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Review

Tau: at the interface between neurodegeneration and cancer?

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Abstract: For its microtubule-binding properties, the expression level of the neurodegeneration-associated protein Tau is pondered as a potential modifier of cancer resistance to chemotherapy since decades. Indeed, Tau binds microtubules at the same site as taxanes, a class of chemotherapeutic drugs designed to stabilize the microtubule network in order to stall cell division and to induce tumor cell death. Whilst independent studies report the association between low Tau expression and superior taxane response, the data were refused by a meta-analysis, suggesting interference of other parameters. Unpredictably, Tau expression level was identified as a prognostic cancer marker, whereby its positive or negative predictive value for survival depended on the cancer type. With recent experimental evidence linking Tau to P53 signaling, DNA stability and protection and to the implication of Tau in cancer is strengthened. The identification of a role of Tau at the interface between two major aging-related disorder families, neurodegeneration and cancer, offers clues for the epidemiological observation inversely correlating these disorders. Elucidating how Tau is mechanistically implicated in cellular pathways common to these devastating illnesses may extend the Tau-targeting therapeutic opportunities to cancer.

Keywords: neurodegeneration; tauopathies; cancer, Tau protein, DNA protection

Coming together: neurodegenerative diseases and cancer, do they share dysregulated pathways?

Neurodegenerative diseases and cancer may appear unrelated disorder families. However, a rapidly expanding body of literature describes the dysregulation, often in opposite directions, of the same proteins or cellular pathways in both disorders. A prominent example is the sharing of altered cellular functions in response to genotoxic stress, with mutations in genes involved in regulation of cell cycle, DNA repair, oxidative stress, cell death and autophagy implicated in both disorders[1-6].

The fundamental abnormality resulting in oncogenesis is a faulty molecular machinery controlling cell division and cell death. Rather than responding appropriately to the signals that restrain cell growth, neoplastic cells divide and invade normal tissues with the potential to colonize multiple organs. In contrast, differentiated neurons display specific molecular and morphological signatures that prevent them from further cell division. Nevertheless, expression of cell cycle activators persists in post-mitotic neurons and, possibly causing neuronal death, they further respond to stress conditions such as trophic factor deprivation, oxidative overload or DNA damage[7]. In fact, hallmarks of DNA replication and active cell cycle are observed in post-mitotic neurons of patients suffering of a neurodegenerative process such as in tauopathies, which include Alzheimer's disease (AD)[8,9]. As in cancer, substantial DNA damage and genetic instability are linked to neurodegeneration[4,10,11]. This evidence conveys the postulation that neurodegeneration, like cancer, is a disease of inappropriate cell-cycle control and/or cell death as a consequence of DNA damage. Reinforcing this notion, an established risk factor for oncogenesis and progressive chronic neurodegeneration is aging - a manifestation of time-dependent accumulation of harmful genetic

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insults[12]. Indeed, both disorder families share key cellular and molecular hallmarks of physiologic aging: genomic instability, telomere shortening, epigenetic alterations, proteostasis loss, nutrient sensing dysregulation, mitochondrial dysfunction, cellular senescence, and altered intercellular communication[13]. Large genome-wide association studies point to genetic components shared between AD and five cancer types (colon, breast, prostate, ovarian, lung) with the largest overlap reported for gene sets described as expression regulators[14]. Whilst some variants modulate in the same direction the risk for both diseases, other variants act in opposite manner.

Epidemiological studies associate neurodegeneration and cancer

Concrete arguments in favor to the concept formulated in the previous paragraph arise from intriguing epidemiological interrelations, which reinforce that the occurrence of neurodegeneration and cancer is the outcome of environmental or genetic factors implicated in shared cellular pathways. An inverse association between oncological and neurodegenerative diseases appears across a variety of cancer types. Indeed, cancer survivors present decreased incidence for AD, Parkinson's disease (PD) and Huntington's disease (HD), and vice versa[15-23]. This suggests that a propensity towards one family of diseases may decrease the risk for the other. As an example, AD patients are less prone to develop lung cancer[24-27], and a history of smoking related cancers has a protective impact against AD[15]. Also for amyotrophic lateral sclerosis (ALS) a decreased frequency of cancer is observed after disease onset[28], although a cancer diagnosis does not affect the occurrence of ALS[29,30]. In contrast, a positive correlation is observed between cancer and aging-related disorders such as stroke, macular degeneration, non-neurodegenerative dementia, and osteoarthritis[16,19,20,22,31]. This is also true for the positive association of PD with melanoma and prostate cancer[31-35]. Cancer chemotherapy is also associated with a lower incidence of AD[36], whereas some pharmacological interventions for e.g. breast cancer disturb white matter structures and neuronal connectivities[37].

The interpretation of epidemiologic studies is complex and confronted with the challenge of identifying the molecular mechanisms influencing occurrence, pharmacological treatment and ultimately the survival of patients affected by one or the other of the two disorder families[38,39]. Incidentally, genes that are strongly associated to neurodegenerative diseases, i.e. because their products are the main constituents of hallmark brain deposits and they may lead to early-onset inherited disease forms, do not exhibit typical features of oncogenes or tumor suppressors. However, a recent analysis of cancer incidence in carriers of FTDP-17 *MAPT* mutations showed increased risk of developing cancer[40]. The tumor types occurring in FTDP-17 families were variable (hematological, lung, breast, and colorectal cancers) suggesting that mutations in TAU, the protein encoded by the *MAPT* gene, may present predisposing oncogenic elements for genomic instability without tissue specificity[40]. In agreement with these data is the increased chromosomal aberration detected in lymphocytes and fibroblasts isolated from carriers of FTDP-17 *MAPT* mutations[41].

TAU is generally described as a protein highly expressed in the central nervous system. Yet, TAU is also present in skeletal muscle, breast, kidney, prostate and in cultured fibroblasts[42-49], and at a lower level in the intestine, skin, liver, and submandibular gland[50]. The human brain express at least six TAU isoforms with molecular weights ranging from 45 to 65 kDa[51,52] generated by alternative splicing of exons 2, 3 and 10 out of the 16 exons composing the *MAPT* gene[51]. The number and relative amount of the TAU splice variants vary in a cell type specific manner, during development and depending on the clinical features of neurodegenerative diseases[51,53,54]. Adding complexity, TAU proteins are modified by a considerable number and variety of posttranslational modifications; which become markedly increased in disease, as e.g. for the hyper-phosphorylated form characterizing tauopathies[51,53,55,56]. A detailed analysis of the TAU species present in peripheral tissues was initially performed in rodents[57]. This led to the identification of a TAU isoform with an apparent molecular weight >100 kDa ("big TAU"), generated by an unspliced 4a exon, present in rat peripheral tissues [52] and in nearly all central nervous system neurons projecting to the periphery[58]. Similar finding were reported in humans [59], with big TAU along additional low molecular weight TAU species present in peripheral tissues [50]. A detailed analysis of TAU

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expression at the level of mRNA, protein and post-translational modifications is crucial to better demonstrate and understand the role played by TAU in neoplastic diseases. However, the study of the efficacy of a therapeutic intervention as a function of protein expression already delivered evidence for a role of TAU in cancer.

TAU and microtubule-targeting chemotherapy

The mitotic spindle is the critical structure organizing the microtubule scaffold enabling chromosomal segregation and cell division. So, targeting microtubules represent a successful mode of action for cancer chemotherapy. A classic example of this class of drugs are taxanes, which bind beta-tubulin at the microtubule inner surface and inhibit microtubule depolymerization. In the presence of taxanes, microtubules are frozen in stable structures due to the inhibition of the dynamic assembly and disassembly. Consequently, taxanes restrict spindle activity and arrest the cell cycle in the G1/G2 phase of mitosis. The cytostatic effect of taxanes results in the subsequent induction of apoptosis, which is partly regulated by the tumor suppressor P53[60]. The taxane Paclitaxel present in the bark of the Pacific yew tree, is produced in a semisynthetic way from *Taxus baccata*, and is used in clinical oncology since almost three decades[61]. The therapeutic efficacy is frequently limited by the resistance to taxanes observed in certain cancer types. Possible causes include the action of xenobiotic efflux pumps, alterations in apoptotic and signal transduction pathways, and abnormalities in target engagement modulated by microtubule interacting proteins[62]. The microtubule-binding protein TAU competes with taxanes for the same binding site on tubulin[63]. Consequently, increased cellular concentration of TAU or its affinity to microtubules are considered factors protecting microtubules against taxane therapy[64-66], and are thus assessed as predictors of therapeutic efficacy for microtubule-targeting drugs[47,63,67]. As an example *MAPT* is the most differentially expressed gene as a function of response to preoperative Paclitaxel intervention in breast cancer[47], whereby low TAU mRNA predicted complete response to taxanes, as confirmed also in additional studies[64,68]. In estrogen receptor (ER)-negative breast cancer, the correlation between low TAU expression and ER status may explain the higher sensitivity to Paclitaxel[47]. Low TAU reflected by a better response to taxanes is reported also in ovarian[69,70], gastric[71], prostate[72] and non-small-cell lung cancer[73]. Notably, retinoic acid-induced TAU expression in neuroblastoma cells results in increased resistance to Paclitaxel[74], although this may be related to their differentiation state. These results feed the concept that anti-TAU drugs may be exploited as a strategy to improve the outcome of taxane-based chemotherapies. Nevertheless, some studies came to an opposite conclusion and several Paclitaxel trials did not confirm the predictive value of TAU determination[75-77]. The discordance between these studies may result from the choice of chemotherapy regimen, the taxane used, the cancer type, and possibly from the limitation imposed by the analysis of a single marker. Additional insights were gained by employing cellular models. Taxane-resistant prostate cells express higher level of TAU compared to parental lines, whereby TAU modulation of PI3K signaling may play a role[78]. The microRNA miR-34c-5p regulates *MAPT* gene expression in gastric cancer cell lines thereby modulating the sensitivity to Paclitaxel[79], whereas in non-small cell lung cancer cells the same effect was modulated by miR-186[80]. The selective ER inhibitor Fulvestrant, differently to Tamoxifen, reduces all TAU protein isoforms and increases taxane sensitivity in ER-positive breast cancer cells[81]. It appears from all these studies that modulation of TAU expression in cancer cells from diverse origins impacts the response to taxanes[65].

Use of TAU as a cytostatic drug

The microtubule-binding characteristic of TAU was exploited in order to generate fusion proteins for a biological therapy based on the targeted delivery of cytostatic molecule to malignant cells. This can be achieved using bifunctional molecules incorporating a targeting and a cytotoxic element. The ability to bind microtubules and thereby act as an anti-mitotic drug was the reason to select TAU as cytotoxic component. A tailored protein fusion of TAU with EGF causes selective

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induction of apoptosis in EGFR-positive pancreatic cancer cells[82], a finding confirmed in other models[83].

TAU and cancer

The modulatory effect of TAU on the potency of microtubule-targeting compounds suggests an active participation of TAU also in the oncogenic process. This likely role of TAU is expected to go beyond its function in modification of microtubule dynamics as suggested by the recently described atypical subcellular localizations, i.e. not associated to the cytoskeleton. Our laboratory has shown that nuclear translocation of TAU is likely to be unrelated to microtubule binding[84]. An important evidence in support to this claim is derived by the analysis of *MAPT* transcription and TAU protein expression in healthy and neoplastic tissues, also performed *in silico* on available cancer databases. In the following paragraphs, we review the outcome of these studies for distinct cancer types.

For breast cancer, TAU protein expression did not correlate with tumor size or nodal status or patient age, but had a prognostic value for outcome and survival independently to the therapy[75-77,85,86]. A positive correlation between TAU expression and the receptors for estrogen (ER) and progesterone (PR) expression was confirmed in multiple studies, in particular for low grade, ER/PR-positive, and HER2-negative cancers [75-77,85-87]. An inducible imperfect estrogen response element was identified upstream of the *MAPT* promoter[87-93], which is consistent with the endocrine sensitivity of TAU- and ER-positive tumors[77]. Among a panel of breast cancer cell lines with different levels of TAU mRNA and TAU isoforms, down-regulation of ER expression and the presence of ER inhibitors affected TAU expression in a cell-specific manner[81,89,94,95]. The inverse correlation TAU/HER2 is remarkable due to the proximity of the two genes in the 17q12 chromosomic region. A thorough analysis of the TCGA cohorts in tumors with high or low TAU expression, demonstrates a positive correlation between *MAPT* transcription and overall survival of patients with breast cancer[96]. However, a study aiming at understanding how circulating tumor cells reattach in distant tissue indicate that in metastatic breast tumor TAU is more expressed and that TAU microtubule binding is necessary and sufficient to promote tumor cell reattachment[97].

For ovarian cancer, immune histochemical analysis shows that about 75% of the cases were TAU-positive and 25% TAU-negative and, notably, 3-year survival was significantly higher in the TAU-negative when compared to the TAU-positive group[69]. These data suggest, in contrast to breast cancer, that high TAU expression is associated with an unfavorable prognostic. However, the results were not confirmed in the TCGA cohorts[96], which is based on gene transcript assessment rather than on protein determination. In view of the complex regulation of TAU protein homeostasis at the level of translation and post-translational modification, a careful TAU protein analysis may be more informative in this context. Notably, the endometrioid carcinoma TOV112D cells showed the highest TAU protein expression among a panel of ovarian cancer cell lines and TAU knock-down inhibited cell proliferation[70], in accordance with the favorable prognostic associated to low TAU expression[69].

An early study in prostate cancer found that TAU protein overexpression was associated with lower Gleason score in a cohort of 30 patients[98]. The use of a dephosphorylated-specific TAU antibody, demonstrated the absence of phosphorylation at the Tau-1 epitope in neoplastic prostate tissue[98]. Immune histochemical analysis on a tissue microarray containing 17,747 prostate samples showed under the selected experimental conditions detectable TAU expression in 8% of the cancer samples and no measurable TAU in the normal tissue, evidence for TAU overexpression as a moderate prognostic feature in a small prostate cancer subset[99]. TAU expression was associated with advanced tumor stage, high Gleason score, positive nodal stage, and risk for recurrence in all cancers independently of the ERG status[99]. About half of prostate cancers are due to gene fusions linking the androgen-regulated transmembrane protease TMPRSS2 with the transcription factor ERG[100,101] resulting in a massive androgen-dependent overexpression of ERG. Other somatic mutations associated to prostate cancer include PTEN genomic deletions, which positively associate to TAU expression with the highest *MAPT* transcription observed in ERG positive cancers. This observation is possibly linked to the suggested regulatory function in microtubule dynamics of ERG

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[102,103], which binds and stabilizes soluble tubulin [104]. The association between high TAU expression and poor overall survival was confirmed in an independent study[105] also describing an inverse interaction between MAPT and PTEN in prostate cancer. However, the transcriptomic-based TCGA cohorts failed to show a positive or negative association between TAU expression and survival in the prostate cancer cohort[96]. A detailed analysis of TAU in prostate cancer cell lines, revealed high expression of multiple TAU splice variants, including big TAU and an previously undescribed variant [49], in comparison to e.g. the primarily fetal TAU isoform present in human neuroblastoma SH-SY5Y cells[106,107] or the six main isoforms described in normal adult human brain[53]. Moreover, the TAU phosphorylation pattern observed in prostate cancer cells reflects what observed in tauopathies when compared to healthy adult brain with a large proportion of TAU not bound to microtubules[49]. Association of TAU to PI3K suggests a microtubule-independent mechanism possibly linked to cell signaling[49,108]. Consistent with this, in docetaxel-resistant prostate cell lines[109] TAU down-regulation inhibits cell proliferation by the PI3K/mTOR signaling pathway[110].

The value of TAU as a biomarker for disease-free survival rate was shown by comparing the bottom and top 20% *MAPT* transcript expressers in low-grade glioma (TCGA data set)[111]. Moreover, the histological tumor grade was inversely correlated with TAU expression. Consistent with these data, in the TAU mRNA-top quintile group, transcriptional activity was higher for pro-apoptotic genes and lower for proliferation-associated genes. A similar analytical approach in pediatric neuroblastoma also revealed a better prognosis for the top quintile according to the *MAPT* transcript analyzed on microarray (NCBO BioPortal)[112]. Again, the data were substantiated with a significant correlation with apoptotic- and proliferation-linked genes. In contrast, increased survival was not associated to the mRNA for alpha-synuclein, another neurodegeneration-associated protein[112]. Evidence that transcription alterations for genes associated with neurodegeneration - with the exception of *MAPT* -are not common drivers of gliomas was confirmed in another study, suggesting an important role of TAU in slowing down or preventing the clinical evolution of these tumors[113]. Histochemical analysis showed that cells from low malignancy glioma display increase TAU protein expression, with the inverse observation for cells from more aggressive tumors. Gliomas with IDH1/2 mutations have a much better prognosis and response to therapy[114,115]. Notably, TAU expression is induced by mutant IDH so that TAU protein is increased in IDH1 mutated gliomas and is detected in the majority of tumor cells expressing the most common R132H IDH1 mutation. More importantly, mutant IDH enzymes favor a TAU-dependent normalization of the vasculature impairing tumor progression[113]. TAU-knockdown also slow-down migration in glioblastoma cell lines by a process that depends on the dynamics of microtubules and actin networks[116].

In colorectal cancer, CpG island hypermethylation in *MAPT* is found in about a quarter of the samples in a cohort with hundred stage II patients, but it was absent in normal colorectal mucosa[117]. A study inspired by the presence of methylation in the *MAPT* promoter in AD[118], PD[119] as well as prostate cancer[120]. *MAPT* hypermethylation is a marker for lower five-year survival indicating that, similarly to breast cancer, low TAU expression is linked to a worse prognostic in both cancers. However, these data are not confirmed by analyzing the TCGA database[96]. At the protein level, increased TAU phosphorylation at Ser199/202 is a predictor of non-metastatic colon cancer[121]. Consistent with a main hypothesis for AD, hyperphosphorylated forms of TAU with impaired microtubule binding were reported in colorectal cell lines[122].

TAU appears implicated in Bloom's syndrome, a rare genetic disorder resulting from homozygous mutations of the *BLM* gene with a high rate of spontaneous chromosome abnormalities and predisposition to cancer[123]. Mutated *BLM* cells experience replication stress and display chromosome segregation defects, but continue to divide indicating a tolerance for DNA damage. TAU was identified in a genome-wide RNAi screen and transcriptomic analysis as a critical protein enabling this phenotype. Indeed, TAU overexpressing Bloom's syndrome cells undergo cell death when TAU is down-regulated[123]. This is interpreted as TAU acting as a negative regulator of DNA damage-induced cell death.

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A comprehensive analysis of the TCGA cohorts shows positive association between TAU expression and survival in glioma, kidney clear cell carcinoma, lung adenocarcinoma and pheochromocytoma. In contrast, a negative association is found for colon and head and neck cancers, and no link to TAU was observed in the other cancer types[96].

The clinical and prognostic value of TAU analyzed at the mRNA and protein level has been investigated for many tumors with results crucially dependent on the cancer type. As an example high TAU protein expression is linked to a better prognosis in breast cancer, glioma, neuroblastoma and clear cell renal cell carcinoma[124] and to poor prognosis in ovarian cancer. Whereas conflicting results are reported for prostate and colorectal cancers. Whether the correlative studies implicating TAU in cancer will eventually demonstrate an active participation of TAU in oncogenesis requires undoubtedly further experimental evidence. As of today, the mechanisms that may explain if and how TAU differentially impact tumor cell aggressiveness in different cancer types remains at large poorly understood. As commented previously, transcriptome analysis does not take into account the pathogenic effects of protein homeostasis, which in the case of TAU is complex and tightly associated to disease. As in the case of neurodegenerative tauopathies, a detailed characterization of *MAPT* transcription and translation as well as the biochemical characterization of TAU protein including its modification and cellular distribution is now necessary in the studies linking TAU to cancer. Likewise important is the definition of the TAU interactom in health and disease.

The interaction of TAU with proteins linked to cancer

In order to unravel the role of TAU in cancer, both direct and indirect interactions between TAU and cancer-associated proteins should be pondered. Physiological TAU is considered a naturally unfolded, scaffold protein, with functional domains intercalated by disordered linker sequences, similarly to most neurodegeneration-associated proteins. Beside the well-established interaction with members of the tubulin family mediated by the microtubule binding domain, TAU binds to a broad pattern of partners, including other cytoskeletal components participating to the regulation of organelle and protein transport[125,126]. The function of TAU in RNA/DNA integrity (cross-reference to Colnaghi et al, same special issue) is likely to require the direct collaboration with kinases, phosphatases, chaperones and membrane proteins[54], protein families with documented tights to cancer development or suppression. The BioGRID interaction database reports over two hundreds TAU interactors[127]. Most relevant are considered those interactions that are confirmed by independent studies and experimental approaches, with the top five represented by GSK-3beta, CHIP, FYN, CDK5, and 14-3-3zeta. In the following paragraphs we will briefly discuss the evidence linking these gene products to cancer, extending the discussion to P53 and PIN1.

The serine/threonine glycogen synthase kinase-3 (GSK-3) was initially identified as a regulator of glycogen synthesis with follow-up evidence for participation to a wide range of cellular processes as highlighted by the identification of about hundred substrates. Aberrant GSK-3 activity is implicated in multiple pathologies including: cancer, bipolar depression, tauopathies and other neurodegenerative diseases, non-insulin-dependent diabetes mellitus and others, and is thus defined as a multitasking kinase[128]. In the context of cancer, GSK-3 functions as a tumor suppressor, e.g. when inactivated by Akt phosphorylation, or displays oncogenic properties, e.g. when stabilizing the beta-catenin complex. Consistent with this, the use of GSK-3 inhibitors remains controversial because of the ambiguous role of GSK-3 in human pathologies[129]. A complex containing TAU, CDK5 and GSK-3beta is present in the brain, with CDK5 phosphorylation of TAU at Ser-235 priming further phosphorylation by GSK-3beta at Thr-231. Alternatively, CDK5-mediated phosphorylation at Ser-404 favors sequential GSK-3beta phosphorylation at Ser-400 and Ser-396[130-132]. The likely contribution of this complex in TAU hyperphosphorylation implicated in neurodegenerative tauopathies suggest that a similar mechanism of protein modification may be implicated in clinically distinct disorders. In fact hyperphosphorylated forms of TAU are detected e.g. in colon cancer HCT116 cells[133] and in prostate cancer cells[49].

The serine/threonine cyclin-dependent kinase 5 (CDK5), is unique among the CDK family members in that it displays no cell cycle or mitotic function since for CDK5 no classical mediators of

 doi:10.20944/preprints202010.0349.v1

cell-cycle transition are known[134]. Its importance in cancer development and progression[135] is suggested by the positive correlation between high CDK5 expression and poor prognosis in pancreatic[136], lung[137], and thyroid cancer[138]. In liver carcinoma cells high CDK5 expression favors angiogenesis though HIF-1alpha stabilization[139,140], and facilitating prostate cancer cell migration[141].

FYN is a non-receptor tyrosine kinase that belongs to the SRC family kinases which under normal physiological conditions is involved in signal transduction pathways in the nervous system, as well as the development and activation of T lymphocytes. The interaction between FYN and TAU is known since two decades, demonstrated by co-immune precipitation in human neuroblastoma cells and ectopic co-localization of TAU in NIH3T3 cells[142]. Whilst this interaction is expected to result in FYN-dependent tyrosine phosphorylation of TAU, the same is also important for targeting FYN to the post-synaptic compartment where it modifies N-methyl-D-aspartate (NMDA) receptor activity and induces excitotoxicity[143,144]. In cancer, FYN contributes to the development and progression of several cancer types through the control of cell growth, death, and motility. Enhanced expression and/or activation of FYN is found in cancers of the prostate and breast, in melanoma and glioblastoma[145]. Recent studies have demonstrated the importance of FYN in the resistance or susceptibility of cancer cells to pharmacological intervention[145].

The *STUB1* encoded E3 ubiquitin ligase CHIP operates as co-chaperone in the folding, transport and degradation of proteins[146]. Taking into account the driving role of protein misfolding in many pathogenic processes including progressive neurodegenerative diseases, cancer, and a large number of rare complaints, the involvement of CHIP-mediated ubiquitination and degradation in disease is not surprising[147,148]. By assisting protein folding as a co-chaperon, CHIP is counted as a tumor suppressor[149]. Its overexpression impairs ovarian carcinoma progression[150], the growth of leukemia cells[151] and the migration and invasion of gastric cancer cells[152]. However, evidence exist of an opposite effect, where oncogenic properties are ascribed to CHIP: improved viability and accelerated tumor growth of thyroid cancer cells[153], or B-type hepatitis virus-associated carcinoma[154] are linked to CHIP overexpression. TAU is a substrate of the HSP70/CHIP chaperone system, which displays homeostatic functions and the selective elimination of aberrant TAU species. Notably, CHIP presents high affinity for truncated Asp-421 TAU generated by caspase cleavage, with preferential poly-ubiquitination of this potentially pathogenic form when compared to full-length TAU. This latter demonstrated by decreased CHIP levels and increased Asp-421 TAU during AD progression[155]. TAU lesions in postmortem tissue are immune positive for CHIP, but CHIP may also accelerate TAU multimerization[156].

14-3-3zeta (also named YWHAZ) is a central hub protein for many signal transduction pathways[157]. Accumulating evidence demonstrates that it acts as an oncogene by targeting downstream protein kinases, apoptosis-associated proteins, and metastasis-related proteins in a wide range of cell activities including cell growth, cell cycle, apoptosis, migration, and invasion. It is frequently up-regulated in cancer cells possibly requiring regulation by microRNAs or long non-coding RNAs[157]. Additionally, 14-3-3zeta has shown value as a biomarker for cancer diagnosis, prognosis and chemoresistance[157]. TAU and 14-3-3zeta form a macromolecular complex[158-160] with GSK-3beta[161]. Moreover, 14-3-3zeta may assist the structural stability of specific TAU domains, the subcellular distribution of TAU[162], the aggregation of TAU[163,164] and ends up associated with hyper-phosphorylated TAU fibrils isolated from brains of patient with AD[165,166] or Pick's disease[167]. Independent studies highlight high 14-3-3zeta expression in AD and Down's syndrome brain[168] and cerebrospinal fluid[169,170].

P53 was not yet listed as a TAU interactor in the BioGRID database despite recent supporting evidence in specific experimental systems[171]. The tumor suppressor activity of the "guardian of the genome" P53 is misreguled in most cancers and may play a major role in neurodegenerative disease. Notably, whilst P53 loss-of-function is a major contributor in cancer[172], P53 expression is upregulated in AD, PD and HD[173-176]. Unusual P53 species are potential biomarkers of AD[177-179], the most common tauopathy with a high incidence of P53 mutations[180] and P53 deregulation[176]. Genetic alteration of P53 variants affects aging, cognitive decline, and TAU

 doi:10.20944/preprints202010.0349.v1

phosphorylation in mice [181,182]. Recently it has been found that P53 is part of a complex containing nuclear TAU, PIN1 and the polyA-specific ribonuclease PARN in the colon cancer cell line HCT116[171], which are also rich in hyperphosphorylated TAU forms[133]. PARN-mediated nuclear deadenylation is activated by TAU, further potentiated by P53 and reduced by TAU phosphorylation. PARN activity in this complex targets expression of genes linked to cancer and/or AD, further supporting the functionally productive interaction of these factors in mRNA 3'-end processing in the nucleus under the modulation of TAU phosphorylation. More recently, our laboratory showed that downregulation of TAU expression impacts P53 stability in neuroblastoma cells, whereby P53 protein stabilization upon DNA damage was reduced in TAU-deficient cells. As a consequence, TAU protein depletion modifies cell fate, with decreased apoptosis counteracted by increased cellular senescence[183]. Although this role of TAU appears independent to a direct interaction with P53, it suggests that the positive association between TAU expression and cancer survival is possibly mediated by a TAU-dependent modulation of wild-type P53 stability and function. Notably a link between TAU and P53 may exist also in the context of neurodegeneration, with P53 displaying a propensity to form oligomers and fibrils upon TAU seed treatment in primary neurons, and to bind TAU oligomers in AD brain and transgenic mouse models[184]. In the same context, markers of P53-mediated response to DNA damage are reduced in AD brain. So, the current evidence indicate that TAU-deficiency as well as TAU deposition in oligomers and fibrils may contribute to an impairment of P53-mediated DNA damage response in neurodegenerative disorders and cancer.

PIN1 is the only known peptidyl-prolyl cis–trans isomerase active on the phosphorylated Ser/Thr-Pro motif. The PIN1-mediated structural conformational switch regulates at the post-translational level the function of a variety of proteins. PIN1 is therefore regulating also cellular pathways that, when dysfunctional, may lead to degenerative and neoplastic disorders. The majority of cancers present PIN1 overexpression and its down-regulation impairs disease progression, evidence for an oncogenic activity on cancer-driving pathways[185]. An opposite property appears involved in AD[186,187]. PIN1 directly binds phophoThr-231 of TAU and acts to restore its biological function on microtubules by promoting its cis/trans isomerization, its dephosphorylation and targeting to the proteasome[188-193]. Also, PIN1 binding to paired-helical TAU filaments results in the depletion of soluble PIN1 that is trapped to AD neurofibrillary tangles[189]. A recent study shows that loss-of-function somatic mutations in the *PIN1* gene are linked to increased TAU phosphorylation and deposition[194].

Other TAU interacting proteins with strong relevance for cancer are the carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase protein CAPON[195], the probable ATP-dependent RNA helicase DDX6[196], the proto-oncogene tyrosine-protein kinase SRC[197], the tyrosine-protein kinase ABL1[198], the dual specificity tyrosine-phosphorylation-regulated kinase 1A DYRK1A[199], the RNA-binding protein EWS[200] and the sirtuin family[201]. Beside a direct interaction with proteins, TAU has been implicated in the regulation of cellular pathways of relevance for cancer.

Mechanistic evidence for a role of TAU in cancer

Variants of the epidermal growth factor receptor (EGFR) are frequently found in glioblastoma (GBM). The most common alterations are gene amplifications and rearrangements, missense mutations, and altered splicing events, which together are observed in 57% of GBMs[202]. Circumstantial evidence of a possible role of TAU in the EGFR pathway is that the activation by phosphorylation of EGFR is inversely correlated with TAU protein levels[113]. More importantly, TAU expression positively correlated with overall survival in the group of amplified wt EGFR GBMs, but lacked clinical relevance when combined with other EGFR variants. Mechanistically, this may be explained with the role of TAU in microtubule stabilization, whereby the presence of TAU may inhibit HDAC6-mediated acetylation of microtubule[203] and the subsequent microtubule-dependent internalization and degradation of EGFR[204]. Consistent with this, TAU overexpression in cells cause a downregulation of EGFR protein, an effect reverted in the presence of protein degradation inhibitors directed to the proteasome or lysosomal hydrolases[113].

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The BReast CAncer BRCA1 and BRCA2 proteins are tumor suppressors whose function is to control the integrity of the genome by promoting efficient and precise repair of double-strand DNA breaks, and mutations in these genes cause familial forms of breast, ovarian and more rarely other cancers[205,206]. A methylome profiling of AD brain, identified hypomethylation of the *BRCA1* locus, increased BRCA1 expression and the presence of BRCA1 in neurofibrillary tangles[207]. BRCA1 association to fibrillary lesions is also observed in other tauopathies, namely Pick's disease and progressive supranuclear palsy[208]. Notably, this effect is reproduced in the presence of the Abeta amyloid peptide, which causes BRCA1 mislocalization to the cytoplasm and its aggregation in a TAU-dependent manner. BRCA1 dysfunction correlates with Abeta burden and deterioration of genomic integrity and of synaptic plasticity, suggesting a disease-promoting interaction between TAU and BRCA[207]. Of possible relevance in this context, is that the DNA damage-activated checkpoint kinases Chk1 and Chk2 are able to phosphorylate TAU[209].

Conclusions

It is without doubt that the main binding partners of TAU are tubulin family members. Under physiological conditions, this results with up to 90% of TAU bound to microtubules and thus not available for other interactions[210]. Accordingly, there is a consensus that TAU plays a role in modifying microtubule-targeting chemotherapeutics and, possibly, also by directly modulating microtubules and their participation to the neoplastic process. However, the binding of TAU to microtubules is highly dynamic, so that TAU is also detected in subcellular sites normally devoid of microtubules such as the nucleus or the dendritic branch of neurons. At these sites, TAU has the ability to co-localize with and bind to non-cytoskeletal proteins, many of which linked to cancer. These additional functions of TAU are likely to develop into relevant roles in physiological and pathological processes.

This review is an effort to compile the data supporting a role of TAU in cancer, which goes beyond microtubule binding and taxane sensitivity. Circumstantial evidence correlates the cellular amount of TAU protein with clinical outcomes, including survival from cancer. As an example, high TAU expression is linked to slower disease progression in gliomas and breast carcinoma, pointing to a tumor suppressor role in these types of cancers. Direct evidence for an active role of TAU in cancer will require elucidating the molecular mechanisms controlling its expression and/or the function in tumor cells or in their microenvironment. Despite initial evidence, a more thorough investigation of the expression, posttranslational modification and interactions of TAU in tumorigenic tissues and cells is needed. This will certainly allow uncovering novel aspects of TAU biology that may facilitate unravelling the etiology of cancer and its relationship to neurodegenerative disorders.

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