Self-enforcing feedback activation between BCL6 and pre-B cell receptor signaling defines a distinct subtype of acute lymphoblastic leukemia.

Journal: Cancer Cell
Publication Year: 2015

PubMed link: 25759025
Funding Grants: Dual targeting of tyrosine kinase and BCL6 signaling for leukemia stem cell eradication

Public Summary: Studying 830 pre-B ALL cases from four clinical trials, we found that human ALL can be divided into two fundamentally distinct subtypes based on pre-BCR function. While absent in the majority of ALL cases, tonic pre-BCR signaling was found in 112 cases (13.5%). In these cases, tonic pre-BCR signaling induced activation of BCL6, which in turn increased pre-BCR signaling output at the transcriptional level. Interestingly, inhibition of pre-BCR-related tyrosine kinases reduced constitutive BCL6 expression and selectively killed patient-derived pre-BCR(+) ALL cells. These findings identify a genetically and phenotypically distinct subset of human ALL that critically depends on tonic pre-BCR signaling. In vivo treatment studies suggested that pre-BCR tyrosine kinase inhibitors are useful for the treatment of patients with pre-BCR(+) ALL.

Scientific Abstract: Studying 830 pre-B ALL cases from four clinical trials, we found that human ALL can be divided into two fundamentally distinct subtypes based on pre-BCR function. While absent in the majority of ALL cases, tonic pre-BCR signaling was found in 112 cases (13.5%). In these cases, tonic pre-BCR signaling induced activation of BCL6, which in turn increased pre-BCR signaling output at the transcriptional level. Interestingly, inhibition of pre-BCR-related tyrosine kinases reduced constitutive BCL6 expression and selectively killed patient-derived pre-BCR(+) ALL cells. These findings identify a genetically and phenotypically distinct subset of human ALL that critically depends on tonic pre-BCR signaling. In vivo treatment studies suggested that pre-BCR tyrosine kinase inhibitors are useful for the treatment of patients with pre-BCR(+) ALL.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/self-enforcing-feedback-activation-between-bcl6-and-pre-b-cell-receptor