Processive amplification of the c-Myc/miR17-92/Pten axis regulates B cell development and reconstitutes CD19 deficiency.

CD19 is a major regulator of B cell receptor (BCR) signaling by controlling activation of the PI3K pathway. Expression and function of CD19 is critical for B cell development, which is mediated by BCR signaling, as mice deficient of CD19 have impaired B cell development. In earlier studies it has been clearly demonstrated that CD19 functions to activate the Akt/GSK3/c-Myc axis, whereas the Phosphatase and tensin homolog (PTEN) antagonizes this pathway by inhibiting the activation of Akt. Thus, CD19 and Pten inversely regulate the PI3K pathway but a direct mechanism controlling the interaction between them to balance B cell development has not been shown.

microRNAs (miRNAs) are small endogenous RNA molecules that regulate gene expression by base-pairing with target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression. miR17-92 is a cluster composed by five miRNAs, which was defined to be the first oncogenic miRNA (oncomir1). One mechanism by which miR17-92 promotes cell proliferation is by repressing the expression of the tumor suppressor gene PTEN. **These findings lead us to hypothesize that in B lineage cells CD19 controls PTEN expression through regulating the production of miR17-92.**

Using primary CD19-deficient cells, as well as B cell lines treated to knockdown or over-express CD19, we show that expression of PTEN is in inverse correlation with CD19 expression. We found that CD19 enhances expression of miR17-92 and that this is achieved through activation of c-Myc, which is a central transcription factor of the miR17-92 cluster. Thus, our results implicate the c-Myc/miR17-92/PTEN as a novel axis regulated by CD19 that controls PI3K activation in B lineage cells.

To demonstrate the central role of this axis in B cell development we bread CD19 deficient mice with mice that conditionally overexpress miR17-92 in B lineage cells. Strikingly, we found that overexpression of miR17-92 completely reconstitutes for CD19 deficiency in B cell development as revealed by analysis of B lymphopoiesis in the bone marrow and development of splenic and peritoneal B1 and B2 cells.

In summary, our results suggest a novel axis that is regulated by CD19 to control the PI3K pathway, where miR17-92 functions as a key regulatory molecule. This conclusion is supported by finding that over expression of miR17-92 reconstitutes for CD19 deficiency in B cell development. To the best of our knowledge this is the first demonstration that alteration of microRNA expression compensates for impaired development of any cell lineage in vivo.