Designing Motif-Engineered Receptors To Elucidate Signaling Molecules Important for Proliferation of Hematopoietic Stem Cells.

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Authors: Shuta Ishizuka, Chen-Yi Lai, Makoto Otsu, Hiromitsu Nakauchi, Teruyuki Nagamune, Masahiro Kawahara

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Public Summary:
The complex intracellular signaling pathways that promote blood stem cell maintenance and growth are still poorly defined. Here, we used engineered signaling receptors to distinguish intracellular signaling pathways involved in blood stem cell proliferation. These findings will help to develop methods to expand blood stem cell ex vivo.

Scientific Abstract:
The understanding of signaling events is critical for attaining long-term expansion of hematopoietic stem cells ex vivo. In this study, we aim to analyze the contribution of multiple signaling molecules in proliferation of hematopoietic stem cells. To this end, we design a bottom-up engineered receptor with multiple tyrosine motifs, which can recruit multiple signaling molecules of interest. This is followed by a top-down approach, where one of the multiple tyrosine motifs in the bottom-up engineered receptor is functionally knocked out by tyrosine-to-phenylalanine mutation. The combination of these two approaches demonstrates the importance of Shc in cooperation with STAT3 or STAT5 in the proliferation of hematopoietic stem cells. The platform developed herein may be applied for analyzing other cells and/or other cell fate regulation systems.