

Polyplloid giant cancer cells are actuators of therapeutic resistance and prostate cancer lethality

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Metastatic prostate cancer (PCa) led to the death of >31,000 men in the US in 2018. Metastatic disease remains incurable because a population of cancer cells within a tumor are resistant to all known compounds. Despite decades of dedicated work by researchers worldwide, the fundamental barrier to prostate cancer survivorship remains unsolved: therapeutic resistance.

Our preliminary data and other recent studies have demonstrated that the appearance of polyplloid giant cancer cells (PGCCs) is associated with therapeutic intervention. PGCCs have been documented in multiple cancer types, including PCa, but their biologic significance remains largely unexplored. The presence of PGCCs in cell culture has long been recognized but generally ignored (e.g., thought to be undergoing irreversible senescence, discounted as technical anomaly). As they are widely considered to be dying cells incapable of survival or proliferation, PGCCs have mostly been considered artifacts, not actuators.

We have found that PGCCs are a rare but stable subpopulation in PCa cell lines, including PC3, LNCaP, DU145. Interestingly, we find that PGCCs emerge in a dose-dependent manner regardless of therapeutic class, including docetaxel (microtubule poison), cisplatin (alkylating agent), and etoposide (topoisomerase II poison). To our knowledge, we are among the first groups to purposefully observe PGCCs visually over time via time-lapse microscopy rather than relying solely on traditional plate-based assays typically used to assess therapeutic efficacy *in vitro*. We find that these cells are live, functioning cells with a wide diversity in motility, morphology, and activity. After treating PCa cell lines with [LD90] therapy for 72h, >90% of the surviving cells are PGCCs. After allowing the cultures to recover in the absence of chemotherapeutic stress for 21 days, PGCCs again represented <5% of the total cell population. Upon re-challenge, this resulting population had increased therapy resistance. Using FUCCI cell-cycle reporters, we found that >90% of PCa cells that survived 1 [LD90] docetaxel for 72 hours existed in G₀/G₁. This data suggests that PGCCs may enter a protective quiescent state to survive therapy, providing a versatile “universal mechanism” of therapy resistance.

These data present a compelling novel model of therapy resistance and disease recurrence following systemic treatment: PGCCs form in response to therapy and enter a protective quiescent state. When therapy is released, the PGCCs re-enter cell cycle and give rise to a now-resistant tumor. Ongoing work is specifically interrogating each aspect of this model, including elucidating the initial emergence of these cells in the tumor microenvironment.

Conflict of Interest:

None

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