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Primary Cilia (Session Summary)

Primary cilia

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There is an increasing body of recent evidence that primary cilia are centrally involved in the cell's ability to sense and respond to changes in their extracellular environment. It is clear that primary cilia have many functions. This can be inferred from the observation that of the cilium genes that result in human disease when mutated, the resulting phenotypes are surprisingly diverse. This suggests that the confluence of distinct sensing and signaling pathways at the primary cilium can have different readouts in different cell types.

An interesting question raised in the session was whether the plasma membrane sheath of the primary cilium is unique or unusual in any way. Although this is not known in detail, it does not appear that the ciliary membrane is particularly unusual. The ciliary membrane does appear to be functionally separate from plasma membrane in general, and this might prevent diffusion of cilia-specific receptors or other membrane proteins away from the cilium. This may also increase signaling kinetics within this membrane microdomain as well as within intracellular volume of the cilium itself. However, it is difficult to address these questions as, thus far, it has proven difficult to manipulate aspects of primary cilia structure and function without affecting the entire cell compartment.

Although there are clear structural differences between primary cilia and motile cilia or multi-cilia, it is unknown whether the primary cilia are structurally different in different cell types. For example, it is not clear whether there are differences in primary cilia frequency or length between different tissue types. Osteoclasts, given their multi-nucleated nature, might express multiple primary cilia, a single primary cilium, or no primary cilia. Other fundamental questions of primary cilia structure and function remain open such as if or to what extent they are anchored intracellularly to the cytoskeletal network and whether this has consequences for chemical or mechanical signaling.

Primary cilia appear to play a critical role in development. Kif3A deletion in nestin expressing cells results in polydactaly but with normal appearing extracellular matrix apparently due to a failure of osteoblast differentiation. Also, this appears distinct from simple loss of cilia-mediated hedgehog signaling. In wnt1 driven deletion of Kif3A neural crest cells appear to be able to migrate properly during development without primary cilia. These mice suggest that the role of the primary cilium in patterning versus changing the rate of the differentiation program may be distinct. This again suggests that the cilium has apparently multiple distinct roles in sensing contexts.

In terms of mechanosensing, it appears clear that in osteocytes, primary cilia are able to sense fluid flow *in vitro*. However, to what extent osteocyte cilia "mechanosense" *in vivo* and whether this is due to pericellular flow is unknown. Additionally, there is evidence for both cilium-dependent and cilium-independent sensing as well as multiple ciliary signaling mechanisms. It is also unknown what role early cilium-dependent molecular mechanotransduction plays in longer-term changes in mineralization. One of the reasons it is very difficult to address these questions is that the location of the cilium within the osteocyte lacuna and its relationship with the pericellular matrix has not been described. *In vitro* it is challenging, but possible, to visualize ciliary motion with flow. Thus, it may be feasible to conduct a detailed fluid-structure interaction analysis to determine the extent to which cilia deform along their length and whether there are visco-elastic or purely elastic mechanisms involved in this motion.

In embryonic skeletal development, primary cilia appear to play a central role in hedgehog signaling in that intraflagellar transport is required for both gli activator and repressor functions. For example, in limb patterning, it appears as if gli-repressor functions are dominant so that loss of cilia results in a phenotype that resembles Shh gain-of -function.

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In contrast, alterations in the growth plate of IFT/cilia mutant mice more closely resemble the hedgehog loss-of-function phenotype although signaling pathways other than hedgehog are also likely affected. Furthermore, cilia in the perichondrium appear to play a major role regulating embryonic endochondral bone formation as evidenced by differences in Col2a-Cre and Prx1-Cre generated mutant mice.

In the columnar cells of the post-natal growth plate there is clear evidence of polarization along the golgi-nuclear axis immediately after mitosis. This polarization is maintained as the cells migrate into the columnar pattern. This process, called rotation, is altered in the absence of IFT/cilia suggesting that the primary cilia might also be polarized. However, this is currently unclear as is the mechanism of IFT/cilia action in the process of rotation.

In conclusion, the discussion highlighted that currently there are many critical unknowns regarding the function of primary cilia in the skeleton. Their role in extracellular sensing is compelling, not only in terms of the number and diversity of signals involved, but also the potential for cross-talk and synergies. What is clear is that this unique structure holds great potential as a signaling nexus where specialized molecular mechanisms for chemical and mechanical sensing co-localize.