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Mouse GLI3 Regulates *Fgf8* Expression and Apoptosis in the Developing Neural Tube, Face, and Limb BudKazushi Aoto ^{a, b} ... Jun Motoyama ^{a, 1}

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Abstract

The zinc finger transcription factor GLI3 is considered a repressor of vertebrate Hedgehog (Hh) signaling. In humans, the absence of GLI3 function causes Greig cephalopolysyndactyly syndrome, affecting the development of the brain, eye, face, and limb. Because the etiology of these malformations is not well understood, we examined the phenotype of mouse *Gli3*^{-/-} mutants as a model to investigate this. We observed an up-regulation of *Fgf8* in the anterior neural ridge, isthmus, eye, facial primordia, and limb buds of mutant embryos, sites coinciding with the human disease. Intriguingly, endogenous apoptosis was reduced in *Fgf8*-positive areas in *Gli3*^{-/-} mutants. Since SHH is thought to be involved in *Fgf8* regulation, we compared *Fgf8* expression in *Shh*^{-/-} and *Gli3*^{-/-}; *Shh*^{-/-} mutant embryos. Whereas *Fgf8* expression was almost absent in *Shh*^{-/-} mutants, it was up-regulated in *Gli3*^{-/-}; *Shh*^{-/-} double mutants, suggesting that SHH is not required for *Fgf8* induction, and that GLI3 normally represses *Fgf8* independently of SHH. In the limb bud, we provide evidence that ectopic expression of *Gremlin* in *Gli3*^{-/-} mutants might contribute to a decrease in apoptosis. Together, our data reveal that GLI3 limits *Fgf8*-expression domains in multiple tissues, through a mechanism that may include the induction or maintenance of apoptosis.

Keywords





GLI3; FGF8; SHH; brain patterning; optic field; limb development; facial malformation; apoptosis






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