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General Summary

We are interested in the developmental and evolutionary aspects of vertebrate organs. By comparing organ development in humans and other animals, we are attempting to reconstitute the evolutionary path that each of our organs has taken, at both the molecular and morphological levels, thus identifying fundamental molecular mechanisms that shape each organ.

Research Activities

Evolutionary origin of the vertebrate lung

Terrestrial vertebrates and fish both possess an organ that is filled with air: the lungs and the swimbladder, respectively. These organs have been postulated to be homologous. Both the lungs and the swimbladder are air-filled sacs that are derived from the digestive tract. On the other hand, the lungs are a paired structure while the swimbladder is a single sac. The lungs extend from the ventral side of the digestive trace, whereas the swimbladder extends from the dorsal side. Due to a lack of fossil evidence, it has been difficult to determine whether the lungs and the swimbladder are actually homologous organs and if so, what they were like when they were first acquired in the ancestral vertebrate. We are comparing gene expression patterns during development of the lungs and the swimbladder in *Xenopus*, Australian lungfish, *Polypterus*, and zebrafish to test this hypothesis. So far, we have found that TBX4, FGF10, and NKX2.1, which have been identified as key regulators of aminiote lung development, are also specifically expressed in the swimbladder of the zebrafish. Knockdown of FGF10 results in loss of NKX2.1 expression and in swimbladder hypoplasia. These results suggest that both the lungs and the swimbladder evolved from a lung-like organ that was present in the common ancestor of teleosts and tetrapods.

Identification of ureteric bud progenitors in chicken embryo

Our goal is to generate kidneys exclusively derived from autologous human mesenchymal stem cells (hMSCs). However, we have not induced differentiation of hMSCs into the ureters and collecting ducts, both of which are derivatives of the ureteric bud. Last year, we identified the ureteric bud progenitor region, where hMSCs should be transplanted for their differentiation into the ureters and collecting ducts, in chicken embryos by lineage tracing with 3,3′-dioctadecylindocarbocyanine iodide. This year, we demonstrated that *Pax2*-transfected hMSCs differentiated into the Wolffian ducts,

which are the parent tissue of the uteric bud when transplanted into the chicken ureteric bud progenitor region. This result suggests that with further research we may be able to induce differentiation of hMSCs into ureters and the collecting ducts.

Apoptosis and compensatory proliferation

Coordination of cell death and cell proliferation during development is critical for consistently producing organs of the correct size and shape. Accidental cell death in *Drosophila* larval imaginal discs leads to "compensatory proliferation." We found that the *Drosophila* initiator caspase DRONC simultaneously triggers cell death and induces compensatory proliferation. When cells are stimulated to undergo apoptosis but are simultaneously kept alive, the "undead cells" induce excessive compensatory proliferation. This abnormal tissue overgrowth is completely suppressed in *dronc* mutants. We also found that jun kinase (JNK) signaling is also required for compensatory proliferation. Genetic epistasis analysis suggests that JNK signaling is activated downstream of DRONC activation. These results suggest that the apoptosis signaling bifurcates at DRONC, with one branch leading to apoptosis and the other branch leading to compensatory proliferation through activation of JNK signaling.

How to make figures and presentations that are friendly to color-blind people

In scientific presentations and publications, color has become a significant vehicle for information and presentation effect. However, color perception varies greatly among individuals; in particular, red-green color blindness is present in 4% to 9% of males in various populations, a frequency comparable to that of the AB blood type. Thus, inappropriate color choices can cause unexpected difficulty in understanding color figures. We are examining how color and color combinations are perceived by various color-vision types to develop a method for presenting color information that can convey maximal information to most color-vision types, including color blindness. We introduced this method on our web site: http://www.nig.ac.jp/color

Publications

Yokoo T, Fukui A, Ohashi T, Miyazaki Y, Utsunomiya Y, Kawamura T, Hosoya T, Okabe M, Kobayashi E (Jichi Med Sch). Xenobiotic kidney organogenesis from human mesenchymal stem cells using a growing rodent embryo. *J Am Soc Nephrol* 2006; **17:** 1026–34.

Williams DW[1], Kondo S, Krzyzanowska A[1] (King's Coll London), Hiromi Y (Natl Inst Genetics), Truman JW (Univ Washington). Local caspase activity directs engulfment of dendrites during pruning. *Nat Neurosci* 2006; **9:** 1234–6.

Kondo S, Senoo-Matsuda N[1], Hiromi Y (Natl Inst Gen), Miura M[1] ([1]Univ Tokyo). (2006) DRONC coordinates cell death and compensatory proliferation. *Mol Cell Biol* 2006; **26:** 7258–68.