This Week's Citation Classic®

Terasima T & Tolmach L J. Variations in several responses of HeLa cells to x-irradiation during the division cycle. *Biophysical J.* 3:11-33, 1963.
[Mallinckrodt Institute of Radiology, School of Medicine, and Committee on Molecular Biology, Washington University, St. Louis, MO]

The use of synchronously growing HeLa cells revealed that (1) X-ray sensitivity of cells as determined by survival fluctuated with two sensitive and resistant peaks during the cell cycle and that (2) progression through the cell cycle was affected by radiation in a stage-dependent fashion. [The *SCI*® indicates that this paper has been cited in over 375 publications.]

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Genome theory of mammalian cell sensitivity to the lethal effect of radiation had long been accepted implicitly in the field of radiobiology. This was mainly based on findings in radiation genetics and radiation therapy in which aberrations of genetic material were recognized as a major subcellular consequence after irradiation. In view of A. Howard's DNA cycle concept and pioneering work in autoradiography, L.J. Tolmach, professor of radiation biology, Washington University School of Medicine, and I, then a research associate from Chiba University School of Medicine in Japan, intended to demonstrate a possible change in radiosensitivity during the mammalian cell cycle. To achieve the goal we needed a technological innovation in cell culture—a technique to synchronize mammalian cells. Discovery of sensitivity change was, therefore, made possible only by the unique synchrony technique that we developed and first reported in *Nature* in 1961.[1] In that report a slope of the survival curve of HeLa cells was shown to undergo remarkable cyclic change during the cell cycle. Subsequently, quantitative data of various responses, including effects on cell progression and DNA synthesis, were collected for the *Classic* paper.

Usually one experiment involved the synchrony procedure, the determination of the DNA synthetic rate per cell, and an extended observation period of cell proliferation in relatively short time intervals. In addition, all the procedures had to be carried out in a room kept at 37° C. Consequently, the entire experimental period, which lasted for 48 hours and allowed for little time to sleep, was rather exhausting.

When I found that the mean lethal dose obtained from dose-survival curves fluctuated approximately twofold depending on cell-cycle stages, I was really struck by the virtue of synchrony, because only that procedure enabled us to disclose the heterogeneity concealed in randomly growing populations.

The change in survival was attributed partly to the amount of DNA synthesized during the time of irradiation[2] and partly to the phase-related change in intracellular, nonprotein sulfhydryl content.[3] It implied that a unitary factor hypothesis was not tenable for the cyclic change of radiosensitivity. The observed cell cycle-dependent response was generalized among various cultured mammalian cell lines by many reports appearing in the 1960s.

The years since the paper was published have shown that it has had an impact on the fields of cancer therapy and cell biology. For example, the research we did for the paper provided us with a reassortment concept that is regarded as one of the biological responses of tumors to radio- and chemotherapy, and it suggested the presence of cell cycle-dependent responses to various exogenous agents, which ranged from chemotherapeutic, antitumor agents[4] to other cytotoxic, mutagenic, and even carcinogenic agents.[5] In 1981 Tolmach received the Failla Memorial Award of the Radiation Research Society.

1. **Terasima T & Tolmach L J.** Changes in X-ray sensitivity of HeLa cells during the division cycle. *Nature* 190:1210-1, 1961. (Cited 280 times.)
2. ————. X-ray sensitivity and DNA synthesis in synchronous populations of HeLa cells. *Science* 140:490-2, 1963. (Cited 85 times.)
3. **Ohara H & Terasima T.** Variations of cellular sulfhydryl content during cell cycle of HeLa cells and its correlation to cyclic change of X-ray sensitivity. *Exp. Cell Res.* 58:182-5, 1969.
4. **Fu K K.** Biological basis for the interaction of chemotherapeutic agents and radiation therapy. *Cancer* 55:2123-30, 1985.
5. **Kinzel V, Richards J & Stöhr M.** Tumor promoter TPA mimics irradiation effects on cell cycle of HeLa cells. *Science* 210:429-31, 1980.

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