CDB SEMINAR

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13:30~14:30 A7F Seminar Room (Updated: Feb.22)

The Hippo Pathway in Tissue Homeostasis

Summary
Size control of multicellular organisms is a fundamental aspect of developmental biology. The Hippo pathway was initially identified through genetic mosaic screens in *Drosophila melanogaster* and has gained great interest in recent years as being strongly involved in organ development, stem cell biology, regeneration, and tumorigenesis. The Hippo pathway limits organ size in a cell-autonomous and organ-intrinsic manner. The upstream signals of this pathway include cell-cell contact, cell polarity, mechanosignal, extracellular signals, and cellular stress signals. Therefore, the Hippo pathway is capable of sensing and responding to the physical organization of cells, functioning as a nexus and integrator for multiple signals. Based on the striking tissue overgrowth phenotype upon disruption of fly or mouse Hippo pathway genes, it is considered to be a tumor suppressor pathway in humans. Intriguingly, however, germline or somatic mutations affecting the core components of the Hippo pathway are relatively rare in most common cancers, posing a major conundrum in the field.

Recently, we have made an unexpected and exciting discovery of both cell-autonomous and non-cell-autonomous mechanisms involved in homeostatic control of the mammalian Hippo pathway. The Hippo pathway normally provides growth inhibitory signals to the cells, and thus it functions to limit tissue overgrowth. Inactivation of the Hippo pathway may be needed to promote cell proliferation during wound healing and tissue regeneration. We found that the cell-intrinsic negative feedback mechanism confers a transient inactivation of the Hippo pathway, preventing tissue overgrowth. However, if the feedback mechanism is disrupted, cells with impaired Hippo pathway activity may over-proliferate. We also found that such undesirable cells can still be eliminated in a non-cell-autonomous fashion because inactivation of the Hippo pathway increases cellular immunogenicity to induce strong immune responses. Therefore, I propose that the Hippo pathway has dual functions: 1. suppress cell proliferation 2. inhibit cellular immunogenicity. These two potentials of the Hippo pathway are important for organ development and tissue maintenance. In this seminar, I will discuss about the physiological role of the Hippo pathway in maintaining tissue and organ homeostasis as well as the therapeutic potential of targeting this pathway for regenerative medicine and cancer immunotherapy.

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Moroishi, T. et al. A YAP/TAZ-induced feedback mechanism regulates Hippo pathway homeostasis. *Genes Dev.* 29, 1271–84 (2015).

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