, et al. Acute myelogenous leukemia–induced sympathetic neuropathy promotes malignancy in an altered hematopoietic stem cell niche. Cell Stem Cell 2014 Jul 10 [Epub ahead of print].

Breast Cancer

Major finding: CDK4/6 inhibitors synergize with PI3K inhibitors to suppress *PIK3CA*-mutant breast cancer growth.

Mechanism: Failure to inhibit CDK4/6-driven RB phosphorylation is correlated with resistance to PI3K inhibitors.

Impact: This combination may overcome intrinsic and adaptive resistance in *PIK3CA*-mutant breast cancer.

CDK4/6 BLOCKADE IMPROVES THE EFFICACY OF PI3K INHIBITION IN BREAST CANCER

Activation of PI3K signaling is a common feature of many breast cancers and frequently occurs via mutations in the *PIK3CA* oncogene encoding the PI3K p110α subunit. However, PI3K inhibitors have shown only modest clinical efficacy, and patients with *PIK3CA*-mutant tumors often develop acquired resistance. Recent studies have shown that dual inhibition of mTOR complex (mTORC) and PI3K is effective in *PIK3CA*-mutant cancer, indicating that mTORC activation contributes to PI3K inhibitor resistance. To identify additional therapeutic strategies to enhance the sensitivity of PI3K inhibitors, Vora and colleagues performed a combinatorial drug screen in *PIK3CA*-mutant, PI3K inhibitor–resistant breast cancer cell lines. Intriguingly, concomitant inhibition of cyclin-dependent kinases 4 and 6 (CDK4/6), which function downstream of mTORC1, broadly increased PI3K inhibitor sensitivity in *PIK3CA*-mutant cells with acquired and intrinsic PI3K inhibitor resistance and synergistically reduced cell viability. The efficacy of CDK4/6 inhibition was mediated, in part, by activation of the tumor suppressor RB; single-agent PI3K blockade failed to inhibit CDK4/6–cyclin D1 activity downstream of mTORC1 in PI3K inhibitor–resistant cell lines, which exhibited persistent RB phosphorylation. Maintenance of RB phosphorylation was also correlated with PI3K inhibitor resistance in patients, including both those classified as nonresponders and those that developed resistant tumors, suggesting that phosphorylated RB may represent a biomarker of clinical response to PI3K inhibitors. Importantly, combined treatment with PI3K and CDK4/6 inhibitors was well tolerated, suppressed AKT activity and RB phosphorylation, and induced xenograft tumor regression in *PIK3CA*-mutant breast cancer models. These findings support further investigation of this combination as a means to overcome PI3K inhibitor resistance in patients with *PIK3CA*-mutant breast cancer. ■

Vora SR, Juric D, Kim N, Mino-Kenudson M, Huynh T, Costa C, et al. CDK 4/6 inhibitors sensitize PIK3CA *mutant breast cancer to PI3K inhibitors. Cancer Cell 2014;26:136–49.*