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Color-coded mouse genes reveal hidden story on cell cycle

A powerful new tool enables a pictorial roadmap of cell transitions from their earliest stage to functional maturity.

Biologists now have a powerful new tool to understand the development of mammalian cells, thanks to a technique orchestrated by a RIKEN-assisted research team that genetically colorizes the stages of cell development in lab mice. Under a camera-equipped microscope, immature stage one cells appear a brilliant red and then turn fluorescent green as they cycle into the next three cell stages. As a result, the cell cycle of animals can be observed and photographed in rich, color-coded detail to create a time and spatial roadmap that researchers can use to study cellular processes.

The new cell tracking methodology is already answering a number of questions about normal and abnormal cell progression, neural brain pathways, tumor development, and even how injuries heal.

The study was published this week in the journal *Cell* by a team of researchers from eight facilities in Japan dedicated to the study of cell biology, genetics, neurology and cancer. They describe how they were able to generate cultured cell markers and then introduce them into mice cell lines to pass the red and green markers on to successive mouse generations. Researchers elsewhere have developed fluorescent cell markers but this is the first documented instance in which cell biologists have been able to create two simultaneous genetic markers so developing cells visibly change colors as they pass through the four stages of the cell cycle.

This allowed the team to perform time-lapse imaging to explore the patterns of cell-cycle dynamics during transitions of cultured cells, migration and differentiation of neural progenitors in brain slices, and the development of tumors across blood vessels in live mice.

The researchers reported that differential profiling of cells at each of the four cell phases can be achieved by sorting cell populations into red, green or a yellowish combination,

then examining various cellular functions, such as gene and antigen surface expression.

Among the observations made by the multi-disciplinary research team:

- Within 8 hours of an "injury" to a cultured cell layer, green early-stage cells formed on the surface of the "wound" to initiate its closure, allowing the observers to identify which specific cells, stages and antigens are involved in wound healing.
- Brain slices showed neural pathways in the developing cerebral cortex, indicating the existence of two main cell populations: mitotic (early stage) neural progenitors and post-mitotic neurons destined to populate different layers in the cortical area.
- By introducing the markers to tumors of living mice and watching tumor development, the types of cells that were tumor related could be identified, as well as the progression of the disease as a function of the cell cycle.

The mice and cell lines are expected to serve as model systems permitting unprecedented spatial and temporal photographic imaging to help better understand how the cell cycle correlates with various biological events. The authors noted that the next challenge facing cell researchers is genetically encoding several extra colors so even clearer distinctions can be seen between each of the four cell stages.

Researchers collaborated from eight facilities across Japan, including the Japan Science and Technology Agency, Tokyo University of Pharmacy and Life Science, the Cancer Institute of the Japanese Foundation for Cancer Research, Nagoya University Graduate School of Medicine, and Tokyo Metropolitan Institute of Medical Science.

Original work:

Sakaue-Sawano, A., Kurokawa, H., Morimura, T., Hanyu, A., Hama, H., Osawa, H., Kashiwagi, S., Fukami, K., Miyata, T., Miyoshi, H., Imamura, T., Ogawa, M., Masai, H., Miyawaki, A.
Visualizing Spatiotemporal Dynamics of Multicellular Cell-Cycle Progression, *Cell*, published online on Feb. 8, 2008.

For more information, please contact:

RIKEN Public Relations Office
Email: koho@riken.jp