Spotlight

By Anne Forde

Sensitizing Dormant Leukemic Cells to Anti-Leukemic Agents

Ikezoe *et al.*
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Leukemia stem cells are thought to initiate and maintain acute myeloid leukemia (AML). Although remission in AML patients can be as high as 85%, relapses often occur. Eradication of these dormant leukemia stem cells is thought to be critical to avoid clinical relapse.

In this study, Ikezoe *et al.,* investigate whether the prosurvival signal pathways that are found in $CD34^+/CD38^-$ populations of AML patients are important for dormant leukemia stem cells' resistance to anti-leukemic agents. Leukemia cells isolated from 11 AML patients were sorted into $CD34^+/CD38^-$ and $CD34^+/CD38^+$ populations and the former showed a higher percentage of cells in a dormant state (68 versus 16%). Higher levels of activated signaling molecules JAK2 and STAT5 were also found in $CD34^+/CD38^-$ than in $CD34^+/CD38^+$ populations. $CD34^+/CD38^-$ cells from 3 different patients proved more resistant to the anti-leukemic agents AraC and the FLT3 kinase inhibitor sunitab relative to their $CD34^+/CD38^+$ counterparts. However, this phenomenon could be counteracted when the authors exposed $CD34^+/CD38^-$ populations to AZ960, a specific inhibitor of JAK2 kinase. When used in combination with either of the two aforementioned anti-leukemic agents, colony formation inhibition went down from 10-15% to 60-70%. The use of AZ960 also stimulated cycling in $CD34^+/CD38^-$ and the down-regulation of the anti-apoptotic protein Bcl-xL.

Although the patient sample was small, this study shows that JAK2 and STAT5 signaling may be differentially activated in $CD34^+/CD38^-$ populations. It appears that using a specific inhibitor of this signaling pathway such as AZ960 could sensitize the $CD34^+/CD38^-$ population to anti-leukemic agents. Further work is required to confirm these results and elucidate their contribution to the phenomenon of dormant leukemia stem cells.