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Reassessing specificity/selectivity of taxane-based chemotherapy

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ABSTRACT

The paramount prerequisite for effective anti-cancer drugs is their ability to eradicate malignant cells while sparing non-cancer cells. The divergence in properties between malignant and non-cancer cells establishes a "therapeutic window," a critical consideration for achieving desirable treatment outcomes. Central to this is the imperative of a cancer drug's "selectivity and specificity." Taxanes, a pivotal class of successful anti-cancer drugs, continue to serve as the linchpin of cancer treatment due to their efficacy across a spectrum of cancer types. Operating as broad-spectrum chemotherapeutic agents, taxanes exert cytotoxic effects on proliferative cancer cells by binding to and stabilizing microtubules, disrupting mitosis, inducing mitotic catastrophe, and resulting in cell death. The distinct proliferative nature of cancer cells, as opposed to less proliferative non-cancer cells, affords taxanes a measure of specificity and selectivity. Nevertheless, sporadic yet recurring evidence suggests that taxanes also operate through non-mitotic mechanisms. Taxanes' binding and stabilization of microtubules lead to micronucleation and subsequent cell death, impacting both mitotic and non-mitotic cells. Recent discoveries indicate that the flexible and weakened nuclear envelope of malignant cells renders them sensitive to taxane-mediated micronucleation and cell death during various phases of the cell cycle. Conversely, non-cancerous cells typically exhibit a more robust and sturdy nuclear envelope, rendering them more tolerant to taxane-induced nuclear envelope fragmentation and subsequent micronucleation and cell death. The expression levels of nuclear envelope structural proteins, particularly Lamin A/C, emerge as indicators of taxane sensitivity. This evolving understanding underscores that nuclear envelope malleability, in conjunction with a high proliferation rate, is a pivotal determinant of taxane specificity and selectivity against malignant cells. These insights necessitate reconsidering oncological strategies to augment taxane efficacy, overcome resistance, and mitigate side effects.

KEYWORDS

taxanes; Taxol; paclitaxel; microtubules; mitosis; proliferation; nuclear envelope; micronuclei; drug resistance; drug mechanism

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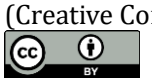

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1. Introduction

Conceptually, targeted therapy is an obviously superior strategy to cytotoxic chemotherapy currently used. However, although targeted therapy had some successes so far, it likely will not in the foreseeable future replace standard chemotherapy, which is still the corner stone of cancer treatment. For major solid tumor types, especially metastatic cancer, taxanes (including paclitaxel, docetaxel, and cabazitaxel) are key drugs with impressive successes (1-7). Taxanes are used in combination with other agents (commonly carboplatin or cisplatin), and also used alone in a dosage dense schedule following the development of drug (generally platinum agents) resistance (8-11). Taxanes are microtubules stabilizing agents that bind beta-tubulins within microtubule filaments and stabilize microtubules that otherwise undergo constant extension or shrinkage, known as microtubule dynamic instability (12). Interfering with microtubule function by taxanes ultimately leads to cell death, as mechanisms of taxanes action downstream have been critically analyzed and pondered (13).

A fundamental requirement of anti-cancer drugs is to eliminate malignant cells while sparing non-cancer cells, a principle known as cancer selectivity and specificity. Selectivity refers to the drug's preferential binding or interaction with the intended target (typically a protein), while specificity indicates the degree to which the drug impacts the target without causing excessive unintended side effects. Often the different properties between the malignant cells and the non-cancer cells provide a "therapeutic window" for a cancer drug to achieve a desirable outcome Fig. 1. In theory, targeted therapy is an ideal cancer treatment where the target, such as a mutated gene or protein, is presumed to be present only in cancer cells, not in normal cells. Thus, targeted therapy often has a wide therapeutic window, effective yet lacking side effects (Fig. 1A). However, in reality, very few targeted therapies have been successfully developed, and those with high selectivity and specificity often become ineffective due to the rapid development of drug resistance. Abundant redundancies and feedback loops enable cancer cells to escape targeted interventions, and a loss of sensitivity to programmed cell death signals in malignant cells further impedes the success of targeted therapy.

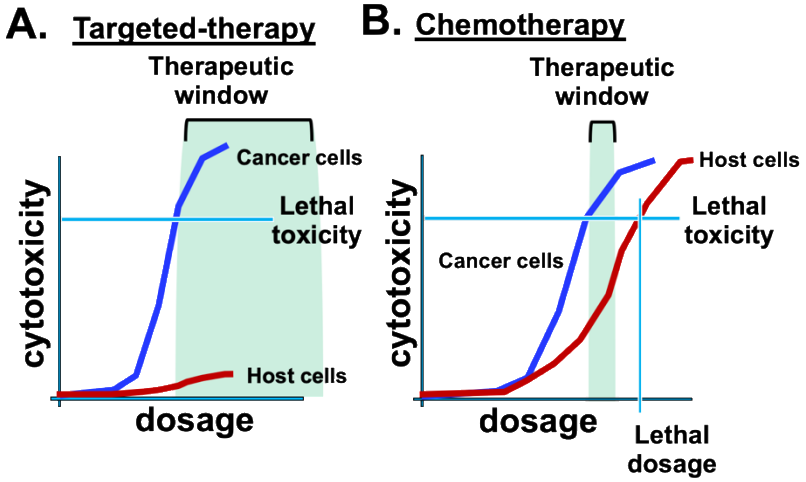

Figure 1. Illustration of therapeutic window of chemotherapeutic agents. (**A**) For targeted therapy, the anti-cancer drug/agent has high specificity since the target (a specific altered/mutated gene or protein) is present in malignant cells but not in host cells. Thus, the dosage of the agent used in the therapy should be at a level causing lethal toxicity to the cancer cells. In theory, the agent does not have an upper limit since it has little toxicity to the host. However, potential side effects likely set an upper limit. Nevertheless, the therapeutic window likely is very wide. (**B**) For cytotoxic chemotherapy, the anti-cancer agent has specificity to cancer cells, and is more toxic to cancer cells than to host cells. The therapeutic window will be defined by lethal toxicity to cancer cells, but lower than unacceptable toxicity to host cells.

Cytotoxic chemotherapy involves using drugs that are somewhat more toxic to malignant cells than benign cells, with lower expectations of high selectivity and specificity. The therapeutic window likely is narrower, and the dosage used may range from lethal toxicity to cancer cells to a level with unacceptable toxicity to host cells (Fig. 1B). Toxicity and drug resistance are vital issues limiting the use of standard microtubule-targeting chemotherapy[14,15].

For taxanes, the microtubule stabilizing agents that are key drugs in the treatment of several major cancer types (7,16,17), one recognized specificity to target malignant cells is the higher proliferative rate of cancer cells versus the majority of normal cells of the hosts, as microtubule functions are vital for mitotic cell division (18-21). However, the molecular mechanisms of taxanes are still mysterious when critically considered (13). Recent progress and new understanding also suggest that a malleable nuclear envelope often found in malignant cells provides another vulnerability for purging by taxanes (22,23). This article reviews and summarizes the concepts raised from new experimental findings and reasoning and suggests factors determining the specificity/selectivity of taxanes in chemotherapy.

2. Taxanes serve as microtubule-targeting agents with the pivotal ability to stabilize microtubules

The discovery of the promoting activity in polymerization and stabilization of microtubule bundles by the paclitaxel prompted the interest in clinical development of the drugs (16,17,24). Paclitaxel, the first taxane drug investigated, was studied extensively for its binding to the beta-tubulin subunits within microtubules and suppressing their dynamic extension and shortening, thus stabilizing the microtubule filaments (21,25). Paclitaxel binds tightly to microtubules, and can reach a near 1:1 ratio with the beta-tubulin subunits within the microtubules (21,25,26). As a consequence, paclitaxel can be sequestered into cells by binding to microtubules and concentrated hundreds of fold over the extracellular level (21,25), such that the microtubule stabilizing and bundling activity is persistent for a long period of time following a brief exposure and drug uptake (27). In patients, paclitaxel can be detected in tumors for several days following infusion (28,29), although circulating drug is cleared in hours (30). Likely, this feature of taxanes to be sequestered and remain within tumor cells by binding to microtubules is a crucial factor contributing to clinical success of taxanes as anti-cancer agents (31). The targeting of microtubules appears to be very consistent as the basis of the cancer cell cytotoxicity of taxanes (7,13,17), although the important events that are downstream of microtubule stabilization are still being decided, as discussed in more detail below.

3. Mechanisms of Taxanes' Specificity/Selectivity for Cancer Cells

Exploring the biological activity of taxanes binding to microtubules, several mechanisms to explain the anti-cancer activity and specificity seem apparent (Fig. 2). First, the inhibition of mitosis is an obvious mechanism since microtubules play an essential role in mitosis (Fig. 2(1)) (32,33). This mechanism was quickly confirmed, showing that paclitaxel causes cell growth arrest (34-36). Taxanes are well accepted to have mitotic blocking activity (21). Additional investigation suggested that interfering with microtubule spindles by taxanes also lead to aberrant mitosis and mitotic catastrophe, suggested as the key mechanism of taxane action (37-40). Since tumor cells are more proliferative than the normal cells counterpart, targeting mitosis appears to be able to distinguish neoplastic from non-cancer cells, providing a logical explanation for cancer specificity/selectivity of taxanes. Thus, the commonly accepted and quoted mechanism of action for taxanes is targeting mitotsis in the proliferative cancer and non-cancer cells.

Considering the functions of microtubules in cell mobility and endocytic trafficking, interference with

these cellular processes by taxanes may provide another distinguishing factor between malignant and non-cancer cells (Fig. 2(2))(41,42). It is reasonable and even likely that malignant cells have altered endocytic trafficking and higher cell mobility. However, no definite or general changes in these microtubule functions have been defined that can be attributed to the specificity or selectivity of taxanes for neoplastic cells.

A new explanation for taxane cancer specificity has been recently suggested, that taxane-induced stabilized and rigid microtubule bundles cause tearing of weakened nuclear envelope of malignant cells (Fig. 2(3))(31). Consequently, the weakened and malleable cancer nuclear envelope, compared to the of sturdier nuclear envelope of benign cells, provides another specificity/selectivity for taxane cytotoxicity to cancer versus non-cancer cells (23).

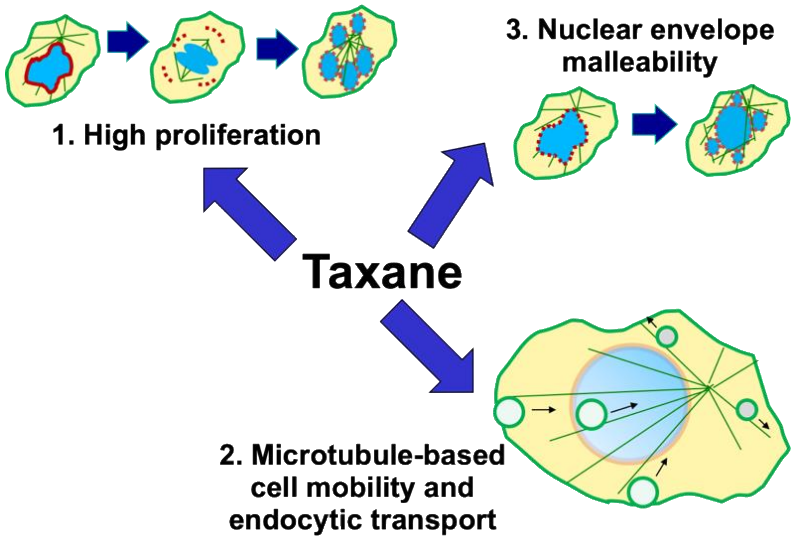

Figure 2. Potential determinants of specificity/selectivity of taxane targeting malignant cells. The possible key determinants of the differences between non-cancer and malignant cells to provide specificity/selectivity for taxanes in cancer therapy are illustrated. (1.) High proliferation rate in cancer: microtubules play essential roles in mitosis/cell division, which provides a key specificity/selectivity of taxanes to the proliferative cancer cells, and cases toxic side effects in chemotherapy. (2.) Role of microtubules in cancer cell mobility and cellular trafficking. Presumably, microtubule-mediated endocytic trafficking and cell mobility differ between benign and cancer cells, which make the cancer cells more sensitive to taxanes than normal cells. (3.) Weakened and malleable nuclear envelope of malignant cells (illustrated by the dotted line). The new understanding is that taxanes stabilize and bundled microtubules, causing breakage of the nuclear envelope as a crucial mechanism of taxane. Malignant cells commonly have weakened and malleable nuclear lamina, which gives taxanes a key cancer specificity/selectivity.

4. Taxanes Targeting Mitotic Cells as a Contributor to Cancer Specificity/Selectivity

Observations The initial observation of the effects of paclitaxel on microtubules provide a unique mechanism to explain the cytotoxic activity of the agent on cancer cells stimulated the enthusiasm in the early clinical development of the successful anti-cancer agent (16,17,21,24). Experiments with cancer cells in cultures indicate that taxanes do consistently cause growth arrest, mitotic catastrophe, and cell death (43,44). Generally, the cytotoxic mechanism of taxanes is accepted as mitotic inhibition (21), as this concept appears very reasonable since cancer is proliferative and uncontrolled growth (Fig. 2(1)). Furthermore, prolonged interfering with mitotic cells by taxanes also lead to aberrant chromosome segregation and mitotic catastrophe, which is recognized as a mode of taxane-mediated cancer cell killing (37-40). Thus, taxanes are considered mitotic inhibitors and have higher toxicity

to proliferative cells (16,17,21,24).

Taxanes commonly are highly effective with tolerable side effects, mainly myelosuppression, alopecia, and peripheral neuropathy (14,45). The main common side effects, myelosuppression and alopecia, are consistent with the idea that taxanes target cells that have a high mitotic index, as the hematopoietic progenitor cells and the hair follicle matrix cells are the most proliferative cells in the body. Neuronal cells are terminally differentiated and non-proliferative. Peripheral neuropathy likely is caused by taxane targeting axonal microtubules, which are essential for neuron structure and function (46,47).

Although taxanes are commonly accepted to be mitotic inhibitors, controversy remains. Some hold that targeting mitosis is not the whole story or perhaps even the key part of their anti-cancer activity of taxanes (48-50). Several arguments are presented: that the drug activity does not correlate with the cell proliferation rate of the cancer, referred as the taxane mitotic paradox (51); that the non-mitotic fractions of tumor cells are also sensitive to taxanes (52); and that other mitotic inhibitors developed do not have clinical efficacy in comparison to taxanes (48,50). These minority opinions persistently question the commonly accepted notion that taxanes act by inhibiting mitosis (48,52) and suggest the importance of non-mitotic mechanisms of taxanes in cancer therapy (31,36,48,52-54).

5. Taxanes' Induction of Micronucleation in Both Mitotic and Non-Mitotic Cells

Either by mitotic and/or non-mitotic modes of action, treatment of cancer cells with taxanes consistently results in the appearance of lobulated or fragmented nuclei in the cancer cells (31,38). Their appearance is referred to as “micronucleated cells” (31,55,56), which is suspected to be important in taxane-induced cell death or drug resistance (31,40,55-57). These multiple micronuclei can be the result of aberrant mitosis (38), but also can be produced by non-mitotic mechanism (31).

In addition to mitotic cells, cells in the gap phase of the cell cycle also show changes in microtubules upon exposure to taxanes, showing strong staining of bundled microtubules (31), and studies identified a correlation between the bundling of microtubules with the efficacy of cell killing (58). A mechanism for the formation of micronucleation by taxanes in non-mitotic cells is suggested, that the stabilized and rigid microtubule bundles tear and break the nuclear envelope into micronuclei (31). Furthermore, the weakened or malleable nuclear envelope in malignant cells is likely more prone to taxane-induced nucleation (23). In cultured cells, it was demonstrated that suppression/deletion of Lamin A/C increased taxane-induced micronucleation and sensitivity of cells to taxanes, while over-expression of Lamin A/C to enhance the nuclear envelope sturdiness caused resistance to taxane-induced micronucleation (31). Additionally in the presence of mitotic inhibitors, cells with a weakened nuclear lamina still undergo micronucleation upon taxane treatment, indicating a non-mitotic mechanism (31).

Micronuclei often undergo catastrophic membrane rupture (59,60), which likely is a key factor in taxane-induced death of cancer cells (22,31). Several mechanisms determining sensitivity and resistance of cancer cells to taxanes have been recognized (7,16,61), such as the expression of ABC transporters to export drugs, components in the apoptotic pathways, and factors influencing microtubule polymerization including microtubule binding proteins and regulators. The recent observation leads to a suggestion for a new mechanism of taxane cell killing activity, the malleability of the nuclear envelope and the propensity to tear and form micronuclei (Fig. 2(3)) (23,31).

6. Increased Nuclear Envelope Malleability: A Crucial Element in Taxane Specificity/Selectivity

In In cultured ovarian cancer cells, the expression level of Lamin A/C was shown to be a key determinant of the sensitivity of the cells to taxanes (31). Cancer cells with a low Lamin A/C protein expression have more malleable

nuclear envelope and thus the propensity is high for the nuclear envelope to break into multiple micronuclei upon paclitaxel treatment (22,23). Based on this idea, it is reasoned that cancer cells with malleable and irregular nuclear envelope likely are more sensitive to taxanes as these agents target nuclear membrane to promote rupture (22,31) (Fig. 3).

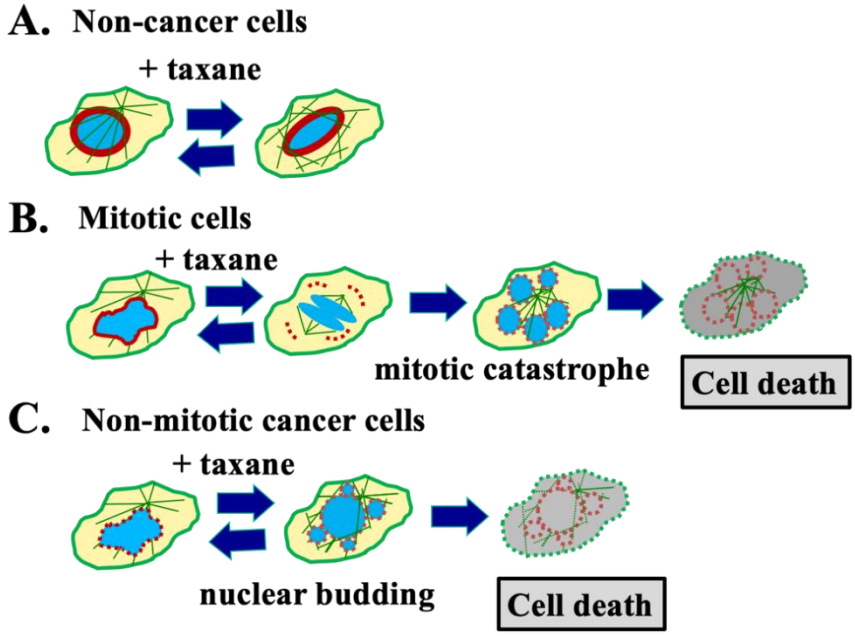

Figure 3. Taxane targets cells with malleable nuclear envelope. (**A**) Non-cancer cells usually have sturdy nuclear envelope, and taxane-induced microtubule stabilization and bundling may cause some deformation but not breakage of the nuclear envelope. (**B**) Mitotic non-cancer and cancer cells have disassembled nuclear envelope (dotted line to illustrate disassembling mitotic nuclear envelope), and taxanes interfere with microtubule mitotic function, leading to mitotic catastrophe and micronucleation. The compromised micronuclei (illustrated by dotted line) undergo frequent irreversible rupture, leading to ultimate cell death. (**C**) Cancer cells commonly have a weakened nuclear envelope (illustrated by the dotted line), which undergoes micronucleation when taxanes cause microtubule stabilization and bundling. Micronucleation is the result of nuclear budding rather than mitosis. The formed micronuclei are defective and undergo rupture, and eventually result in cell death.

Non-cancer cells usually have sturdy nuclear envelope, and taxane-induced microtubule stabilization and bundling may cause some deformation but not breakage of the nuclear envelope. Mitotic non-cancer and cancer cells have a disassembled nuclear envelope, and taxanes interfere with microtubule mitotic function, leading to mitotic catastrophe and micronucleation. The compromised micronuclei undergo frequent irreversible rupture, leading to ultimate cell death (59,60). Since cancer cells commonly have a weaker and malleable nuclear envelope even at non-mitotic states, micronucleation results from nuclear budding rather than mitosis. Cancer cells with a malleable nuclear envelope undergo micronucleation when taxanes cause microtubule stabilization and bundling and the formed micronuclei are defective and undergo rupture, and eventually result in cell death (31). Thus, the propensity of nuclear envelope to tear by taxane-induced microtubule bundles provide a specificity for non-mitotic cells to taxanes (Fig. 3).

Lamin A/C proteins (but not mRNA) are found to absent or reduced in several cancer types (62-65), and Lamin A/C is considered a potential cancer prognostic marker (66,67). The causes and consequences of the aberrant expression of Lamin A/C proteins in cancer have been an actively investigated topic (68). Deletion of Lamin A/C has been shown to cause nuclear envelope mechanical and shape changes, and the nuclear envelope of Lamin A/C-

deleted cells becomes malleable (69).

An obvious consequence of reduced/lost Lamin A/C is the malleability and deformity of nuclear envelope in cancer cells (64,68), which is often a characteristic of malignancy in several cancer types (70). Loss and reduced Lamin A/C is thought to enable the generation of genomic instability and generation of aneuploidy (65,71-74). Based on the association between reduced Lamin A/C and aneuploidy, it is probable that aneuploid cancer cells likely are more sensitive to taxanes.

Thus, potentially, the expression of Lamin A/C may serve as a marker to predict sensitivity and resistance of cancer cells to taxanes (23). Hence, loss and reduction of Lamin A/C, or the increased malleability of nuclear envelope in malignant cells, provides another mechanism for the selectivity for taxanes in killing cancer cells rather than benign cells (Fig. 3).

7. Conclusions

Three distinct mechanisms contributing to the specificity or selectivity of taxanes against cancer cells are propose (Fig. 2). Firstly, the long-recognized and well-accepted targeting of taxanes to highly proliferative cells. Secondly, alterations in microtubule-mediated endocytic trafficking and cell mobility may contribute to taxane anti-cancer specificity, although specific changes supporting this notion are yet to be identified. Lastly, the recent understanding of taxane mechanisms in breaking nuclei of cancer cells presents a newly recognized specificity or selectivity: the weakened and malleable cancer nuclear envelope. As an irregular nuclear envelope is often a characteristic of malignant cells, it serves as a higher sensitivity indicator to disruption by taxane-induced microtubule bundles (Fig. 3).

Cancer cells sensitive to taxanes, such as ovarian cancer, metastatic breast cancer, hormone-insensitive and metastatic prostate cancer, and metastatic non-small cell lung cancer, often exhibit high nuclear grades and severe nuclear morphological abnormalities, indicating nuclear envelope malleability. Consequently, the degree of nuclear deformation and the expression of nuclear lamins may serve as predictive markers for sensitivity or resistance of cancer cells to taxanes. Combining agents or methods to perturb nuclear envelope sturdiness may enhance the efficacy of taxanes. In conclusion, the new understanding suggests that nuclear envelope malleability determines sensitivity to taxanes and is another critical factor, alongside a high proliferation rate, contributing to the specificity and selectivity of taxanes toward malignant cells. These revelations prompt a reevaluation of strategies to enhance taxane efficacy, overcome drug resistance, and prevent or reduce taxane side effects.

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Conflict of interest

The authors declare no competing interests.

Author contributions

Conceptualization: Xiang-Xi Xu; Investigation: Elizabeth R. Smith, Zheshen Li; Methodology: Zhe-Sheng Chen; Formal analysis: Zhe-Sheng Chen, Xiang-Xi Xu; Writing – original draft: Elizabeth R. Smith; Writing – review & editing: Zhe-Sheng Chen, Xiang-Xi Xu.

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