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THE HONG KONG UNIVERSITY OF SCIENCE & TECHNOLOGY
Division of Life Science
Center of Systems Biology and Human Health

Disorderly conduct and disturbing the peace: the genetic program for cellular asymmetry directs cell fate, tissue architecture and cancer progression in the mammary gland

by

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Cell polarity, the universal property of all cells to be asymmetrical, coordinates cell movement, differentiation, proliferation and cell fate decisions to build and maintain complex epithelial tissues such as the mammary gland. Loss of polarity and the deregulation of these processes are critical events in malignant progression but precisely how and at which stage cell polarity loss impacts on mammary development and tumourigenesis is unclear. To provide insight as to how cellular asymmetry can regulate epithelial organ formation, we investigated *Scrib* and *GPSM2*/*Pins,* core mammalian members of two highly conserved key cell polarity complexes that act as tumour suppressors and regulate asymmetric cell divisions in *Drosophila* progenitors.

Utilizing a conditional mouse model, we report that *Scrib* is essential for mammary duct morphogenesis and inhibits the initiation and progression of sporadic mammary tumors. *Scrib*-deficiency resulted in fully penetrant ductal hyperplasia characterized by high cell turnover, MAPK hyperactivity, polarity loss, aberrant progenitor function, spindle orientation defects and expansion of atypical luminal cells.

Utilizing a functional genomics screening approach to examine how the cell polarity program effected tumour suppression, we identified the GPSM2 complex as a novel mammalian tumour suppressor. Similarly to *Scrib*, GPSM2 loss can cooperate with activated oncogenes to allow invasion and anchorage independent growth in MCF10A mammary epithelial cells and also accelerated tumour growth in an orthotopic xenotransplant model of breast cancer. Using a mouse model of GPSM2 loss, we show that in contrast to Scrib, deregulation of GPSM2 inhibits the repopulating frequency of mammary stem cells and favours the ectopic expansion of luminal progenitor cells previously identified as the cell of origin for estrogen receptor negative breast cancers. These studies identify distinct and essential roles for cell polarity regulators Scrib and *GPSM2* in mammary gland development and highlight the importance of the proper regulation of cellular asymmetry in the suppression of breast cancer.

Date : 25 Jan 2017 (Wednesday)
Time : 3:00 p.m.
Venue : Lecture Theater F
(Host faculty: Prof. Mingjie Zhang)

All are Welcome!