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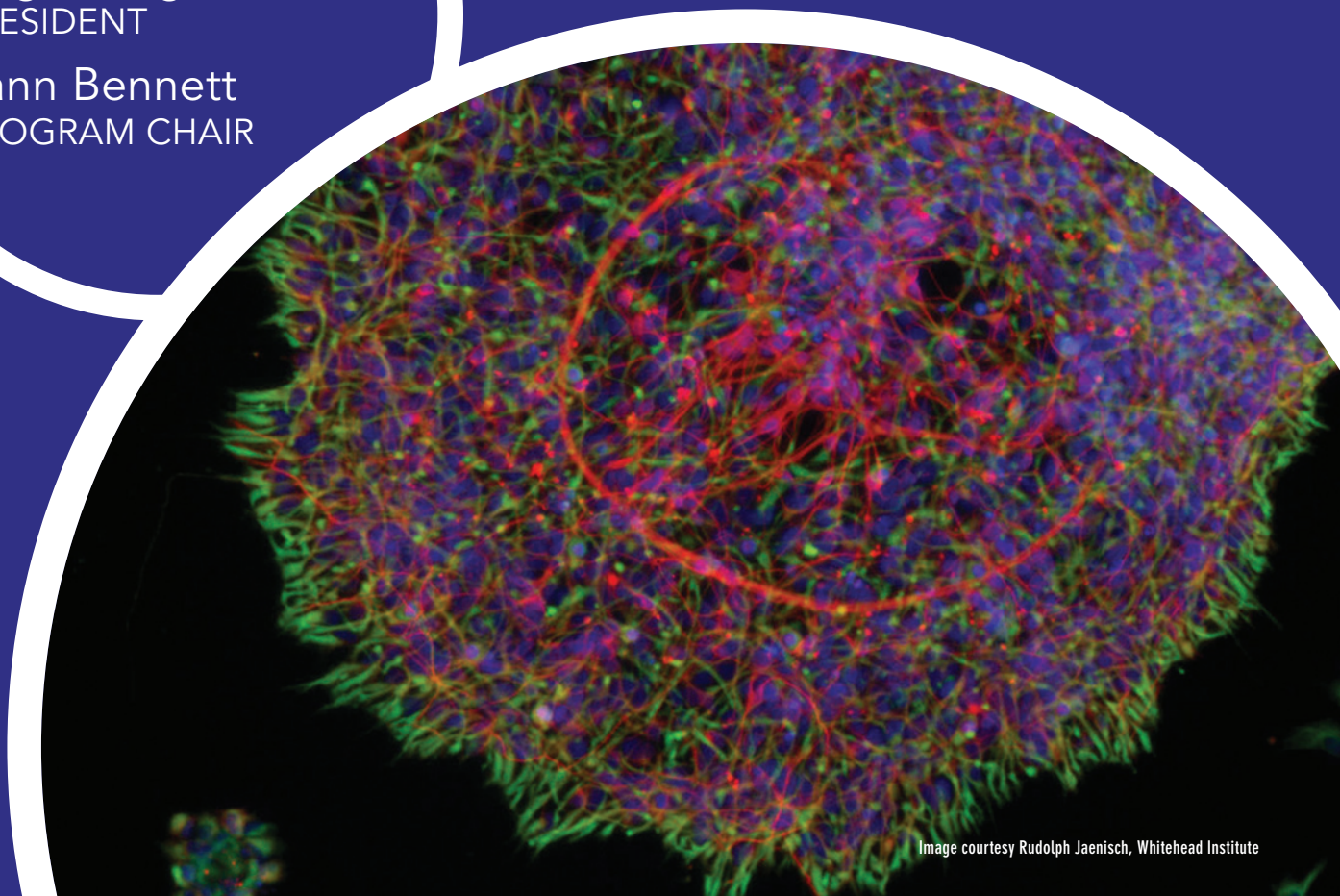

Image courtesy Rudolph Jaenisch, Whitehead Institute

In adult animals, differentiated tissues must continually adapt to changing environmental and physiological demands. Remodeling of the vertebrate intestinal lining in response to fluctuating dietary loads is a prime example of such adaptation. However, the cellular mechanisms of such post-developmental morphogenesis are poorly understood. Using a new model of adult organ remodeling, we show that intestinal stem cells in the mature *Drosophila* midgut interpret an instructive nutrient signal to direct tissue growth toward the functionally appropriate state. Food ingestion causes an increase in intestinal size and cell number. This adaptive growth occurs via insulin-activated stem cell proliferation. Synthesis of insulin matches the kinetics of stem cell proliferation in fed and fasted conditions. Insulin receptor activation in stem cells stimulates both symmetric and asymmetric divisions, thereby elaborating the intestinal epithelium when food is abundant. Altogether, these data suggest that mature organs can respond to external cues for adaptive change by leveraging programs of stem cell renewal. We postulate that in the gut, the nutrient-triggered stem cell response enables organ morphogenesis to be tuned to functional need.

410/B357

The Role of Insulin Signaling and Nutrition in the Regulation of *Drosophila* Male Germline Stem Cells.

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A steady supply of differentiated cells from adult stem cells is critical to maintain tissue homeostasis. Defective control of stem cell number either results in loss of stem cells leading to tissue degeneration, or excess proliferation of stem cells leading to tumorigenesis. The *Drosophila* male germline stem cell (GSC) provides an excellent model system to study stem cell behavior in the context of the stem cell niche. Their niche is located at the tip of the testis. GSCs attach to a cluster of somatic cells called the hub, which provides an essential ligand (Upd) for stem cell identity, and divide asymmetrically by orienting their mitotic spindle perpendicularly to the hub. Stereotypical positioning of centrosomes with respect to the hub sets up this spindle orientation; one centrosome (mother centrosome) always locates close to the hub-GSC junction, while the other centrosome (daughter centrosome) migrates to the opposite side of the GSC. Recently, we have shown that GSCs with misoriented centrosomes, where neither of the two centrosomes is juxtaposed to the hub-GSC junction, undergo cell cycle arrest until their centrosomes reorient, suggesting a novel cell cycle checkpoint to monitor correct centrosome positioning. Here we show that nutrition, through the insulin pathway, may have an effect on centrosome orientation in GSCs. Flies grown in poor nutrient conditions have significantly higher frequency of GSCs with misoriented centrosomes. This response appears to be mediated via the insulin signaling pathway, since expression of constitutively active insulin receptor in GSCs restores centrosome orientation even when cultured in poor nutrient conditions. We propose that the nutrients' condition modulates GSC division rates by controlling centrosome orientation, which can regulate cell cycle progression via the centrosome orientation checkpoint.

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Reserve Stem Cells of Asexually Reproducing Organisms.

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Asexual reproduction is a natural cloning of oozooid, with development of many genetically and morphologically identical blastozooids. In asexually reproducing animals, the lineage of reserve stem cells ensures both sexual and asexual reproduction, being predecessors of germline and all somatic cells. We studied morphological and functional organization of reserve SCs in five animal types: Porifera (Oscarella malakhovi), Cnidaria (Obelia longissima), Platyhelmintes (Girardia tigrina), Arthropoda (Peltogasterella gracilis, Polyascus polygenea), Chordata (Botryllus tuberatus) and mouse ESC in vitro. Asexual reproduction without separation of blastozooids in

some rhizocephalans results in the emergence of colonial organization that is unique among crustaceans, all arthropods, and all Ecdysozoa. Blastogenesis and coloniality in the rhizocephalans involve a radical, evolutionary secondary rearrangement of the ancestral reproductive biology due to the transition to parasitic life. We found germinal bodies in all or most blastomeres in cleaving embryos of P. polygenea. Each body selectively expresses mRNA transcript of vasa-like gene. This data indicates a saltatory evolution from determined mosaic cleavage with preformation to regulative development with epigenesis. The morpho-functional organization of stem and gonial cells in the studied species shares common properties: A high nuclear/cytoplasmic ratio, a large nucleus with diffuse chromatin and a large nucleolus, basophilic cytoplasm including specific perinuclear germinal granules, the positive reactions revealing proliferating cell nuclear antigen and alkaline phosphatase activity. We observed electrondense granular structures in mESCs similar to germinal granules in metazoan oogenic cells. Similar structures were found in reproductive cells of lower and higher plants. This similarity indicates a very conservative pattern of reproductive cells in Metazoa and Metaphyta. Thus, our data indicates evolutionary conservatism and common morpho-functional organization of germ cells from all studied multi-cellular animals and unlimited morphogenetic potential of reserve stem cell capable of both gametogenesis (and embryogenesis) and asexual reproduction (blastogenesis).

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Notch Signaling Is Activated during Regeneration of the Airway Epithelium.

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Objective: Notch signaling plays an important role in establishing the balance between ciliated and secretory cell fates in the developing airways. However little is known whether this mechanism is present during regeneration of the airway epithelium in adult life. The goal of the study is to identify the Notch pathway components in adult airways undergoing regeneration after naphthalene injury. Methods: Adult CD1 mice were injected intraperitoneally with naphthalene and airway epithelium desquamation and regeneration were investigated, including changes in morphology, expression of differentiation markers and Notch components. We used in situ hybridization and immunohistochemistry on lung tissue sections. Results: Overall expression of Notch components/expression was nearly undetectable in adult lungs. at 52 hr of naphthalene injury, when secretory cells were ablated in the airway, the Notch signaling effectors (Hes1, Hey1, Hey2 and HeyL) remained low in the remaining cells. However by 72 hr, when the regeneration process started, Notch1 and the ligand Jagged1, as well as Hes1 and Hey1 were up-regulated in the airway epithelium with distinct patterns. Expression of Hey2 and HeyL remained low at all time points. Interestingly, up-regulation of Notch1 and Hes1 correlated with increased expression of Scgb3a2 (secretoglobin, family 3A, member 2), an early secretory cell marker. Additionally, increased Notch1 and Hes1 expression was observed almost exclusively in cells negative for Foxj1 (forkhead box j1), an early ciliated cell marker. These suggest that activation of Notch signaling, likely by Notch1, may favor the acquisition of the secretory cell phenotype during the repopulation of the airway epithelium after injury. Conclusions: Thus Notch signal may be crucial for the balance of differentiated cell fates during airway regeneration, as it is in development.

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Inscuteable Drives Asymmetric Cell Divisions in the Mouse Epidermis.

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Asymmetric cell divisions (ACD) are used throughout development to promote different fates between two daughter cells. In the mouse epidermis ACD within the proliferative basal layer promote stratification and differentiation. Unlike invertebrate model systems for ACD, which undergo obligate asymmetric divisions, basal cells have the capacity to undergo both asymmetric and symmetric divisions. Thus, a basal cell must be able to direct the proper orientation of its mitotic spindle to achieve the correct type of division. We provide evidence on how and when this decision is made. To this end, we used two transgenic mouse lines that labeled either the centrosomes or spindle poles. By quantifying their localization throughout the cell cycle, we have determined that basal cells do not establish their axis of division until metaphase via spindle