There also appears to be massive cell death in the somites and notochord of double mutants. We have also examined gene expression using RNA in situ hybridization to look at the effect of the deletion of Foxa1 and Foxa2 on other genes required for notochord formation and NP development. Study of the role of Foxa family action in IVD development may provide insight into new treatments for disk degeneration.

doi:10.1016/j.ydbio.2011.05.401

Program/Abstract #440
Differential requirement of ZIC3 function in cardiac development and X-linked heterotaxy
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Heterotaxy, contributing to ~5% of congenial heart defects (CHD), arises from abnormal left-right patterning. Mutations of ZIC3 gene (Zinc finger protein of cerebellum 3) are associated with human X-linked heterotaxy. A mouse model with targeted disruption of Zic3 exhibited ~75% early lethality, and recapitulated the phenotype seen in human patients. However, it is not known whether ZIC3 is required in a single developmental field or whether it has pleiotropic roles in multiple developmental processes, and the detailed mechanism remains elusive. To address these questions, we generated a conditional allele of the Zic3 gene by flanking its 1st exon with loxP sites. Sox2-cre, Wnt1-cre and T-cre lines were used to delete Zic3 in epiblast, neural crest and mesoderm, respectively. Deletion of Zic3 in epiblast and mesoderm, but not in neural crest, led to ~50% early lethality. Examination of epiblast conditional embryos by microscopy revealed multiple CNS and neural tube defects similar to the null embryos. But these defects were not found in mesoderm or neural crest conditional embryos, suggesting that Zic3's function in CNS development likely remains intact in these mutants. MRI scanning of Zic3 epiblast and mesoderm conditional embryos also uncovered multiple heterotaxy related visceral abnormalities. Gene expression analysis by microarray in the hearts of embryos at 15.5 dpc revealed a similar expression pattern between Zic3 epiblast conditional and null males, which was significantly different from control males. Perturbed expression of several cardiac genes and direct targets of Zic3 suggested that Notch, BMP and TGF-β signaling might be affected, and requires further investigation.

doi:10.1016/j.ydbio.2011.05.402

Program/Abstract #441
Hox genes control the axis elongation process in chicken embryo
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The vertebae's precursors, the somites, are formed periodically by the segmentation of the presomitic mesoderm (PSM) which forms by progressive cell deposition from a posterior growth zone. The number of somites is precisely defined for any given species but varies widely from one species to another. In order to maintain a precise number of somites, the body axis elongation has to be tightly controlled. Indeed, using time-lapse imaging of developing chicken embryos we observed that elongation process slows down few hours before the termination of the axis. We previously showed that a gradient of random cell motility within the PSM is implicated in axis elongation (Benazeraf et al., 2010). However the precise control of how the elongation will slow down to define the axis length remains unknown. To address this issue, we used the electroporation technique coupled to time-lapse imaging of developing chicken embryos. Using these techniques we show that cell motility in the PSM decreases progressively at the end of axis elongation. Nevertheless this decrease in cell motility is not sufficient to explain the slowing down of axis elongation. We previously showed that Hox genes are expressed in a collinear fashion in the PSM precursors and control the timing of ingression of the PSM precursors (Iimura and Pourquie 2006). Overexpression of different Hox genes alters body axis elongation. This effect takes place in part by controlling cell motility in the posterior PSM but mainly by regulating the flux of cells ingressing in the PSM. Altogether we propose a new mechanism explaining how the collinear expression of the Hox genes regulates the length of the body axis.

doi:10.1016/j.ydbio.2011.05.403

Program/Abstract #442
Role of 5′HOXD genes in the endochondral ossification
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Mutations with gain and loss-of-function of Hoxd genes present notably osteogenic defects indicating the involvement of these genes in the endochondral ossification. To clarify the role of Hoxd genes in endochondral ossification, we have analyzed the osteochondrogenic program in the autopod of mice lacking Hoxd11 to 13 (HoxdDel11–13/Del11–13), the animal model for the human synpolydactyly. This mutant is characterized by short and sometimes biphalangeal digits and by an extremely ossification delay. The maximum phenotypic defect occurs in the metacarpals/metatarsals that at birth lack the primary ossification center and collar bone. Ossification center the phalanges is partially abnormal and ventrally biased. During embryonic development Ihh and Runx2 expression is undetectable in the chondrocytes and perichondrium respectively, reflecting the abnormal organization and differentiation of the bone anlagen. The similarity of the phenotype with that of Ihh mutants prompted us to perform the compound Gli3; HoxdDel(11–13) mutant. Interestingly, removal of Gli3 from the HoxdDel(11–13) background rescued ossification in the hindlimb (metatarsals) but only partially in the forelimb (metacarpals). Our results support the involvement of Hoxd11–13 in the formation of the perichondrium and in the regulation of Ihh expression. Supported by grant BFU2008-00397 from the Spanish Ministry of Science and Innovation.

doi:10.1016/j.ydbio.2011.05.404

Program/Abstract #443
HMGB factors are required for posterior digit development through integrating Shh, Wnt and BMP signaling pathways in the forelimb
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