

Editorial

# Anticancer Treatment-Induced Tumor Repopulation: Roles for Giant Cancer Cells Undergoing Proliferation Arrest (Dormancy)

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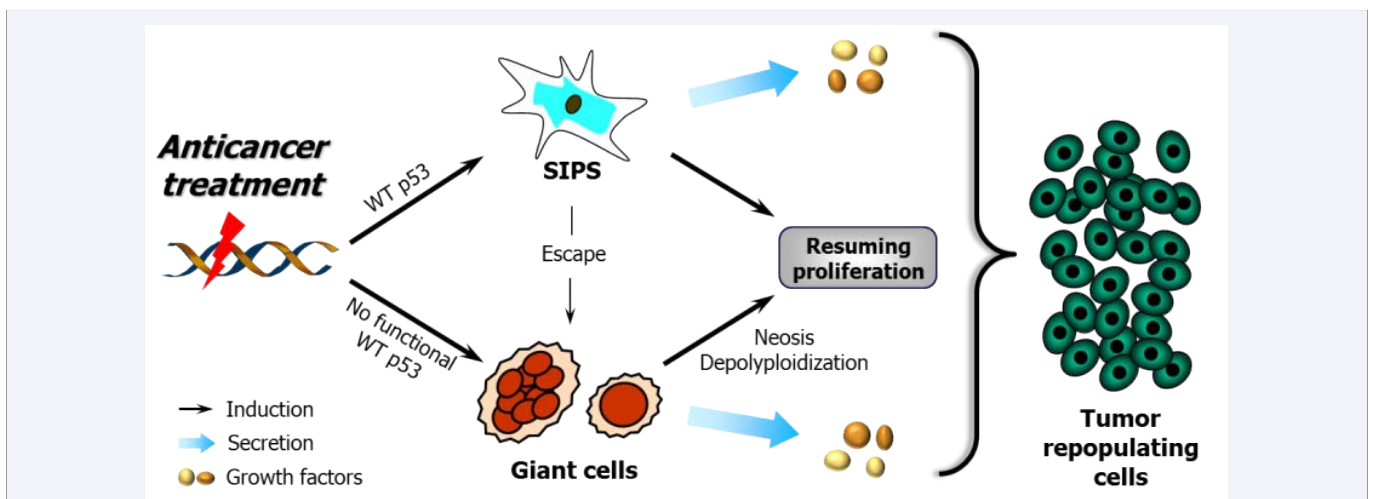
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It is widely stated that treatment of human cells with genotoxic agents either results in activation of cell cycle checkpoints to facilitate DNA repair and promote cell survival, or leads to apoptosis or other modes of cell death (e.g., necrosis). However, as extensively discussed recently [1-3], this reigning paradigm (i.e., repair and survive or die through apoptosis/necrosis) has been challenged by numerous discoveries with different mammalian cell types. For example, studies with solid tumors and solid tumor-derived cell lines have demonstrated that the primary response triggered by moderate, clinically relevant doses of cancer therapeutic agents is sustained proliferation arrest (cancer cell dormancy) and not cell death. The proliferation arrest predominantly reflects stress-induced premature senescence (SIPS) and the creation of polyploid/

multinucleated giant cells (MNGCs), depending on the status of the p53 tumor suppressor and other factors.

Dormant cancer cells emerging post-treatment exhibit an extremely enlarged morphology, either as a result of their increased cytoplasmic mass (cells undergoing SIPS) or nuclear contents (a highly enlarged nucleus or multiple nuclei). Such highly enlarged cells cease to proliferate and hence are often misinterpreted to be “dead” in conventional cell-based radiosensitivity/chemosensitivity assays (e.g., the gold standard colony formation assay). However, such cells remain viable for long times (weeks) post-treatment, secrete a myriad of growth-promoting factors, and can give rise to progeny with stem cell-like properties that exhibit marked resistance to therapeutic agents [1-3] (Figure 1).



**Figure 1** The DNA damage response of human solid tumor-derived cell lines with differing p53 status (adopted from ref. [2]). Treatment with clinically relevant doses of anticancer agents triggers proliferation arrest through stress-induced premature senescence (SIPS) in p53 wild-type (WT) cells, and the development of giant cells (containing multiple nuclei or a single enlarged nucleus) within cultures of cancer cells lacking wild-type p53 function. Genotoxic stress can also trigger the development of multinucleated giant cells in p53 wild-type cultures either through somatic cell fusion (not shown) or through cells “escaping” the proliferation arrest associated with SIPS. Cells undergoing SIPS can contribute to tumor repopulation by secreting growth promoting factors as well as by resuming proliferation. Polyploid/multinucleated giant cells can contribute to tumor repopulation by: (i) secreting growth promoting factors; (ii) undergoing depolyploidization and resuming proliferation; and (iii) giving rise to stem cell-like progeny through nuclear budding (neosis). For details, consult [1-3].

MNGCs, for example, can give rise to tumor-repopulating cells through depolyploidization as well as nuclear budding or bursting similar to simple organisms such as fungi [1-3]. Studies with mouse models have demonstrated the significance of MNGCs in cancer metastasis [4,5]. Somewhat surprisingly, only a single MNGC has been reported to be sufficient to generate metastatic tumors [4].

We recently reported studies with commonly used human solid tumor-derived cell lines with differing p53 status, and demonstrated that such cells respond to moderate doses of ionizing radiation (between 2 and 8 Gy) [6,7] or the chemotherapeutic agent cisplatin (between 2 and 10  $\mu$ M) [8], typically used in the colony formation assay, by exhibiting sustained proliferation arrest but not apoptosis or other modes of cell death. As expected from previous studies, the proliferation-arrested response was attributed to SIPS in p53 wild-type cells and the emergence of MNGCs in cells lacking wild-type p53 activity. In addition, virtually all cells (including MNGCs) that remained adherent to the culture dish for long times (e.g., 3 weeks) post-treatment retained membrane integrity and exhibited the ability to metabolize the tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) to its water-insoluble formazan derivative [6-8]. Single-cell observation methods demonstrated that the level of metabolic activity per cell was markedly (~10 times) greater for radiation exposed [7] or cisplatin treated [8] cultures, which were mainly comprised of enlarged cells, than in sham-treated controls.

Collectively, these observations underscore the significance of cancer cell dormancy (through SIPS, polyploidy and/or multinucleation) as a survival mechanism for cancer cells expressing wild-type p53, mutant p53 or no p53. They also suggest that identifying pharmacological agents capable of inducing apoptosis of dormant cancer cells before they can promote tumor repopulation may have important clinical ramifications. To this end, we have recently demonstrated that treatment of MNGCs with pharmacological activators of apoptosis (e.g., sodium

salicylate) triggers their death [6].

Caution should be exercised to avoid misinterpreting the radiosensitivity and chemosensitivity data obtained with widely-used short-term (multi-well plate colorimetric/fluorimetric) and long-term (colony formation) assays in terms of loss of viability and hence lethality [7-9].

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