COUP-TFII regulates hemoglobin switching by activating the BCL11A-XL repressor LIN28B and directly binding δ and β globin promoters in fetal versus adult erythroid cells

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Abstract:

The reactivation of fetal globin genes is the most promising treatment for β-hemoglobinopathies. This implies the reversal of the naturally occurring haemoglobin switching.

Here, we show that expression of the orphan nuclear receptor COUP-TFII in adult HUDEP2 erythroid precursor cells activates γ-globin (HbF) at the expense of β-adult globin by specific occupation of the “adult” δ-β-region within the β-locus.

Notably, although COUP-TFII and the main γ-globin repressor BCL11A-XL share a similar DNA binding consensus and a large number of chromatin targets, including the locus control region of the β-locus itself, they bind differentially to the γ and β promoters, eliciting an opposite transcriptional outcome.

In addition, we find that COUP-TFII activates LIN28B, a known post-transcriptional repressor of BCL11A-XL. Our work identifies a molecular mechanism that could be leveraged to increase γ-globin levels in patients affected by β-hemoglobinopathies.