



CDB SEMINAR

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16:00~17:00 A7F Seminar Room

Mechanical forces influence three-dimensional cell behaviours during mouse mandibular arch development

Summary

An essential unanswered question in biology is how embryonic tissues are shaped in 3D. Morphogenetic mechanisms that control head and facial development are important because one-third of all human congenital birth defects exhibit craniofacial abnormalities. *WNT5A* mutations are associated with autosomal dominant Robinow syndrome that causes mandibular dysmorphology in humans, although the morphogenetic basis of early mandibular development is poorly understood. Although cell behaviours that shape 2D epithelial sheets are extensively studied, far less is known about mechanisms that shape a volume of cells. We employed live light sheet microscopy of intact transgenic reporter embryos combined with a custom 4D (3D + time) cell tracking algorithm to show that the middle narrow region grows anisotropically relative to the distal bulbous region. To test the basis for this anisotropic growth, we measured cell cycle times, epithelial and mesenchymal elasticity and viscosity using atomic force microscopy. A finite element model based on optical projection tomography of the arch showed that all of these parameters are inadequate to explain how the mandibular arch is shaped. Therefore, we examined cell behaviours at high resolution and observed that mesenchymal cells intercalate in 3D in a manner that is analogous to an unstable foam. These intercalations result in volumetric convergent extension of the waist portion of the arch but are absent in the bulbous portion, helping to explain differences in tissue shape. To measure forces that underlie these cell intercalations at cellular resolution *in vivo*, we generated a transgenic FRET-based vinculin force sensor in the mouse embryo. Using this tool, we observed that relatively high amplitude cortical force oscillations are associated with cell rearrangements in 3D, likely to overcome the energy barrier to cell intercalation. Using mouse mutants, we found that *Wnt5a* promotes cell intercalation and branchial arch outgrowth by regulating cortical force oscillations as well as cortical actin polarity. Interestingly, nuclear Yap is significantly reduced in *Wnt5a* knock-out embryos and conditional *Yap/Taz* mutants partially phenocopy *Wnt5a* phenotypes, suggesting that these regulators act in the same pathway. Finally, we show that *Wnt5a* regulates Piezo1 mechanosensitive ion channels and Calpain2 protease. Therefore, multiple molecular mechanisms control cellular forces that drive intercalations and shape tissue in 3D.

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