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Regulation of endoderm development by zebrafish Nipbl
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Heterozygous loss of the \textit{Nipped-B-like} gene (\textit{Nipbl}) is the most common cause of Cornelia de Lange Syndrome (CdLS). Although \textit{Nipbl} is a cohesin-associated protein conserved among all eukaryotes, recent studies suggest that it regulates gene expression through mechanisms independent of cohesin’s established role in chromatid cohesion. There are 2 \textit{Nipbl} genes in zebrafish, \textit{zNipbl-1} and \textit{zNipbl-2}, and embryos injected with morpholinos targeting either gene (\textit{zNipbl}-morphants) show defects in formation of the gut/visceral organs and heart with a range of severity from looping defects to organs duplication. Such morphants show significant reductions in \textit{sox32}, \textit{sox17} and \textit{foxa2} expressions in endoderm cells, and we found that combined \textit{sox17/foxa2}-double morphants exhibited gut bifurcations similar to \textit{zNipbl}-morphants. Interestingly, the degree of \textit{sox17} and \textit{foxa2} suppression in \textit{zNipbl}-morphants was greater than could be explained by the reduction in \textit{sox32} (a known positive regulator of these genes), and the response of these genes to ectopic \textit{sox32} was significantly blunted. These data suggest that \textit{zNipbls} may influence \textit{sox17} and \textit{foxa2} transcription directly. In \textit{zNipbl}-morphants, we also observed abnormal spatial expression of the left–right patterning genes, \textit{lefty2} and \textit{southpaw}, although Kuppfer’s vesicle (KV), a critical organ for left–right patterning that depends on \textit{sox32} function, formed normally, implying that \textit{zNipbls} act downstream of KV formation. These results support the idea that \textit{zNipbls} regulate embryonic development through modulating gene expression at multiple levels. Supported by NIH P01-HD052860.

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