The replicative factor MCM10 maintains patient-derived breast cancer stem-like cells that constitutively experience DNA replicative stress

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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.

We uncover a critical role of the replication factor mini-chromosome maintenance protein 10 (MCM10) in enabling breast cancer-derived CSCs to deal with constitutively accumulating DNA replicative stress. Transcriptomic analysis of patient-derived cultured breast cancer cells revealed that MCM10 was strongly upregulated in CSC-enriched spheroid cells. Elevated MCM10 expression was significantly correlated with worse prognosis in breast cancer patients. Moreover, CSC-enriched spheroid cells showed high levels of DNA replicative stress, suggesting that elevated MCM10 levels are important for CSC survival and proliferation. Consistent with this hypothesis, MCM10 depletion decreased cell proliferation, tumorigenesis, tumor sphere-forming capacity, expression levels of stemness markers, and tumor-initiating capacity of breast cancer patient derived xenograft (PDX) model. Furthermore, we demonstrated overexpression of MCM10 helped cells to proliferate in medium containing hydroxyurea (HU), a chemotherapeutic agent that induces DNA damage and replicative stress. Conversely, MCM10 depletion made cells more sensitive to HU and mitomycin C (MMC), another inducer of replicative stress. We therefore conclude MCM10 plays critical roles for cancer cell proliferation under DNA replicative stress, which is more pronounced in CSCs and in cells treated with chemotherapeutic agents, and propose to target MCM10 for therapy of both CSCs and other cancer cells.

1998 Human Frontier Science Program Organization (HFSPO), Long Term Fellowship
1999 The Uehara Memorial Foundation, Research Fellowship
2006 The NOVARTIS Foundation for the Promotion of Science, Novartis Research Grant
2007 The Naito Foundation, Research Grant
2007 The Cell Science Research Foundation, Research Grant
2018 Princess Takamatsu Cancer Research Fund, Research Grant

[References]

1. Murayama T, Gotoh N.: Patient-derived xenograft models of breast cancer and their application. *Cells*, on line publication 20 Jun, 2019.
2. Tominaga K, Minato H, Murayama T, Sasahara A, Nishimura T, Kiyokawa E, Kanauchi H, Shimizu S, Sato A, Nishioka K, Tsuji E, Yano M, Ogawa T, Ishii H, Mori M, Akashi K, Okamoto K, Tanabe M, Tada K, Tojo A, *Gotoh N.*: Semaphorin signaling via MICAL3 induces symmetric cell division to expand breast cancer stem-like cells. *Proc Natl Acad Sci, USA*, 116, 625-630, 2019.
3. Nishimura T, Nakata A, Chen X, Nishi K, Meguro-Horike M, Sasaki S, Kita K, Horike S-I, Saitoh K, Kato K, Igarashi K, Murayama T, Kohno S, Takahashi C, Mukaida N, Yano S, Soga T, Tojo A, Gotoh N.: Cancer stem-like properties and gefitinib-resistance are dependent on purine synthetic metabolism mediated by the mitochondrial enzyme MTHFD2. *Oncogene*, 38, 2464-2481, 2019.
4. 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.
5. 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.
6. 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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