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Editorial

The Second Selectivity of Taxanes to Malignant Cells --- Nuclear Envelope Malleability

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We wish to suggest a cellular mechanism expanding to the understanding of the cancer selectivity/specificity of taxanes, a group of commonly used cancer drugs by the action of microtubule stabilization.

The current frontline treatment of several major solid tumors is a taxane-based chemotherapy that was formulated nearly forty years ago, though with refinement over time. Taxanes work through a mechanism of microtubule stabilization [1-4]. Currently, several principal taxanes, such as Taxol/paclitaxel, Taxotere/docetaxel, and Jevtana/cabazitaxel, are used as a frontline regimen in combination with other drugs (often platinum agents), as well as second line drugs for recurrent cancer. Taxanes are highly active in many major solid tumors, and especially useful for treating malignant and metastatic cancers, including those of breast, lung, prostate, ovarian, head and neck, and cervical carcinomas, with mostly tolerable side effects [5-9]. Nearly all cancer patients with these tumor types will likely be treated with taxanes at one point in the course of managing their diseases.

The initial discovery of the activity of paclitaxel/taxol (the first taxane) in stabilization of cellular microtubules and consequential mitotic arrest of cancer cells propelled the enthusiasm for the development of paclitaxel as a cancer drug [10,11]. Commonly, paclitaxel's anti-cancer activity (and also of all other taxanes) is thought to be conferred by its binding to and stabilizing cellular microtubules, which interferes with mitosis and leads to cell growth arrest [1-3,12] and subsequent mitotic slippage and mitotic catastrophe [13,14]. Thus, taxanes are considered mitotic inhibitors. The major side effects of taxanes, myelosuppression and alopecia, are consistent with the idea that taxanes target mitotic cells, such as the rapidly renewing hematopoietic cells and the continuously proliferating hair matrix cells [15,16]. However, the molecular mechanism leading to cell death has not been clearly deciphered [17-20].

Overtime, some skepticisms persisted with regards to the idea that blocking mitosis is the sole mechanism of action for taxanes on cancer cells [17,21-24]. For one, taxane cell killing activity does not correlate with the rate/index of mitosis or proliferation of the treated tumors [25], an observation known as the mitotic paradox [26]. The lack of clinical activity of other mitotic inhibitors also casts doubt on mitotic inhibition as the sole mechanism of taxanes [22,27].

In laboratory studies using cancer cells, upon treatment with taxanes, the nuclei of cancer cells fragment into multiple micronuclei, a process known as micronucleation [20,28-30]. The taxane-induced generation of multiple micronuclei occurs in both mitotic [13,29,31] and also in non-mitotic cells [32]. A mechanism was proposed that the paclitaxel-induced rigid microtubule bundles physically pull the nuclear envelope through the LINC (Linker of nucleoskeleton and cytoskeleton) bridges and break the nucleus off to form micronuclei [33]. Additionally, the generated multiple micronuclei have a weakened nuclear envelope and membrane, for which the stretching of

surface to form multiple spheres of micronuclei from a single nucleus is one of the feasible explanations [33]. The catastrophic rupture of the micronuclei consequently leads to cell death [20,28-30].

Here, nuclear envelope malleability/fragility refers to softened nuclear membranes and envelope, presented as nuclear morphology deformation that is a common characteristic of cancer cells. Laboratory experiments using cultured cells led to a conclusion that nuclear envelope malleability/fragility, which is modulated and controlled by overexpression or suppression of nuclear envelope lamina Lamin A/C, determines sensitivity of cells to paclitaxel-induced micronucleation and cell death [32-34]. This new mechanistic understanding provides an explanation for the non-mitotic action of taxanes, by inducing micronucleation as a result of rigid microtubule bundles pulling the malleable and fragile nuclear envelope of cancer cells [33,34].

This new understanding of taxane mechanism beyond mitotic inhibition prompted us to reassess the reason(s) why taxanes are more successful in clinic than expected, and how taxanes are more toxic to cancer than to normal host cells in addition to inhibiting the cell proliferation rate [35]. Further appraisal of the experimental conclusions leads to the recognition of the susceptibility of cancer nuclear envelopes subjected to fragmentation by the drug-induced rigid microtubule bundles as a second selectivity/specificity of taxanes (**Fig. 1**). Nuclear envelope malleability/fragility is often determined by nuclear envelope lamina proteins [33-36], and particularly Lamin A/C level for cancer cells [37,38]. Cancer cells generally have a reduced Lamin A/C protein level [37-41], which has been also suggested to be a cause of aneuploidy through nuclear budding [42]. Another consequence of reduced Lamin A/C protein in cancer cells and the property of nuclear envelope malleability is the morphological deformation of the cancer nucleus [37,43], which is the basis in diagnosis of malignant cells in the PAP smear test [38]. Thus, cancer cells with deformed nuclear morphology and massive aneuploidy, which are commonly present in malignant and metastatic carcinomas, can be predicted to be sensitive and responsive to taxane treatment. In contrast, benign cells with a sturdy nuclear envelope presenting a smooth and oval shaped morphology are more resistant to taxane-induced micronucleation and rupture (**Fig. 1**).

In summary, we suggest that nuclear envelope malleability/fragility that is often caused by a reduced nuclear envelope structural protein (Lamin A/C) which is the second selectivity/specificity of cancer cells to taxanes (**Fig. 1**). These two properties of cancer cells, high proliferation rate and malleable nuclear envelope, may provide two aspects of specificity and selectivity to taxanes and contribute to the surprising success of taxanes in cancer treatment over the last four decades. The recognition of a second selectivity/specificity likely will prompt oncologists to revisit the rationale for optimal use of taxanes in cancer management. Subsequent new understanding may enable additional rational combinations of taxanes in oncology, and may inspire new strategies to more efficiently counter cancer.

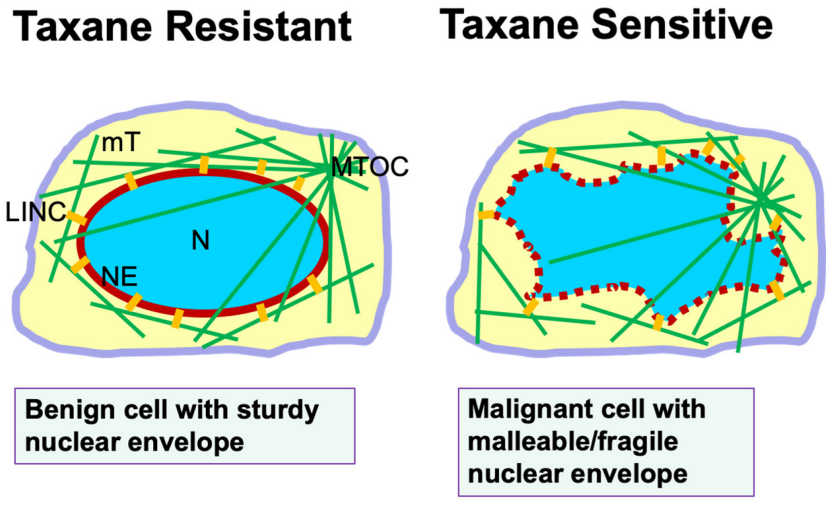

Figure 1. Nuclear envelope malleability/fragility is a predictor of taxane sensitivity. Illustration shows a benign cell with sturdy nuclear envelope and exhibiting a smooth and oval-shaped morphology. Microtubules extend out from the microtubule organizing center (MTOC). The nuclear envelope is connected to the microtubule cytoskeleton through the LINC bridges (short yellow lines). In a malignant cell, the malleable nuclear envelope (depicted by a dotted red line) is disturbed by physical pulling from microtubules through the LINC bridges. In the presence of taxanes, cellular microtubules are stabilized and bundled, and the rigid filaments pull apart the fragile nuclear envelope to form multiple micronuclei, leading to cell death. Thus, the property of a malleable/fragile nuclear envelope in cancer cells provides a second specificity/selectivity for taxane killing though micronucleation and nuclear envelope rupture. Benign cells with a sturdy nuclear envelope are more resistant to taxane-induced micronucleation, and are taxane resistant. **Abbreviations: mT,** microtubules; **LINC,** linker of nuclear and cytoplasmic skeleton; **N,** nucleus; **MTOC**, microtubule organizing center; **NE,** nuclear envelope.

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Competing Interests

The authors have declared that no competing interest exists.

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