乳がんの三次元培養と PDX を用いたがん幹細胞制御機構解明へのアプローチ

Analysis of regulatory mechanisms in breast cancer-stem like cells by using spheroid cultures and PDX models

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Breast cancer is the most common type of cancer among women throughout the world. The increasing rate of mortality due to breast cancer raises serious problems. Recent evidence indicates that tumor tissues are comprised of heterogeneous cell populations including a relatively small number of cancer stem-like cells (CSCs) and large number of differentiated cancer cells. CSCs tend to survive irrespective of conventional chemotherapy, radiotherapy, and following treatment with molecular targeted drugs, because these treatment strategies target rapidly proliferating differentiated cancer cells but not CSCs. Targeting CSCs is thus important to improve the prognosis of cancer patients, however, molecular targeting drugs against CSCs are still unmet needs, since it is still largely uncertain the molecular mechanisms how CSCs are maintained in tumor tissues. CSCs are surrounded by a variety of cell types, including differentiated cancer cells and cancer associated fibroblasts (CAFs). All these cells create a microenvironment that is called the CSC niche. Recent emerging evidence indicates that CSCs survive by utilizing the CSC niche. However, the underlying molecular mechanisms are still unclear.

In order to clarify the molecular mechanisms how CSCs are maintained in CSC niche in human breast cancer tissues, we established patient-derived tumor spheroid culture and patient-derived xenograft (PDX) models by using primary breast cancer tissues from the patients. We also established co-culture system of patient-derived tumor spheroids and CAFs.

Growth factor or cytokine signaling plays important roles for a variety of biological aspects in physiological and pathological conditions, including tumorigenesis. It is thought that inflammatory microenvironment creates a pro-tumorigenic state through production of growth factors or cytokines.
We found that growth factor/cytokine signaling plays critical roles for the communication between cancer stem-like cells and CSC niche. We identified key growth factors or cytokines that are derived from cancer cells or CAFs. We uncovered the various key mechanisms mediated by signaling through NF □ B, IGF1 receptor, beta-catenin, semaphorin, and so on. There are various mechanisms: autocrine-paracrine mechanisms, regulation of stemness, regulation of symmetric-asymmetric division and regulation of metabolism. CSCs appear to survive and divide by using these mechanisms in order to adapt in the different conditions of the CSC niche. Among them, we have been able to identify proper molecular targets for CSCs to eradicate tumors. I would like to talk about several key mechanisms we have recently identified for maintenance of CSCs in the CSC niche.

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[文献]

1. Sasahara A, Tominga K, Nishimura T,Yano M, Kiyokawa E, Noguchi Miki, Noguchi Masakuni, Kanauchi H, Ogawa T, Minato H, Tada K, Seto Y, Tojo A, Gotoh N.: An autocrine/paracrine circuit of growth differentiation factor (GDF) 15 has a role for maintenance of breast cancer stem-like cells. *Oncotarget*, 8, 24869-24881, 2017
2. Tominaga K, Shimamura T, Kimura N, Murayama T, Matsubara D, Kanauchi H, Niida A, Shimizu S, Nishioka K, Tsuji E, Yano M, Sugano S, Shimono Y, Ishii H, Saya H, Mori M, Akashi K, Tada K, Ogawa T, Tojo A, Miyano S, Gotoh N.: Addiction to the IGF2-ID1-IGF2 circuit for maintenance of the breast cancer stem-like cells. *Oncogene*, 36,1276-1286, 2017
3. Murayama T, Nakaoku T, Enari T, Nishimura T, Tominaga K, Nakata A, Tojo A, Sugano S, Kohno T, Gotoh N.: Oncogenic fusion gene CD74-NRG1 confers cancer stem cell-like properties in lung cancer through a IGF2 autocrine/paracrine circuit, *Cancer Res*, 76, 974-983, 2016.
4. Nakata A, Yoshida R, Yamaguchi R, Yamauchi M, Tamada Y, Fujita A, Shimamura T, Imoto S, Higuchi T, Nomura M, Kimura T, Nokihara H, Higashiyama K, Kondoh K, Nishihara H, Tojo A, Yano S, Miyano S, Gotoh N.: Elevated beta-catenin pathway as a novel target for patients with resistance to EGF receptor targeting drugs. *Sci Rep*, 5, 13076, 2015
5. Hinorara K, Kobayashi S, Kanauchi H, Shimizu S, Nishioka K, Tsuji E, Tada K, Umezawa K, Mori M, Ogawa T, Inoue J, Tojo A. & Gotoh N:
ErbB/NF-κB signaling controls mammosphere formation in human breast cancer. *Proc. Natl. Acad. Sci., USA*, 109, 6584-6589, 2012.

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