Review

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Cancer nuclear envelope rupture and repair in taxane resistance

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Abstract: Taxanes, including paclitaxel, docetaxel, and cabazitaxel, are key agents in cancer treatment, often used as frontline chemotherapy drugs in combination with other agent(s) (commonly carboplatin) and as second-line treatments alone. Generally, taxanes are highly effective, but drug resistance unavoidably develops following repeated treatment. Taxanes work by binding to and stabilizing microtubules, leading to mitotic arrest, mitotic catastrophe, and micronucleation. The long-recognized mechanisms of drug resistance generally can be classified into three categories: drug efflux, microtubule polymerization, and apoptotic pathway. A recent new addition to this list is a mechanism related to the nuclear envelope, as cancer cells undergo micronucleation and nuclear membrane rupture when treated with taxanes. All these mechanisms may operate simultaneously as taxane resistance is multi-factorial. Here, we review the cell biology understanding of nuclear envelope breaking in production of micronucleation, and nuclear membrane rupture and repair, and propose that these processes are involved in taxane resistance.

Keywords: chemotherapy; drug resistance; taxanes; paclitaxel; microtubules; nuclear envelope

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General introduction of taxane resistance mechanisms

Paclitaxel, the first taxane, was a fortuitous finding during screening of natural compounds in a USDA (United States Department of Agriculture)-sponsored project in 1960s [1, 2]. Since then, taxanes (paclitaxel, docetaxel, and cabazitaxel) have become a cornerstone in the management of many major solid tumors, including ovarian cancer, metastatic breast cancer, lung cancer, and castration resistant and metastatic prostate cancer [1, 3–7].

The mechanism of action of taxanes, which involves the stabilization of cellular microtubules, seems to be a surprisingly successful strategy in purging malignant cells of these various cancer types. Mitotic inhibition and mitotic catastrophe, which are what microtubule stabilization is thought to result in, has been assumed to be the key factor in the anti-cancer activity of taxanes [8–14], but increasingly non-mitotic mechanisms are also thought to account for the success of taxanes [15–20].

Today, taxanes such as paclitaxel, docetaxel, and cabazitaxel, are widely used as frontline drugs for chemotherapy and as secondary agents for recurrent cancer [1, 3–7, 21]. Moreover, formulations such as albumin-bound paclitaxel (Abraxane, Nab-paclitaxel) and liposome-paclitaxel, etc., are used to enhance delivery [22, 23]. New taxanes and non-taxane molecules are being developed based on the mechanism of microtubule stabilization to optimize efficacy and overcome drug resistance [24, 25]. These new developments will enhance the utilization of the microtubule stabilizing drugs in terms of delivery, as reducing allergic reaction, shortening infusion time, oral delivery, etc., leading to increased efficacy and reduced toxicities. It appears that taxanes and other microtubule stabilizing agents will remain important in the foreseeable future of oncology.

Despite the success of taxanes in cancer treatment, the eventual development of drug resistance and side effects like myelosuppression, peripheral neuropathy, and alopecia present debilitating problems [1, 6, 26–28]. Myelosuppression and peripheral neuropathy can be dose-limiting factors that require treatment to be paused and the drug dose to be

reduced [5, 29, 30]. In addition, although about 90 % of taxane-induced alopecia ceases following the completion of treatment, severe hair loss is often considered the most concerning issue for many patients [31]. In ovarian cancer as an example, the initial response rate to paclitaxel and carboplatin (or cisplatin) is around 60 %, ranging from 40 % to 86 % in various reports (Figure 1) [5, 6, 21, 32]. Thus, around 40 % of ovarian cancer is intrinsically resistant to both paclitaxel and carboplatin, which is defined as tumor progression within 6 months post-chemotherapy [5, 6, 21, 32, 33]. In recurrent cancer that is commonly platinum resistant, treatment with dose dense (weekly) paclitaxel has a 30 % response rate (Figure 1). Eventually all cancer cases will become resistant to taxanes following repeated treatment [1, 7, 26–28].

Therefore, considerable efforts have been devoted to understanding and overcoming drug resistance [1]. Generally, taxane resistance can be classified into four categories [20, 26]: (1) resistance related to an increased expression of transmembrane transporters for drug efflux; (2) resistance related to microtubule stability in which the microtubules are less inclined to bind to paclitaxel, caused by microtubule mutation and expression of isoforms, changes of microtubule binding proteins, and other tubulin regulatory proteins; (3) resistance caused by the genes related to apoptotic pathways that set the threshold for cell death activation; and (4) resistance related to the properties of the nuclear envelope [20]. This fourth category stems from new understandings of the taxane mechanism that suggest the importance of the nuclear envelope in taxane resistance. There are two factors that may be considered here: first, the mechanical sturdiness of the nuclear envelope, which may determine the propensity of the nuclear envelope to deform and undergo micronucleation; and second, the tendency of the micronuclei formed to rupture. These four key mechanisms of taxane resistance may operate simultaneously with differing levels of importance in the development of resistance by cancer cells.

Increased expression of ABC drug efflux transporters is a well-recognized multi-drug resistant mechanism [34, 35]. This mechanism accounts for a portion of drug resistant activity [20, 26]. Some taxanes such as cabazitaxel are poor substrates for the glycoprotein cell surface transporters, and thus these drugs may be used even when other taxanes become less effective due to the overexpression of ABC transporters [35–37].

There were a number of studies looking at altered expression or mutation of apoptotic genes [38, 39]. Bcl-2 expression and phosphorylation have been studied and reported [40]. Cancer commonly has loss or mutation of Tp53, which is a key regulator of the apoptotic cell death program, rendering cancer cells more resistant to cytotoxic stress and chemotherapy agents [39].

Since taxanes work by stabilizing microtubules, factors affecting microtubules stabilization are reasonable or likely contributors to taxane resistance [41, 42]. However, tubulin mutations affecting affinity to taxane binding were found in laboratory but not in clinical samples [43, 44]. Therefore, tubulin mutations are not a common mechanism for clinical drug resistance.

Most cell types normally express tubulin beta1, but some cancer cells were found to also express tubulin beta3, which is normally restricted to neuronal cells [45]. The change of expression to another tubulin type is known as isoform switching [46–48]. The expression of tubulin beta3 in cancer cells was suggested to be a mechanism contributing to taxane resistance since it was reasoned that tubulin beta3 may be less sensitive to taxanes [46–50]. However, additional follow-up studies found that the expression of tubulin beta3 did not seem to predict the sensitivity of microtubules made of tubulin beta3 and host cells to taxanes [51]. Changes in microtubule binding proteins [52, 53], regulatory kinases [54–57], etc., that are related to microtubule stabilization, are suggested to affect taxane resistance. It is likely that numerous factors influencing microtubule biology, to varying extents, will determine cellular sensitivity and resistance to the cytotoxic effects of taxanes.

The new understanding of the taxane mechanism related to nuclear envelope sturdiness [20] provides additional possibilities that determine sensitivity and resistance

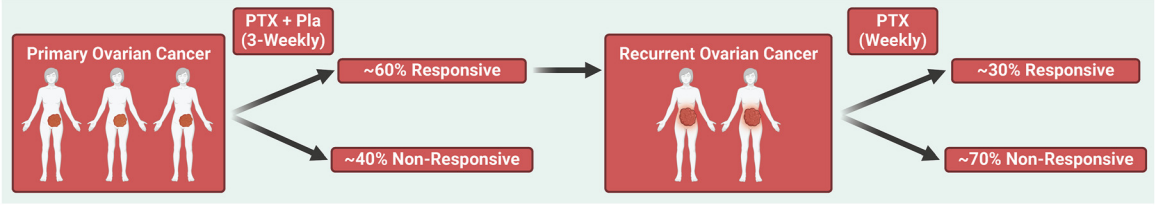

Figure 1: Chemotherapy responsiveness in ovarian carcinomas. Primary ovarian carcinomas are first treated with paclitaxel and carboplatin combination (PTX+Pla). The response rate is about 60 % (reported from 40 to 85 %). In the recurrent cancer, only about 30 % of the cases are responsive to dose dense paclitaxel (weekly rather than 3 weeks). Eventually, all cases are resistant to taxanes after repeated treatments. The illustration was created using software from Biorender.com.

of cancer cells to taxanes, as discussed below. All these mechanisms are not mutually exclusive and may coalesce to reach the observed clinical resistance to taxanes.

New understanding of taxane action: micronucleation

The phenomenon of taxane-induced micronucleation has been observed previously [58–60], and further explored in more details recently [19, 61]. The finding of paclitaxel-induced micronucleation opens up a new area of taxane resistance [20, 61]. Upon addition of paclitaxel, it was observed that nearly all cancer cells in culture became micronucleated, often presented as multiple micronuclei associated with a larger primary nucleus, or a collection of lobulated micronuclei [61]. In proliferative cancer cells in culture, the formation of multiple micronuclei is largely a result of multipolar division or mitotic catastrophe [2, 13, 60, 62]. It also results from a non-mitotic mechanism, through the pulling of the nuclear envelope by attached paclitaxel-induced rigid microtubule bundles [19, 61].

There are several proposals on the consequences of taxane-induced micronucleation. One proposition is that the persisting micronuclei may be able to recover and reform a single nucleus, as a mechanism of resistance to taxanes [58, 59]. Another notion is that the micronuclei may stimulate the cGAS-Sting cellular DNA sensing pathway, and induce inflammatory reaction in neighboring cells, as part of taxane anticancer mechanism [63]. Additionally, an intriguing theory asserts that the paclitaxel-induced multiple nucleated cells can further develop into the polyploid giant cancer cells (PGCC) [64]. These PGCCs are at a dedifferentiated embryonic cell-like state and may serve as cancer stem cells [65], and these PGCCs contribute to drug resistance in chemotherapy [66]. Lastly, a new idea suggests that micronucleation produced through both mitotic and non-mitotic mechanisms is the key mechanism for taxane-induced cell death [19, 61]. It is proposed that the formation of multiple micronuclei stretches the nuclear lamina and membrane to the points of irreversible rupture, leading to cell death [19, 67].

Nuclear rupture during interphases is observed to be more frequent in cancer cells [68]. Micronuclei are also observed to undergo catastrophic rupture [69, 70], leading to chromosome fragmentation and massive genomic changes known as chromotripsy [71, 72].

In sum, the taxane-induced formation of multiple nuclei, or micronucleation, is proposed to be a key mechanism of cancer cell killing by taxanes [19, 20, 61]. Subsequently, the micronuclei will then rupture irreversibly, leading to cancer cell death [67, 69, 70].

Regulation of nuclear lamin and nuclear envelope sturdiness: lamin phosphorylation and acetylation

In the new model of paclitaxel-induced cell death by micronucleation and nuclear membrane rupture, there are two steps that may be considered: (1) the mechanical sturdiness of the nuclear envelope, which may determine the propensity of the nuclear envelope to deform and undergo micronucleation; and (2) the propensity for the rupture of the nuclear membrane:

While non-neoplastic cells normally have strong nuclear lamina and are resistant to nuclear envelope distortion, the more malleable nuclear envelope of cancer cells is readily pulled apart to form multiple nuclei in gap phases, and the nuclear lamina is also weakened by cyclin kinases in mitotic cells [73–77]. A gene knockout study indicates that components of nuclear lamina such as Lamin A/C and emerin determine nuclear envelope sturdiness [78]. Loss and reduction of Lamin A/C proteins are suggested to be a major cause of aneuploidy in cancer cells [79–83].

Cancer cells often have a malleable nuclear envelope and are characterized by their nuclear morphological deformation and a high nuclear grade [84]. Particularly, these high-nuclear-grade cancers are sensitive to taxanes [85]. Lamin A/C content is a key determinant of nuclear envelope sturdiness [61], and Lamin A/C levels are variable in cancer cells [79, 80]. It appears that Lamin A/C in cancer cells is regulated on protein rather than mRNA levels [79, 80]. Thus, factors that control Lamin A/C protein levels are also important in determining nuclear envelope sturdiness and mechanical properties.

The regulation of gene expression and post-translational processing of Lamin A/C, the major nuclear cytoskeleton proteins, have been well investigated [76, 86]. The cellular functions of Lamin A/C have been highlighted by a larger number of heterogenous human diseases in various tissues caused by a wide range of mutations of the LMNA gene (encoding Lamin A/C proteins), collectively known as laminopathies [86, 87]. These abnormal phenotypes can be attributed to the cellular function of Lamin A/C in nuclear envelope structure, nuclear and cell mechanical property, roles in chromatin organization and subsequently regulation of gene expression [76, 86, 87].

Lamin A/C is phosphorylated by cyclin kinases [73–75]. This is a step in the nuclear envelope disassembly of the mitotic phase, enabling the separation of chromosomes to two daughter cells [76, 77]. However, Lamin A/C can also be phosphorylated in the gap phase, leading to partial lamina disassembly and increased lamin degradation [88]. Additional

kinases such as AKT are shown to phosphorylate Lamin A/C and regulate its stability [89, 90], and ATR also phosphorylates Lamin A/C leading to nuclear envelope rupture [91]. Thus, elevated lamin kinase levels reduce Lamin A/C function and stability, and render the cells more sensitive to taxanes, while a reduction of lamin kinases would increase resistance to taxanes.

At the completion of mitosis, phosphatases dephosphorylate Lamin A/C, leading to the reassembly of the nuclear lamina layer [92–95]. It is reasoned that altered expression of lamin-phosphatases associated with the nuclear envelope will also modulate lamin properties [96], and thus influence sensitivity and resistance of the cells to taxanes (Figure 2).

A recent interesting study suggests that acetylation of Lamin A/C also provides function and stability of the lamina formed, and blocking of Lamin A/C acetylation leads to a weakened lamina and increased nuclear envelope malleability, promoting micronucleation [97–99]. In the study [97], Lamin A/C was identified as a key substrate for the lysine acetyltransferase MOF (KAT8), and acetylation of Lamin A/C affords its function and polymerization into nuclear lamina. In contrast, deletion of MOF leads to augmented and extensive formation of micronuclei. The role of Lamin acetylation was also demonstrated by histone deacetylase (HDAC) inhibition or rescuing using acetylation-mimicking Lamin A mutations [97]. These interesting findings will need further confirmation and replication to verify the importance of Lamin A/C acetylation in its function, and potential alterations leading to excessive formation of micronuclei and genome instability in diseases [98, 99]. Accordingly, increased MOF and decreased HDAC would elevate Lamin A/C function and contribute to taxane resistance (Figure 2).

Thus, these are the factors involved in nuclear lamina modifications that determine nuclear envelope sturdiness and thus the ability of taxane-induced rigid microtubule bundles to distort and break the nuclear envelope into multiple micronuclei. Accordingly, lamin kinases and phosphatases, and lamin acetyltransferase and deacetylase may be related to taxane resistance.

Nuclear envelope transient rupture and repair

In recent years, significant advances have been made regarding the understanding of nuclear membrane rupture and repair [100]. Nuclear membrane rupture can be caused by a number of factors, including apoptosis, infection or external force, and, most importantly for this paper, irregularities in lamin expression in the nucleus [101]. In cancer cells, a higher frequency of nuclear envelope rupture during interphase has been observed [68]. This is perhaps due to a weakened nuclear envelope, caused by the loss of lamina proteins like Lamin A/C and emerin [79, 80]. Furthermore, suppression of Lamin A/C leads to increased mitotic failure and thus aneuploidy in cells, a common feature of cancer [81–83].

Micronucleation is a result of chromosomal lagging during mitosis, in which a part of or a whole chromosome is separated from the rest of the DNA material [69]. Micronucleation can also be caused by nuclear budding, in which DNA leaks out of the nucleus through gaps in the lamina due to a deformed or malleable nuclear envelope [79, 80, 101]. Though ruptures in the primary nucleus are usually repaired within minutes and at a relatively high success

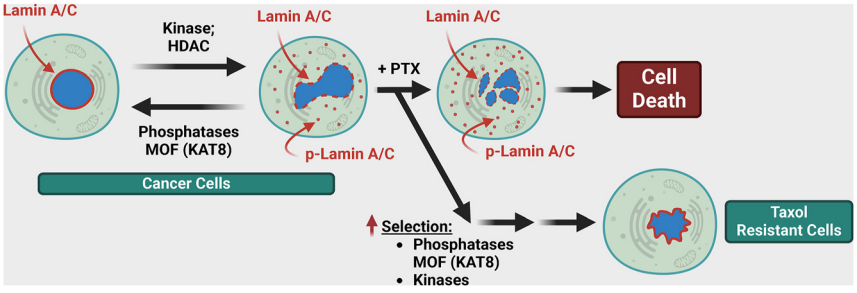

Figure 2: Expression and modification of Lamin A/C by nuclear lamina kinases and phosphatases determines Taxol/paclitaxel sensitivity and resistance. Cancer cells often lose or have reduced Lamin A/C due to phosphorylation and/or other posttranslational modifications (de-acetylation by HDAC), which makes the nuclear envelope malleable (depicted as red dots). Phosphorylated and de-acetylated Lamin A/C disassembles. The malleable nucleus of malignant cells is more sensitive to breakage from the physical forces of paclitaxel bound rigid microtubule filaments. Hence, paclitaxel induces breakage of cancer nuclei, and causes subsequent cell death. A fraction of cells undergoing selection in the presence of paclitaxel likely regain Lamin A/C expression and become resistant to paclitaxel-induced nuclear breakage and death. The strong dashed brown color nuclear outline illustrates increased Lamin A/C and sturdiness but abnormal nuclear envelope of the paclitaxel-resistant cells.

rate [69], ruptures in micronuclei formed during interphase are almost always irreversible, which is the so-called catastrophic rupture [69].

The irreparable nature of micronuclei rupture is suggested to be key in the treatment of cancer cells using paclitaxel, as paclitaxel induces multimicronucleation in cancer cells, but not normal cells, and is therefore tumoricidal [20, 61], but the success of the drug may be limited by repair mechanisms to avoid irreversible nuclear membrane rupture.

The nuclear envelope can be repaired through a number of suggested mechanisms, such as endoplasmic reticulum (ER) sheets attaching to exposed chromatin, the existing outer nuclear membrane spreading out over the rupture, or the resealing of the rupture via protein complexes [101] (Figure 3A). BAF, which is a double stranded DNA binding protein, is thought to be a first responder in nuclear envelope repair [102]. Unphosphorylated BAF travels from the cytoplasm to the rupture site, binds to exposed DNA, lamin, and LEM-domain proteins on the INM, perhaps preventing DNA leakage in the process by clotting the hole [101]. BAF can then recruit CHMP7 which recruits ESCRT-III which works alongside VPS4 to seal the nuclear envelope and sever microtubules that have traversed through the rupture and attached themselves to chromatin discs [102–104]. Cytoplasmic cyclic GMP-AMP synthase (cGAS), which detects nuclear DNA at rupture sites early on, is also present in the repair process, and is suggested to work concertedly with BAF and Lamin A/C to accumulate at the site and repair the ruptured membranes [105] (Figure 3A). Particularly, the ESCRT-III complexes are crucial for nuclear envelope repair in sealing the membranes [102–104] (Figure 3A).

The capacity to repair nuclear envelope rupture generally is robust and efficient [103, 106]. However, taxane-induced micronucleation likely stretches the nuclear membrane extensively, and the size and extent of the rupture overwhelm the repair capacity, resulting in irreversible nuclear membrane rupture and cell death (Figure 3B).

Roles of nuclear envelope biology in taxane resistance

With the recognition of mechanisms of cell death by taxanes treatment through micronucleation and subsequent nuclear membrane rupture, the possibilities of mechanisms and genes/proteins involved in taxane resistance are expanded. The propensity of the cells to undergo taxane-induced micronucleation and the ability of these micronucleated cells to recover are potential factors for taxane resistance (Figure 4(1)). These factors include the malleability of the nuclear envelope, which is determined by the expression of nuclear lamins and their modification (Table 1). As such, Lamin A/C levels determine the sensitivity of cells to paclitaxel [20, 61], and cancer cells are more sensitive to taxane because malignant cells often have reduced Lamin A/C levels [85]. Thus, an increased Lamin A/C proteins would render cells more resistant to taxanes.

Phosphorylation of Lamin A/C leads to reduced polymerization to form lamina and protein stability, thus, reduction of lamin kinases would increase Lamin A/C and resistance to taxane (Table 1). In contrast, increases in phosphor-lamin phosphatases would enhance Lamin A/C function and stability and boost taxane resistance.

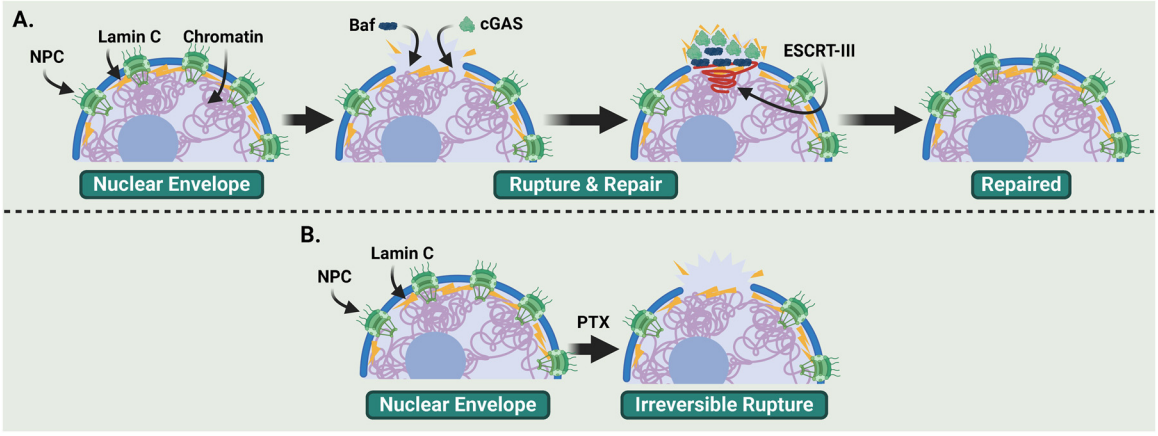

Figure 3: Nuclear envelop rupture and repair: hypothesis of paclitaxel-induced irreversible nuclear rupture. (A) The nuclear envelope consists of a double membrane and lamina layer imbedded with nuclear pore complexes (NPC). Transient rupture of nuclear envelope is repaired following recruitment of Lamin C, cGAS, and Baf to the rupture site, and sealed by ESCRT-III complex. (B) It is observed and proposed that paclitaxel-induced nuclear envelope rupture is extensive and irreversible, often beyond the capacity of the repair machinery.

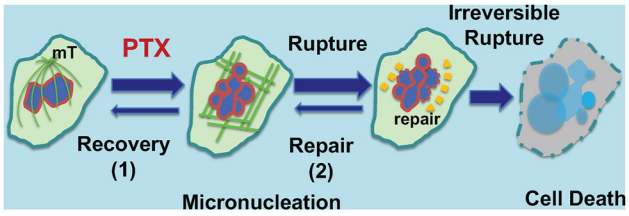

Figure 4: Taxane-resistance related to nuclear envelope: micronucleation and nuclear envelop rupture and repair. (1) Paclitaxel (PTX) and other taxanes promote the stabilization and bundling of microtubules (mT), and the breaking of the nuclear envelope and the formation of multiple micronuclei. The propensity of the nuclear envelope to undergo micronucleation and its ability to recover are factors in taxanes resistance. (2) The membranes of the micronuclei of the micronucleated cells are defective, and irreversible rupture leads to cell death. The heightened ability to undergo repair of the envelope ruptures may be a mechanism contributing to taxane resistance. The rupture of nuclear membrane (red line) is depicted by the dashed line. The dashed yellow lines represent factors of the membrane repairing machinery (Lamin C, cGAS, and Baf recruited to the rupture site, and the ESCRT-III complex).

Table 1: List of potential factors in taxane resistance related to nuclear envelope.

Factors	Genes/ proteins	References
Lamina: nuclear envelope malleability		
Nuclear lamin	Lamin A/C; Lamin B1/2	Smith et al. (ref. [20, 61])
LINC	Nesprin-1, 3; SUN	Smith & Xu (ref. [19])
Nuclear lamina modification by phosphorylation and acetylation		
Lamin kinases	AKT; ATR	Bertacchini et al. (ref. [89]); Kovacs et al. (ref. [91])
Lamin kinase: CDKs	CDK1, CDK4	Nakayama et al. (ref. [107])
p-Lamin phosphatases	PP2A; PP1A	Hunt (ref. [93])
Lamin acetylation	MOF; HDAC	Karoutas & Akhtar, (ref. [99]); Karoutas et al. (ref. [97])
Nuclear envelope repair		
Lamins	Lamin C	Kono et al. (ref. [105])
Chromatin binding	BAF; cGAS	Halfmann & Roux, (ref. [102])
ESCRT-III complex		
	CHMP4C	Zhang et al. (ref. [108])
Nuclear envelope reformation from multi-micronuclei		
Lamins	Lamin A/C	Smith et al. (ref. [20, 61])
Chromatin binding	BAF	Margalit et al. (ref. [109])
Lamin kinases	CDKs	Nakayama et al. (ref. [107])
p-Lamin phosphatases	PP2A	Hunt (ref. [93])

A report proposes that acetylation of Lamin A/C also provides function and stability of the assembled lamina, and blocking of Lamin A/C acetylation leads to nuclear envelope malleability and promotes micronucleation [97–99]. Accordingly, the genes/proteins that mediate Lamin A/C acetylation and de-acetylation may also determine taxane sensitivity and resistance (Table 1).

The rupture and repair of the nuclear membrane are also factors affecting the ability of cells to recover from taxane cytotoxicity and a heightened ability of the cells to repair nuclear envelope ruptures may be a mechanism contributing to taxane resistance (Figure 4(2)). If the activity and robustness of these repair mechanism are increased, then this may be a circumstance for cancer cells to develop resistance to taxanes. In this situation, altered genes/proteins involved in nuclear rupture and repair may contribute to taxane resistance (Table 1).

An incomplete list of the potential factors involved in micronucleation and the repair of nuclear envelope rupture may contribute to the resistance of the cancer cells to taxanes (Table 1). These genes/proteins will provide us with notions in future integration of data from profiling and investigating tumor specimens in the study of drug resistance.

Summary

A new mechanism of taxane-induced cancer cell death and taxane resistance related to nuclear envelope sturdiness has come to light in the past few years [19, 20, 67]. This proposal adds another category to the decades-old list of taxane resistance mechanisms including drug pumps, apoptosis, and microtubules.

In this new understanding of how taxanes kill cancer cells by inducing micronucleation and nuclear envelope rupture, two aspects of cell biology may contribute to the resistance of taxanes: the nuclear lamins that determine nuclear envelope sturdiness and its propensity to break, and the repair machinery for nuclear envelope rupture. These concepts may provide clues for us to investigate clinical cases and tumor specimens to determine if proteins involved in the processes are altered in taxane resistant tumors and to develop new strategies to overcome drug resistance.

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Research ethics: This is a review article. The local Institutional Review Board deemed the study exempt from review.

Informed consent: Not applicable.

Author contributions: ERS, ZSC, and XXX discussed and produced the initial idea. All authors participated in an extensive literature review and discussion of the topic to develop the concepts underlying the basis of the article. APX collected and extracted information from the cited references. All authors participated in drafting one or more sections of the article, and especially APX contributed to many parts of the article. LBX made and improved illustrations and figures, and JSH produced the final artistic illustration. XXX assembled and prepared the first draft, and all authors edited and agreed to the final version.

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Data availability: Not applicable.

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