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Docetaxel-induced polyploidization may underlie chemoresistance and disease relapse

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Abstract

Although docetaxel significantly improves survival in a variety of malignancies, its clinical utility is severely restricted by acquired chemoresistance and disease relapse. To uncover the mechanisms underlying these all too common occurrences, an abundance of research has focused on mutations and gene expression patterns; however, these findings are yet to translate into improved outcomes for patients being administered this drug. These analyses have overlooked a promising lead in the quest to discern key mediators of resistance and relapse following docetaxel therapy: polyploidization. This process is manifested following docetaxel-mediated mitotic arrest by the appearance of giant, multinucleated cells, which slipped from mitosis without undergoing cytokinesis. Polyploid cells generally possess supernumerary centrosomes, are chromosomally instable, and resist chemotherapy. We thus suspect that chemoresistance and relapse following treatment with docetaxel might be combated by co-administration of centrosome declustering drugs, which could selectively destroy polyploid cells given that normal cells do not possess amplified centrosomes, an intriguing paradigm that warrants further investigation.

Keywords

Docetaxel; Polyploidy; Recurrence; Chemoresistance; Centrosome declustering

Introduction

Chemotherapy is an indispensable tool in the oncologist's armamentarium for cancer treatment, besides radiation, surgery, hormonal therapy and immunotherapy. Among the available chemotherapeutics, taxanes continue to be a mainstay even amid the outpouring of

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Conflict of interest

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Uncited references

[26], [27], [28]

targeted agents in recent years. Despite a quarter century since its debut in Phase I clinical trials, docetaxel remains secure as a cornerstone of chemotherapy for over a dozen malignancies, for which it is standard of care alone or in combination with other drugs in more than 30 regimens (Table 1). In many cases docetaxel prolongs overall and progression-free survival, but eventual chemoresistance and relapse following a transient, specious improvement are widespread and vexing problems. The acquisition of chemoresistance is enabled by intratumor heterogeneity, as highly heterogeneous tumors tend to harbor minor subpopulations of clones bearing mutations in a drug target (e.g., β -tubulin in the case of docetaxel) or proteins more globally involved in apoptosis, senescence, or DNA repair; such mutations then permit the malignant cell to survive the pharmacologic assault and repopulate the tumor. As a result, the disease resurges with a vengeance, and the patient ultimately succumbs to the disease. Several lines of thought exist to explain disease relapse after an initially successful response; however, one especially intriguing and clinically important paradigm is germane to docetaxel, in light of a deviant phenotype that this drug evokes: polyploidy. It has been posited that tumor cells with elevated genomic content underlie chemoresistance because they have been demonstrated to drive tumor evolution [1]. Fortuitously, polyploid cells possess Q2 unique features and thus may have the potential to be selectively targeted, sparing normal cells. If the engine by which docetaxel accelerates disease progression and induces relapse is indeed polyploidization, then it may be possible to improve clinical outcomes by eradicating the docetaxel-induced polyploid cells or the process by which they are generated. Targeting crucial drivers of tumor evolution, such as polyploid cells or the process of polyploidization, in tandem with administering cytotoxic chemo-therapy may be an exponentially more effective strategy than solely administering cytotoxins (or drugs that target other aspects of tumorigenesis besides evolution, such as proliferation or angiogenesis), which otherwise foster the development of chemoresistance by exerting selective pressure on tumors. In this Mini-Review, we expound our argument that cancer relapse is kindled, at least in part, by docetaxel-induced polyploid cells, which can possibly be combated with minimal toxicity in carefully designed novel combination-chemotherapy regimens.

Mitotic slippage enables escape from docetaxel-mediated cytotoxicity and induces polyploidy

Also known by its trade name, Taxotere, docetaxel functions by binding to microtubules with high affinity and suppressing their dynamic behavior, which is critically needed for vital cellular activities, including mitotic spindle formation, cell polarization, directional migration, and cell signaling [2]. Stabilizing microtubules is cytotoxic to vulnerable cells and induces apoptosis. Myelosuppression is dose-limiting, and secondary leukemia, although exceedingly rare, has occurred in combination with other drugs like carboplatin, doxorubicin, and cyclophosphamide [3,4]. Evidence across various cancers, including cancers of the prostate, breast, and lung, has demonstrated that at least some cancer cells exposed to docetaxel escape its cytotoxic effects not simply unscathed but rather revitalized, even more proliferative and apoptosis-reluctant. A common characteristic of these tenacious survivors is polyploidy, which is causally linked to docetaxel-mediated mitotic arrest. Which cells sidestep death and which meet their demise depends strongly on the cell cycle stage they occupy when they encounter the drug. Following treatment with docetaxel, cancer cells

in S/G2 phase accumulate sufficient levels of pro-apoptotic factors during mitotic arrest to be overtaken by mitotic catastrophe-mediated death. By contrast, cancer cells in other cell cycle phases do not accumulate enough of these factors to trigger mitotic catastrophe; as a result, they surreptitiously slip from mitosis without undergoing cytokinesis and march unimpeded through the subsequent cell cycle, replicating their DNA and growing with abandon. One or several rounds of mitotic slippage and chromosome duplication result in multinucleated “giant” cells, which are highly malignant, possibly even more so than their progenitors. There is evidence that it is these grotesque giant cells that wreak the demise of the cancer patient by inducing treatment-refractory disease.

Polyploidy as a mediator of tumorigenesis, clonal evolution, and epithelial–mesenchymal transition

Ample support for the robust role of polyploidy in carcinogenesis can be found in the preclinical literature. There is a wealth of evidence that tetraploid cells can initiate tumor formation. Mice injected with tetraploid p53-null mouse mammary epithelial cells exhibit elevated tumor numbers in contrast to those injected with diploid p53-null cells of the same kind [5]. In addition, mouse embryonic fibroblasts that have become tetraploid following endoreduplication (induced by telomere damage secondary to POT1a silencing) form colonies on soft agar and produce tumors following transplantation in mice [6]. Overexpression of c-Myc exacerbates the tumorigenicity of these tetraploid cells, although it is not a prerequisite; the non-malignant cells can be ushered into malignancy solely by doubling their genomes. The tetraploid murine fibroblasts evolve rapidly into an array of lines with diverse karyotypes, most of which are subtetraploid but occasionally a hypertetraploid line emerges. Therefore, tetraploidization can single-handedly precipitate tumor heterogeneity, a notorious mediator of treatment resistance and tumor recurrence. Among colon cancer cells, isolated tetraploid clones exhibit chromosomal segregation errors and resist apoptosis more staunchly in the face of chemotherapy than diploid parent cancer cells [7]. Chromosome segregation errors may arise because the process that prompts tetraploidization concomitantly induces centrosome amplification, with which cancer cells cope by clustering the excess centrosomes into two polar groups to preclude spindle multipolarity and mitotic catastrophe [8]. The process of centrosome clustering engenders lagging chromosomes due to aberrant, merotelic microtubule-kinetochore attachments [9]. Furthermore, the tetraploid state in and of itself confers competitive advantages that enable these cells to initiate tumors. The presence of a genomic surfeit buffers chromosome losses, liberating the cancer cell to mutate and lose chromosomes to sample a variety of karyotypes until it achieves one of superior aggressiveness [8]. Polyploid cells are also predisposed to adopt a mesenchymal phenotype via upregulation of epithelial–mesenchymal transition-related transcription factors, as illustrated by Zhang et al. in ovarian tumor cells [10]. These informative studies may help to partly explain why docetaxel-treated aggressive cancers almost inexorably recur, although detailed studies designed to test this hypothesis are yet to be performed.

How tetraploid cells may overcome a Hippo signaling-mediated block to proliferation

Rather astoundingly, 37% of the tumors in The Cancer Genome Atlas Pan-Cancer dataset (which includes ~5000 tumors of 11 different types) appear to have undergone whole-

genome doubling, a phenomenon associated with elevated rates of other somatic copy-number alterations, *TP53* mutations, and *CCNE1* amplifications, the latter two of which are associated with tolerance of tetraploidy [11]. Somatic copy-number alterations were found to generally have occurred after the whole-genome doubling event, suggesting that tetraploidy induces chromosomal instability. This observation is especially pertinent since a recent study [12] illuminated that the tetraploid state, precipitated by a failure of cytokinesis, tends to induce tumor suppressor mechanisms. Basically, cytokinesis failure triggers the Hippo tumor suppressor signaling pathway due partially to the presence of supernumerary centrosomes, which nucleate more microtubules and thus hyperactivate Rac1 [12]. Rac1 activation suppresses RhoA, thereby stimulating LATS2 kinase, which inhibits cell proliferation by binding to and inhibiting MDM2, an E3 ubiquitin ligase that otherwise targets p53 for destruction. Activated LATS2 also phosphorylates and thereby inactivates YAP and TAZ, paralogous oncoproteins that serve as co-activators of a pro-proliferative and anti-apoptotic transcriptional program [13]. Clearly, for tumors to evince evidence of genome doubling and tetraploidy that occurred earlier in their life histories, at least a small fraction of tetraploid cells must have found the means to overcome the tumor suppression mechanisms induced by tetraploidy. It has been postulated that, in order to overcome these Hippo signaling-induced blocks to proliferation, some “evolved” tetraploid cells suppress a collection of genes that are required to activate or maintain p53-dependent G1 arrest following cytokinesis failure [12], although how this is accomplished is unclear. We posit that some docetaxel-induced tetraploid cells may similarly escape a block to proliferation by attenuating transcription of p53-activating/stabilizing genes. However, although p53 suppression can help to rescue tetraploid cells from the anti-proliferative effects of the Hippo pathway, YAP activation may be necessary to maintain the proliferative state because tetraploid tumors tend to exhibit YAP amplification [12]. It is conceivable that tumor cells exposed to docetaxel may undergo mitotic slippage, become tetraploid, and then capitalize on the chromosomal instability conferred by their excess centrosomes to achieve a karyotype that (a) abrogates Hippo signaling-induced blocks to proliferation and maintains YAP activation and (b) promotes invasive tumor behavior [14].

Multipolar mitosis and neosis: mechanisms by which docetaxel-induced polyploid cells generate aneuploid daughter cells

What is the fate of docetaxel-induced polyploid cells? Polyploid cells may deploy centrosome clustering mechanisms during subsequent mitotic divisions to achieve pseudo-bipolar spindle geometry. Merotelic kinetochore-microtubule attachments frequently occur during centrosome clustering and result in low-grade whole-chromosome missegregation events; pseudo-bipolar mitotic division may thereby engender aneuploid progeny still harboring extra centrosomes. Some slippage in the efficiency of centrosome clustering is conceivable, leading to occasional tripolar divisions that could also yield viable progeny cells with abnormal chromosomal complements. Aneuploidy is thus the dangerous sequela of docetaxel-induced polyploidy. Another less familiar process by which polyploid cells give rise to aneuploid daughter cells may seem the stuff of science fiction. After a cancer cell slips from mitosis and dodges cytokinesis, the resultant giant cell can undergo a stunning manner of cell division called neosis, which is reminiscent of budding in parasitic protozoans and budding yeast. The giant cell can reconstruct its genome to at least

temporarily cope with the increased gene dosage, and subsequently it buds off portions of its genome (via intracellular cytokinesis) without nuclear envelope fragmentation [15,16]. A majority of the resultant mononuclear-but-aneuploid daughter cells are viable, and they exhibit anchorage-independent growth.

The preclinical literature is rife with examples of neosis and descriptions of how it contributes to malignancy. Makarovskiy et al. revealed that treatment of PC-3 cells with docetaxel leads to growth arrest, the formation of multinucleated cells, delayed cell death, and the generation of docetaxel-resistant progeny [17]. The resistant clones overexpress the beta-tubulin iv isoform, and their pheno-type is independent of P-glycoprotein, Bcl-2, and Bcl-xL, factors that contribute to chemoresistance in specific contexts and cancer cell types. Sundaram et al. demonstrated that transformed p53^{+/+} and spontaneously transformed p53^{-/-} multipotent mesenchymal cells give rise, through budding, to giant cells that produce smaller, mono-nuclear daughter cells that exhibit anchorage-independent growth [18]. Zhang et al. found that polyploid cells isolated from ovarian cancer cell lines and patient tumors display chemoresistance, cycle infrequently, and produce smaller, near-diploid daughter cells through budding [10]. Collectively, these studies suggest that a dangerous corollary of antimicrotubule agents such as docetaxel may be the stimulation of disease progression and relapse through generation of giant cells that give rise to viable aneuploid daughter cells.

Senescence protects polyploid cells from chemotherapy and imparts aggressive cellular features

In addition to the riveting process of neosis, polyploid cells can also escape cytotoxicity by burrowing into a senescent state and subsequently re-entering the cell cycle with a chemoresistant phenotype. Against internal or external stressors (such as chemotherapy), cancer cells attempt to survive by undergoing therapy-induced senescence [19]. Colon adenocarcinoma cells arrested in G₁ through the overexpression of p27^{Kip1} are more resistant to numerous chemo-therapeutic agents [20]. Hyperdiploid cell populations derived from patient glioblastoma tumors contain three times more quiescent cells than diploid lines derived from the same tumor [21]. It is also plausible that, following the initial therapy that stimulates the birth of polyploid cells, they step out of the cell cycle until they have achieved a size of a certain threshold, independent of a survival-like response against chemotherapeutic stress. The extended senescent period may empower the cells to complete all the necessary transcription and translation that is a consequence of their increased genome content. They can also remodel their genome to deal with the increased gene dosage. Whatever the impetus for this stably arrested period, the infrequent cycling of polyploid cells enables them to circumvent the lethal effects of cytotoxins, which generally must act during a specific cell cycle phase. Once the polyploid cells have weathered the chemotherapeutic storm, they re-enter the cell cycle through the overexpression of mitotic kinase CDK1, which phosphorylates survivin [22]. Cells emerging from chemotherapy-induced senescence often exhibit stem cell-like features and more aggressive behavior [23]. On its face, targeting senescence seems like another potential mechanism to combat the genesis of polyploid cells following docetaxel therapy; however, senescence is also a

protective, anti-cancer mechanism [24], so systemic antagonism of this process may have the potential to promote carcinogenesis.

Perspectives

That docetaxel induces these giant cells, well-documented as having a malignant character even when derived from non-malignant progenitors, should give pause to clinicians. The nettle that clearly must be grasped is how to swiftly eliminate the giant cells following docetaxel treatment. An array of features distinguishes giant cells from healthy cells, most noticeably their overabundance of DNA and centrosomes. The latter feature is an especially alluring target because several centrosome declustering drugs have a long track-record of non-toxicity coupled with potent anti-cancer activity [25]. These drugs wrench apart the two centrosomal clusters so neatly fashioned by the mitotic cancer cell at opposite spindle poles, forcing the spindle into a persistently multipolar configuration that is not compatible with survival. Thus, declustering drugs may be able to slay these monstrous docetaxel-induced giant cells, so much like Goliath in appearance, strength, and treacherousness, but similarly in possession of a fatal flaw that can be exploited. We envision that a declustering drug, such as griseofulvin, could be included in a docetaxel regimen to destroy the giant cells as soon as they are created, as depicted in Fig. 1. Future studies employing docetaxel must offer proof for these principles, but we are heartened by how solid the foundation of this paradigm appears, as it may hold the key to suppressing relapse following this clinically essential drug.

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Fig. 1. Mechanistic rationale for combining docetaxel with a declustering drug like griseofulvin. When a prostate cancer cell with amplified centrosomes (depicted here as bearing two centrosomes in G1 phase) (A) traverses S and G2 phases in the presence of docetaxel (B), it arrests in mitosis after assembling a multipolar spindle (C). Sustained mitotic arrest can conclude in different ways on the basis of two competing networks: a prosurvival cyclin B1-driven cascade and a proapoptotic caspase-3-driven cascade. Cells that accumulate proapoptotic signals in high enough levels may succumb to mitotic catastrophe [MC, as shown for the cell in (D)]. By contrast, other cells may gradually degrade cyclin B1, fail to execute cytokinesis correctly, erroneously exit mitosis by undergoing mitotic slippage (MS), and ultimately form giant polyploid cells with an even higher degree of centrosome amplification (E and F) in the subsequent cell cycle. These polyploid cells could repopulate the tumor once docetaxel treatment ceases. Selective targeting of these polyploid cells

harboring supernumerary centrosomes by administering a centrosome declustering drug, such as griseofulvin, in combination with docetaxel may induce high-grade spindle multipolarity during the subsequent mitosis due to persistent centrosome declustering (G). High-grade spindle multipolarity inevitably culminates in cell death (H).

Table 1

Cancers for which docetaxel is administered alone or in combination with other drugs.

Cancer	Regimen
Bladder	Cisplatin-docetaxel-gemcitabine
	Docetaxel
Breast	Capecitabine-docetaxel
	Fluorouracil-epirubicin-cyclophosphamide followed by docetaxel every 3 weeks
	Docetaxel-trastuzumab followed by fluorouracil-epirubicin-cyclophosphamide
	Docetaxel
	Docetaxel every 3 weeks-trastuzumab
	Doxorubicin-cyclophosphamide followed by docetaxel every 3 weeks
	Docetaxel weekly-trastuzumab
	Carboplatin-docetaxel-trastuzumab
	Pertuzumab-trastuzumab-docetaxel
Cervical	Docetaxel
Esophageal	Docetaxel-oxaliplatin-leucovorin-fluorouracil
	Docetaxel-oxaliplatin-fluorouracil
Gastric	Capecitabine-docetaxel
Gastric/esophageal	Docetaxel-cisplatin-fluorouracil
Head and neck	Docetaxel-cisplatin-fluorouracil
Non-small cell lung	Cisplatin-docetaxel
	Docetaxel-gemcitabine
	Docetaxel
Ovarian	Docetaxel-oxaliplatin
	Carboplatin-docetaxel
	Docetaxel
Prostate	Docetaxel-prednisone
Small cell lung	Docetaxel
Soft tissue	Docetaxel-gemcitabine
Unknown primary, adenocarcinoma	Carboplatin-docetaxel
	Cisplatin-docetaxel
	Docetaxel-gemcitabine
Unknown primary, squamous cell	Carboplatin-docetaxel
	Cisplatin-docetaxel
	Cisplatin-docetaxel-fluorouracil
Uterine	Docetaxel-gemcitabine