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To cite this version:

Marta Smoter, Lubomir Bodnar, Renata Duchnowska, Rafal Stec, Bartlomiej Grala, et al.. The role of Tau protein in resistance to paclitaxel. Cancer Chemotherapy and Pharmacology, 2011, 68 (3), pp.553-557. 10.1007/s00280-011-1696-7 . hal-00713061

HAL Id: hal-00713061

https://hal.science/hal-00713061v1

Submitted on 29 Jun 2012

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The role of Tau protein in resistance to paclitaxel

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ABSTRACT

Resistance to taxanes, related to limited efficacy of systemic therapy in cancer patients, is multifactorial. Among mechanisms of resistance to taxanes, those related to microtubule-associated proteins (MAP), including protein tau, are of great importance. Protein Tau (50-64 kD) binds to beta tubulin in the same place as paclitaxel. In preclinical studies low expression of Tau in cancer cells was associated with increased sensitivity to paclitaxel. High expression of Tau protein in ER-positive breast cancers indicates resistance to taxane-containing chemotherapy and sensitivity to hormonal treatment. This article reviews current knowledge on predictive value of protein Tau in response to taxanes. Better understanding of its role may facilitate patients selection to this sort of treatment and lead to treatment optimization.

Key words: protein tau, microtubules, taxanes, chemoresistance

INTRODUCTION

Taxanes, which are widely used in clinical practice in the treatment of gynaecological cancers (ovarian cancer, cervical cancer, endometrial cancer), as well as many others (breast, gastric, non-small-cell lung cancer), are known to improve the patients' outcome and prognosis. However, it is likely that some patients do not benefit from the treatment due to the chemoresistance mechanisms.

Intrinsic chemoresistance appears on the early stage of carcinogenesis and involves the lack of response to the first line systemic treatment. Acquired chemoresistance results from mutations and epigenetic changes in the cells previously sensitive to the treatment.

Taxanes, paclitaxel and docetaxel, interfere with spindle microtubule dynamics causing cell cycle arrest and apoptosis. Protein Tau, one of microtubule-associated proteins (MAP) may interact with paclitaxel due to the binding to beta tubulin in the same point.

This paper approaches the mechanisms of taxanes activity, mechanisms of resistance to these agents, with a particular consideration of the role of protein Tau in the process.

MECHANISMS OF PACLITAXEL ACTION

Paclitaxel was derived from the bark of the Pacific yew tree, *Taxus brevifolia* in 1962. Currently, it is produced in semisynthetic way from *Taxus baccata*, and since 1992 it has been widely used in clinical oncology.

Paclitaxel activity is connected with the spindle, consisted of microtubules. While paclitaxel binds to a pocket in beta tubulin, on microtubule's inner surface, the microtubule depolimerisation process is inhibited.[1] Microtubules, usually dynamically unstable, are changing into stable structures. It unables spindle division and causes cell cycle arrest in phase G1/G2 of mitosis.

Cytotoxic effect of paclitaxel results also from induction of apoptosis by regulation of tumor suppressor gene p53, as well as genes bcl-2 and bax. Disruption of microtubules results in induction of an inhibitor of cyclin-dependent kinases p21WAF1/CIP1 (p21) and leads to phosphorylation of Bcl-2, associated with protein kinases.[2] Phosphorylation of Bcl-2 protein induces the apoptosis. Ling and al. noticed increased phosphorylation of Bcl-2 in cervical cancer cells HeLa subjected to paclitaxel, which caused cell cycle arrest in phase M of mitosis.[3]

Furthermore, Ferlini et al. [4] showed that paclitaxel binds directly to Bcl-2 which elicits the apoptosis. The authors presented an unique similarity between the paclitaxel binding sites in Bcl-2 and beta tubulin. They also confirmed that paclitaxel mimics Nur77, an endogenous peptic ligand, in its structure and activity.

Paclitaxel enhances apoptosis through p53-indepentent way, that probably involves bax gene. Patients with mutant p53 tumors benefit from addition of paclitaxel to platinum-based chemotherapy.[5,6] The inverse resistance to paclitaxel and platinum agents, seen on cell models, explains the clinical use of such chemotherapy combination.[7]

MECHANISMS OF THE RESISTANCE TO PACLITAXEL

Mechanisms of the resistance to chemotherapy are complex and still rather little studied processes. They include cellular transport disorder, aggravation of detoxication, enhancement of DNA repair and interference with apoptosis. Additionally, resistance to taxanes results also from alterations in microtubule dynamics.

In preclinical studies, P-glycoprotein (P-gp) efflux pomp, a product of the multidrug resistance gene MDR1, was identified as membrane-associated ATP-binding cassette transporter which decreased intracellular drug levels. In many tumour cell lines, where P-gp was overexpressed, drug cytotoxicity was limited. High P-gp expression is related to cross resistance to the following chemotherapeutics: anthracyclines, vinca alkaloids, epipodophyllotoxines and taxanes. However, the role of P-gp in clinical practice has not been established.

Changes in genetic material, caused by chemotherapy, lead to p53 gene activation and beginning of DNA repair. When DNA damage is too large or repair mechanisms not adequate, apoptosis starts.

Tumour cell lines researches revealed that p53 gene mutations are involved with drug resistance and reversal of its functions sensitize tumour cells to chemotherapy.[8] It is likely that the resistance to chemotherapy in the cells with mutant p53 gene, might be broken by the use of drugs, which omit p53-dependent track of apoptosis, such as microtubule-targeting agents, for example – taxanes.[9] Additionally, ovarian cancer patients with mutated p53 gene treated with paclitaxel better respond to the therapy (86% of them) than patients with natural p53 gene (47%).[10]

It is possible that the resistance to paclitaxel might be caused also by the mechanisms involved with microtubules and MAPs as the main target of taxanes action. Microtubules are components of the cytoskeleton and with the variety of functions such as intracellular transport, maintenance of cell shape, polarity, cell signalling and mitosis.[11] They form mitotic spindle that transports daughter chromosomes to separate poles of the dividing cell. And that is why the anti-microtubule agents inhibit cancer cells multiplication. Microtubules are polymers of alpha and beta tubulin heterodimers, building tube-shaped filaments, with (-) and (+) endings.[12] Microtubules, with their dynamic nature, constant growing and shortening, caused by the GTP-dependent association and dissociation of the heterodimers at the both ends, are the crucial organelle during cell division. Microtubule associated proteins

(MAP) are attached to the microtubule organising center (MTOC). Some of them stabilise microtubules structure (MAP2, MAP4, tau, STOP, Mip-90, statmin), other modulate microtubule space arrangement (MAP1, MAP2, Tau) or unable the organelle migration among microtubules (kinesin, dynein, dynamin).[13]

Resistance to paclitaxel might result from the changes in microtubule structure. Some preclinical studies showed the correlation between overexpression of beta tubulin class III or class IVa and resistance to paclitaxel.[14,15] Poor prognostic value of the overexpression of beta tubulin class III or its influence on paclitaxel resistance was also confirmed in some clinical studies.[16,17,18,19] On the other hand, the role of Tau and delta2-alpha tubulin [17] nor statmin or MAP4 [20] was not confirmed in the process. Studies assessing the prognostic value of beta tubulin class III and the correlation between its expression and benefit from paclitaxel are listed in the Table 1.

Table 1

STRUCTURE OF TAU PROTEIN AND ITS ROLE IN THE RESISTANCE TO PACLITAXEL

Tau protein (50-64 kD), a product of gene located in chromosome 17 (17q21), was described for the first time in 1975.[21] Six isoforms are found which are assigned to one of two groups, depending on the number of domains combined to tubulin (3R group includes Tau-3L, Tau-3S, Tau 3; while 4R group includes: Tau-4L, Tau-4S, Tau-4). Tau activity is regulated in the phosphorylation processes by serin threonin kinases.[22]

As one of the MAPs, Tau shows the ability of combining to tubulin. It may bind to the exterior as well as interior microtubules surface, in the same binding site as paclitaxel, and consequently compete with this drug. The loop combined with Tau stabilizes microtubules in the same way as paclitaxel, but with greater reversibility.[23] Tau overexpression enhances the polymerization and diminishes cells flexibility.[24]

The role of Tau in the regulation of processes in the nervous system is quite well-known. Overphosphorylation of this protein, occurring mainly in the axons, leads to neurofibrillary degeneration and is probably involved with cells dysfunction and death. They are significant in pathogenesis of Alzheimer disease as well as the other “taupathies” (Pick’s disease, Parkinson disease and frontotemporal dementia), which demonstrate clinically with limitation of cognitive functions.[22]

SIGNIFICANCE OF TAU IN CANCER DISEASES

The attempt to define the prognostic and predictive value of Tau expression concerning mainly breast cancer patients treated with taxanes has already been undertaken by some researchers.

Several studies indicated that patients with low Tau expression benefit from paclitaxel therapy.[25,26,27,28,29] Among 82 breast cancer patients who were applied with paclitaxel-based neoadjuvant chemotherapy those with low Tau mRNA expression achieved complete pathologic response more frequently, with the statistical significance ($p<0.001$). At the same time, high Tau mRNA expression was significantly associated with no recurrence (at 5 and 10 years; $p=0.005$ and $p=0.05$, respectively) in patients treated with tamoxifen, indicating a predictive value for endocrine therapy. Additionally, high Tau mRNA expression showed borderline non-significant association with better prognosis in the patients not receiving systemic adjuvant therapy.[25]

Tumours with pathologic complete response (pCR) to preoperative paclitaxel-containing chemotherapy had significantly lower Tau mRNA expression. Therefore, Tau expression was assessed immunohistochemically (IHC) in 122 independent patients applied neoadiuvant paclitaxel-based treatment.[26] Among 31% of the patients who achieved pCR, 74% of them had low Tau protein expression (0,1+). The odds ratio for pCR in tau-negative tumours was 3.7 (95% CI; 1.6-8.6; $p=0.0013$). Furthermore, suppression of Tau expression in breast cancer cell lines (*in vitro*) with small interfering RNA (siRNA) increases their sensitivity to paclitaxel, but not epirubicin.[26]

Low expression of Tau protein (IHC) was correlated with better time to disease progression in advanced breast cancer patients (n=35) treated with paclitaxel. 60% of tau-negative patients responded to chemotherapy, while 85% of tau-positive presented progressive or stable disease.[27]

Other study, including 54 advanced breast cancer patients receiving paclitaxel and cisplatin showed that high Tau protein expression (IHC) is an independent good prognostic factor, while low Tau protein expression predicts response to chemotherapy.[28]

Significance of Tau expression was also evaluated in one study concerning different than breast cancer site. The analysis revealed that low Tau protein expression (0;1+) in advanced gastric cancer patients may predict benefit from paclitaxel-containing treatment. All the patients with low Tau expression had clinical response confirmed in computed tomography (CT) examination. 86% of the patients with high Tau expression (2+; 3+) did not

take any advantage from this therapy. Even though the study group was not numerous (n=20), the results are suggesting that Tau expression may predict the response to paclitaxel.[29]

Conversly, in the retrospective analysis of 274 high-risk early breast cancer patients treated with paclitaxel, the predictive role of Tau was not confirmed.[30] The authors studied the prognostic and predictive role of estrogen receptor (ER) mRNA, progesterone receptor (PgR) mRNA and Tau mRNA. Higher sensitivity to paclitaxel in low Tau RNA tumours was observed only in ER-negative patients, but not in ER-positive. It is possible, that paclitaxel treatment effects in low Tau RNA patients receiving also hormonal therapy (ER-positive) were interfered by resistance to hormonal therapy. Tau mRNA expression is induced by estrogen and correlates with ER expression.

It was noticed for the first time that high Tau mRNA expression was significantly associated with reduced risk of relapse (HR=0.50; 95% CI; 0.32-0.78; p=0.002) and death (HR=0.49; 95% CI; 0.29-0.83; p=0.008) in high-risk early breast cancer patients. Consequently, high Tau mRNA was related to good prognosis in these patients. Nevertheless, its significance in predicting the response to taxanes or hormones remains unclear. Considering relationship between Tau and estrogen, further studies with the separate analysis of ER-positive and ER-negative patients are warranted.

In the presence of contradictory results of the studies, the retrospective analysis of 1942 breast cancer patients enrolled to NSABP-B28 study, was of the great interest.[31] The predictive and prognostic role of Tau expression in breast cancer patients was assessed. The ER-positive and ER-negative patients were analysed separately.

The correlation between Tau and ER was confirmed. High Tau expression was more frequent among ER-positive patients (57%) than ER-negative (15%). It was likely that these disproportion resulted from the estrogen regulation of Tau gene. Tau expression is induced “in vitro” by estrogen as well as tamoxifen. In case when ER-positive patients were receiving tamoxifen for 5 years, Tau expression could increase progressively during the therapy, comparing to the initial record.

Co-expression of Tau and ER was considered as a good prognostic factor, involved with better overall survival (OS) as well as disease free survival (DFS). ER-positive tumours with high Tau expression are sensitive to hormonal therapy and poorly respond to paclitaxel-containing chemotherapy. In ER-negative tumours, prognostic value of Tau was not confirmed, but non-significant trend of better response to paclitaxel was noticed.

The authors of that study concluded that, high Tau expression in ER-positive patients is good prognostic factor, but, despite of ER status, predictive value of Tau for paclitaxel

treatment was not proved. The studies assessing prognostic and predictive value of Tau are listed in the Table 2.

Table 2

SUMMARY

Some studies revealed that low Tau expression is involved with better response to paclitaxel.[25,26,27,28,29] Studies with numerous groups of patients receiving paclitaxel did not confirm predictive value of Tau protein.[30,31] Non-significant trend of higher sensitivity to paclitaxel in ER-negative tumours suggests that Tau interactions with estrogen and tamoxifen may influence the results. Furthermore, mechanisms of resistance are complex and hard to explain on the basis of one marker. It is possible that predictive value of low Tau expression does not exist or the other molecular mechanisms, such as tubulin mutations, expression of multidrug resistance proteins or Bcl-2, prevail its significance.

Modulation of response to taxanes by reduction of Tau expression with siRNA remains a very interesting phenomenon even though it had good results only in preclinical researches on cancer cell lines.[26]

At the same time, high Tau expression was confirmed as a good prognostic factor, however in one study this correlation was observed only in ER-positive breast cancer tumours.[28,30,31]

In conclusion, Tau expression might be an important biomarker of resistance to paclitaxel in other cancers treated with taxanes. Its predictive and prognostic significance should be evaluated in well-projected prospective studies. There is no doubt that treatment individualisation with determination of predictive factors enhances benefits from the treatment and reduces its toxicity.

Conflict of Interest Statement.

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

Role of the Funding Source. The authors declare no sponsors involvement into the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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Table 1. Studies on the correlation between expression of beta tubulin class III and resistance to paclitaxel.

Author	Cancer site	Expression of beta tubulin class III	Benefit from paclitaxel	Prognostic value of beta tubulin class III
Burkhart CA et al. [14]	Breast, lung	↑	No	Not assessed
Kavallaris M et al. [15]	Ovary	↑	No	Not assessed
Seve P et al. [16]	Unknown	↑	No	Poor
Seve P et al. [17]	Unknown	↑	No	Poor
Seve P et al. [18]	NSCLC	↑	No	Poor
Ferrandina G et al. [19]	Ovary	↑	Not assessed	Poor
Aoki D et al. [20]	Ovary	↑	Yes	Not assessed

Abbreviation: NSCLC: non-small-cell lung cancer

Table 2. Predictive and prognostic value of Tau.

Study	n	Method of Tau evaluation	Prognostic value	Predictive value for paclitaxel treatment
Andre F et al. [25]	82	mRNA	Possible (borderline significance)	Yes
Rouzier R et al. [26]	122	Tau protein (IHC)	Not assessed	Yes
Tanaka S et al.[27]	35	Tau protein (IHC)	Not assessed	Yes
Shao YY et al. [28]	54	Tau protein (IHC)	Yes	Yes
Mimori K et al. [29]	20	Tau protein (IHC)	Not assessed	Yes
Pentheroudakis et al. [30]	274	mRNA	Yes	No (non-significant trend for ER-)
Pusztai L et al. [31]	1942	Tau protein (IHC)	Yes (for ER+)	No

Abbreviation: IHC: immunohistochemistry;