Cell Cycle 14:22, 3523; November 15, 2015; © 2015 Taylor & Francis Group, LLC

Mimicking in vivo tumors to visualize the cell cycle

Comment on: Yano S, et al. Cancer cells mimic in vivo spatial-temporal cell-cycle phase distribution and chemosensitivity in 3-dimensional Gelfoam® histoculture but not 2-dimensional culture as visualized with real-time FUCCI imaging. Cell Cycle 2015; 14(6):808-19; PMID:25564963; http://dx.doi.org/10.1080/15384101.2014.1000685

Jung-Joon Min*; Laboratory of In Vivo Molecular Imaging; Department of Nuclear Medicine; Chonnam National University Medical School; Gwangju, Korea;
*Correspondence to: Jung-Joon Min; Email: jjmin@jnu.ac.kr; http://dx.doi.org/10.1080/15384101.2015.1039368

Visualizing the cell-cycle behavior of cancer cells aids better understanding of how cancer cells respond to a given chemotherapeutic drug because cancer cells in G0/G1 phase are resistant to cytotoxic chemotherapy. Characterization of cell-cycle behavior by imaging was first performed by Miyawaki and colleagues using fluorescent ubiquitination-based cell cycle indicator (FUCCI).[1] The original FUCCI probe was generated by fusing mKO2 (monomeric Kusabira Orange2) and mAG (monomeric Azami Green) to the ubiquitination domains of human Cdt1 (hCdt1) and human geminin (hGem), respectively. These two chimeric proteins, mKO2-hCdt1 and mAG-hGem, accumulate reciprocally in the nuclei of transfected mammalian cells during the cell cycle, labeling nuclei of G0/G1-phase cells orange and those of S/G2/M-phase cells green.

To quantify fluorescence-based molecular events that occur during cancer growth and the therapeutic response, it is important to develop in vitro tumor models mimicking the microenvironments and metabolite gradients in human tumors. Collagen-sponge-gel histoculture developed by Leighton in 1951[2] enables cell aggregation similar to that found in tumors in vivo with lumina and stromal elements. Tumor cylindroids developed by Forbes[3] contain proliferating, quiescent, and necrotic cells, and have been used to demonstrate the penetration of tumor-targeting bacteria.

In the present issue of *Cell Cycle*, Hoffman and colleagues demonstrate FUCCI imaging in Gelfoam® tumor histoculture.[4] Gelfoam® tumor histoculture provides an in vivo-like microenvironment for cancer cells, enabling cancer cells to mimic the spatio-temporal cell-cycle phase distribution found in tumors in vivo. For example, in monolayer culture of MKN45 cells (poorly differentiated stomach adenocarcinoma derived from a liver metastasis), approximately 50% of cells in both the central and edge areas were in S/G2M phase. In tumor spheres, most cells were in G0/G1 phase at both the surface and center. Both in vivo and in Gelfoam® histoculture, the majority of the surface cells of the tumor were in S/G2/M phase, whereas only approximately 10% of cells in the central area of the tumor were in S/G2/M phase.

Cancer cells grown on Gelfoam® have the same cell-cycle response to cytotoxic agents as in vivo tumors. FUCCI imaging demonstrates that cancer cells in monolayer culture and spheres on agar have a different response to chemotherapy from cancer cells in tumors in vivo, whereas those in Gelfoam® tumor histoculture have a similar response to chemotherapy as in vivo tumors. In Gelfoam® histoculture and in vivo tumors, approximately 20–30% of cells were in S/G2/M phase before chemotherapy, almost 100% of cancer cells were in G0/G1 phase during chemotherapy, and approximately 20% of cancer cells re-entered S/G2/M phase after termination of cisplatinum and paclitaxel chemotherapy.

An imaging-based approach to visualize real-time cell-cycle dynamics has the potential to affect almost all aspects of anti-cancer medicine. The results presented in this issue of *Cell Cycle* suggest that the combination of FUCCI imaging and Gelfoam® histoculture provides a new platform for developing and evaluating anticancer agents, as well as studying basic cancer biology, such as the cell cycle.

References

1. Sakaue-Sawano A, et al. Cell 2008; 132:487-498; PMID:18267078; http://dx.doi.org/10.1016/j.cell.2007.12.033.
2. Leighton J. J Natl Cancer Inst 1951; 12:545-61; PMID:14889259.
3. Kasinskas RW, Forbes NS. Cancer Res 2007; 67:3201-9; PMID:17409428; http://dx.doi.org/10.1158/0008-5472.CAN-06-2618.
4. Yano S, et al. Cell Cycle 2015; Mar 19; 14(6):808-19. PMID: 25564963; http://dx.doi.org/10.1080/15384101.2014.1000685.