In vivo imaging of cell-cycle phase of individual cancer cells throughout growing tumors in live mice

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In vivo imaging of cell-cycle phase of individual cancer cells throughout growing tumors in live mice. S. Yano¹, Y. Tome¹, M.A. Digman², M. Momiyama¹, A. Suetsugu¹, H. Kishimoto³, H. Tazawa⁴, T. Fujiwara³, E. Gratton², R.M. Hoffman¹; ¹AntiCancer Inc., San Diego, CA, ²Department of Biomedical Engineering, Physics, and College of Medicine, University of California, Irvine, CA, ³Department of Gastroenterological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharma Sci, Okayama, Japan, ⁴Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan

The phase of the cell cycle can determine whether a cancer cell can respond to a given drug. This report presents imaging methodology to obtain real-time cell cycle information on cancer cells throughout tumors in live mice using a fluorescence ubiquitination cell cycle indicator (FUCCI). In nascent tumors in nude mice, approximately 30% of the cells in the center of the tumor were in G₀/G₁ and 70% in S/G₂/M. In contrast, approximately 90% of cancer cells in the center of an established tumor were in G₀/G₁ phase. Similarly, approximately 75% of cancer cells far from (>100 μm) tumor vessels were in G₀/G₁. Although 60–70% of cancer cells near the surface in an established tumor (< 100 μm) or near blood vessels were in S/G₂/M, these cells are a small minority of an established tumor. Moreover, static tumors in mice consisted of mostly G₀/G₁ cells, suggesting they are dormant. Real-time imaging of the cancer cell cycle has profound implications for cancer therapy, since most drugs currently in use target cells in S/G₂/M, which are a minor fraction in an established tumor. With the imaging method developments reported here, drugs that target non-dividing cancer cells can be readily identified.