Department of Genetics

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Research Projects:

Cell-cell interactions in multicellular organisms play crucial roles in coordination of cell proliferation, differentiation, and cell death during development and homeostasis. However, little is known how cells communicate each other within animals to establish a multicelular system. We are exploring the molecular basis of cell-cell communication utilizing a powerful genetics of *Drosophila*. Especially, our research focuses on the mechanisms of cellular 'competition' and 'cooperation' within epithelium.

1) Mechanism of cell competition

'Cell competition' is a form of cell-cell interaction in which cells with higher fitness ('winners') survive and proliferate at the expense of neighboring cells with lower fitness ('losers'). Loser cells, but otherwise viable cells, are eliminated by cell death when confronted with winner cells. It has been suggested that cell competition is involved in a variety of biological processes such as organ size control, tissue homeostasis, cancer progression, and the maintenance of stem cell population. In developing *Drosophilai* maginal epithelia, clones of cells mutant for apico-basal polarity genes such as *scribble* (*scrib*) or discs large(*dlg*) lose their epithelial integrity and are eliminated by cell competition when confronted with wild-type cells. We have discovered that the *Drosophila* tumor necrosis factor (TNF) Eiger and its downstream JNK signaling play a central role in this process. Interestingly, Eiger-JNK signaling is required for both losers and winners to drive cell competition. Elevated Eiger signaling in mutant 'loser' cells promotes JNK-dependent cell death of these cells (Igaki *et al.*, *Dev Cell*, 2009), while elevated Eiger signaling in surrounding wild-type 'winner' cells facilitates elimination of mutant neighbors through JNK-dependent engulfment machinery (Ohsawa *et al.*, *Dev Cell*, 2011) (Fig. 1). Our study reveals that cell competition could be an evolutionarily conserved fail-safe mechanism by which animals protect against neoplastic development. To dissect the upstream mechanisms of cell competition, we have established and performed a genetic screen for genes that regulate this cell elimination. We have also established new models of cell competition using different types of mutations to understand the molecular mechanism and the physiological roles of cell competition.

2) Mechanism of tissue growth and tumor progression through cell-cell communication

Cell-cell interactions between oncogenic cells and surrounding normal cells in the tumor microenvironment play crucial roles in cancer progression. However, the mechanisms by which each oncogenic alteration cooperates with others to drive tissue growth and tumor progression through cell-cell communication remain elusive. We have been studying the mechanism of tumor growth and metastasis using the *Drosophila* model of tumor progression (Igaki *et al.*, *Curr Biol*, 2006). Furthermore, we have performed a genetic screen in *Drosophila* imaginal epithelium to identify mutations that cause 'non-autonomous' tumor progression through cell-cell communication. The results from our screen revealed that defects in mitochondrial respiratory function in conjunction with Ras activation potently induce tumor progression of surrounding tissue. Mechanistically, Ras activation and mitochondrial dysfunction cooperatively stimulate production of ROS, which causes activation of JNK signaling. JNK cooperates with oncogenic Ras to inactivate the Hippo pathway, leading to upregulation of the inflammatory cytokine Unpaired (Upd, an IL-6 homolog). The secreted Upd further cooperates with Ras signaling in neighboring cells with normal mitochondrial function, causing benign tumors to exhibit metastatic behavior (Ohsawa *et al.*, *Nature*, 2012) (Fig. 2). These findings provide a novel mechanistic basis for interclonal tumor progression driven by 'oncogenic inflammation' through Ras activation and mitochondrial dysfunction, the frequent alterations in human malignancies. We have also discovered that oncogenic cells with elevated Src activity promote growth of surrounding tissue via JNK-dependent regulation of the Hippo pathway (Enomoto and Igaki, *EMBO Rep*, 2012). are also establishing new models of cellular 'cooperation' that regulate tissue growth and/or tumor progression through cell-cell communications.

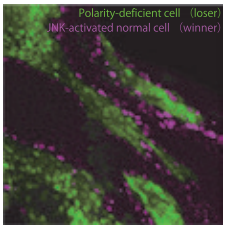

Fig. 1 Cell competition in *Drosophila* epithelium

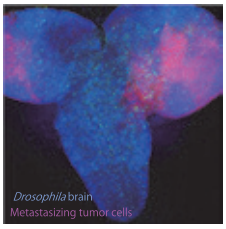

Fig. 2 Tumor metastasis in the *Drosophila* brain

Recent publications

- Yamamoto *et al.*,
  The ligand Sas and its receptor PTP10D drive tumour-suppressive cell competition"
  Nature, 542, 246-250 (2017)
- Vaughen and Igaki
  Slit-Robo repulsive signaling extrudes tumorigenic cells from epithelia"
  Developmental Cell, 39, 683-695 (2016)
- Nakamura *et al.*,
  Mitochondrial defects trigger proliferation of neighbouring cells via a senescence-associated secretory phenotype in *Drosophila*
  Nature Communications 5, 5264 (2014)
- Ohsawa *et al.*,
  Mitochondrial defect drives non-autonomous tumour progression through Hippo signalling in *Drosophila*.
  Nature, 490, 547-551 (2012)
- Ohsawa *et al.*,
  Elimination of oncogenic neighbors by JNK-mediated engulfment in *Drosophila*.
  Developmental Cell 20, 315-328 (2011)