Mouse Disp1 is required in sonic hedgehog-expressing cells for paracrine activity of the cholesterol-modified ligand

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There was a reanalysis of data required to support the findings in Development 132, 133-142.

We have repeated the facial analysis reported in Fig. 2 to provide the data required to support some of the original findings of this study (see Publisher’s note). Our findings substantiate the original conclusions drawn from Fig. 2 of a dose-related genetic interaction between Disp1 and Shh alleles, and of the function of Disp1 within Shh-producing cells. Some differences are reported below, which might reflect slight differences in embryonic staging or increased sensitivity of the whole-mount in situ hybridization procedure here. Importantly, they do not alter the key conclusion that reducing Disp1 levels in Shh-producing cells results in a phenotype similar to that of genetically matched embryos with reduced Disp1 activity throughout the embryo. These data support the overall conclusions of the paper, and, together with other data in the same report, support a model in which the principal requirement for Disp1 activity is in Shh-producing cells.

Fig. 2. Attenuating Disp1 activity specifically in Shh-producing cells phenocopies Disp1 hypomorphic mutants. Attenuating Disp1 activity specifically in Shh-producing cells produced facial phenotypes that resembled genetically matched embryos with Disp1 reduction throughout the embryo. (A-E) External facial views of E18.5 embryos with the indicated genotypes. (F-J) Whole-mount in situ hybridization with Fgf8 probes to E10.5 embryos of the indicated genotypes. The separation of Fgf8 expression domains in the frontal nasal processes of wild-type embryos (bracket in F) reflects the normal development of midline structures that were lost to varying degrees in embryos with attenuated Disp1 and Shh activity (G-J). (K-O) Alcian Blue (non-mineralized cartilage)-stained and Alizarin Red (mineralized cartilage and bone)-stained head skeletal preparations of E18.5 embryos with indicated genotypes. A variable loss was observed in both upper (arrow in K) and lower (arrowhead in K) jaw structures, including the midline incisors. (P-Y) Whole-mount in situ hybridization with (P-T) Ptch1 and (U-Y) Shh probes to E9.5 embryos of the indicated genotypes. Ptch1 and Shh expression was evident in midline cell populations rostral to the optic lobes in wild-type embryos (arrows in P and U). Their expression was either markedly reduced or lost, depending on the specific combination of Disp1 and Shh alleles (Q-T and V-Y). Ptch1 and Shh expression was detected in the midbrain region (indicated by arrowheads in P and U) of all genotypes, albeit at reduced levels.
Disp1 Δ2/Δ2; ShhCre/+ embryos in which Disp1 activity was specifically knocked down in Shh-producing cells have a facial phenotype with a narrowing of the face and reduction of the premaxilla. However, the length of the snout is similar to wild type and the mandibular incisors are not fused (Fig. 2A,C,K,M). Thus, the phenotype is, as expected, generally less severe than that of the Disp1 Δ2/Δ2; Shh+/− embryos (Fig. 2B,L). The severity of the conditional phenotype is enhanced when Disp1 activity is further lowered in Disp1 Δ2/C829F; ShhCre/+ mice (Fig. 2E,O) but the phenotype is slightly weaker than that in Disp1 Δ2/C829F (data not shown) or Disp1 Δ2/C829F; Shh+/− embryos (Fig. 2D,N); the tubular nasal process was shorter and the premaxillary bone was more extensive. In a proportion of the latter, truncated fused mandibles lack incisors (Fig. 2N); however, mandibular fusion was not observed in Disp1 Δ2/C829F; ShhCre/+ embryos. The slightly weaker facial phenotype seen at term with each of the conditional removal combinations was evident at E10.5 when the distance between the Fgf8-expressing frontal-nasal processes is compared by whole-mount in situ hybridization (Fig. 2F-J). Variable weak midline Shh expression was observed rostral to the optic stalk in Disp1 Δ2/Δ2C; ShhCre/+ embryos at E9.5 (Fig. 2U-W). As expected, this resulted in Ptch1 expression in adjacent nascent facial structures (Fig. 2P-R). Small, weak domains of Shh and Ptch1 expression were observed close to the midline, localized to the region of the optic stalk in Disp1 Δ2/C829F; ShhCre/+ embryos (not readily visible in Fig. 2T,Y). Only Disp1 Δ2/C829F; Shh+/− embryos, the strongest genetic combination, completely lacked Shh and Ptch1 expression rostral to the diencephalon (Fig. 2S,X).

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Publisher’s note


In 2005, the McMahon laboratory reported that a re-examination of two papers published by their group in Development (Tian et al., 2004; Tian et al., 2005a) had revealed a duplication of Dr Tian’s data in these papers. Following their analysis, the authors announced, with regret, that they must retract Tian et al. (2004), and this retraction was published by Development in November 2005, along with their apology to the editors and readership of the journal (Tian et al., 2005b). With respect to the second paper (Tian et al., 2005a), the authors’ review, overseen by the Committee on Professional Conduct (CPC) for the Faculty of Arts and Sciences at Harvard University, found that the principal conclusions of the paper were supported by appropriate documentation but that the documentation for Fig. 2 was inadequate, requiring a replication of those data. The replicated data have been reviewed by Development and are published in this Corrigendum.

References

