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REVIEW

Molecular Interplay Between Cancer and Neurodegeneration: Shared Pathways and Emerging Biomarkers and a Narrative Review

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Abstract

Overview: Neurodegenerative diseases (NDs), including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), are characterized by progressive neuronal loss, protein aggregation, oxidative stress, mitochondrial dysfunction, and impaired proteostasis. In contrast, cancer arises from uncontrolled cell proliferation, invasion, and metastasis. **Methods:** Despite their opposing clinical outcomes, mounting evidence highlights a complex interplay between these conditions, with epidemiological studies consistently revealing an inverse relationship: patients with NDs exhibit reduced risk of many cancers, while certain malignancies, such as melanoma in PD, occur at increased frequency. Shared molecular pathways including DNA damage response, unfolded protein response, mitophagy, redox imbalance, and chronic inflammation underpin this reciprocal association, where the same regulators can promote degeneration in neurons but survival in cancer cells. **Results:** Proteins central to neurodegeneration, such as tau, amyloid-β (Aβ), α-synuclein, SOD1, and TDP-43, also contribute to tumor biology by modulating apoptosis, proliferation, chemoresistance, and metastasis. For instance, tau influences microtubule stability in both AD and cancers, while Aβ and APP drive invasion in gliomas and breast cancer. Similarly, α-synuclein promotes melanoma progression, SOD1 enhances oxidative stress resistance in tumors, and TDP-43 regulates oncogenic splicing events. These dual roles position ND-associated proteins as promising biomarkers and therapeutic targets across oncology and neurology. Blood-based biomarkers derived from these proteins further expand their clinical potential, offering minimally invasive tools for early cancer detection, prognosis, and therapy monitoring. Standardized detection protocols and multimodal diagnostic strategies integrating ND-related proteins could improve patient outcomes by enabling timely intervention and personalized treatment. **Conclusion:** The shared yet divergent molecular networks of cancer and neurodegeneration highlight opportunities to uncover novel biomarkers and design targeted therapies that exploit common mechanisms while minimizing adverse effects, thereby bridging insights across two seemingly opposing disease domains.

Keywords: Cancer- Proteostasis/UPR- Mitophagy- Oxidative stress- Blood biomarkers

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Introduction

Cancer research is rapidly advancing, with a growing focus on targeted therapies, epigenetic regulation, and the impact of environmental factors on tumor development in cancers [1-4]. Examples of cancer types discussed in recent studies include hepatocellular carcinoma, breast cancer, prostate cancer, cervical cancer, and various gynecological malignancies, each demonstrating distinct molecular and therapeutic profiles relevant to translational oncology [5-8]. Neurodegenerative disorders (NDs), including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), represent clinically and etiologically heterogeneous conditions that nevertheless exhibit convergent pathological hallmarks, such as aberrant protein aggregation, progressive neuronal degeneration, and the emergence of early non-motor manifestations [9]. In contrast, cancer is defined by uncontrolled cellular proliferation, invasive growth, and metastatic potential features that ostensibly oppose the accelerated neuronal loss observed in NDs [9, 10]. Despite their contrasting outcomes, both neurodegeneration and cancer are governed by intersecting regulatory pathways that determine cellular fate, directing it either toward degeneration or unchecked proliferation. Key processes implicated in both include oxidative stress, mitochondrial impairment, chronic inflammation, cell-cycle abnormalities, and deficiencies in DNA repair mechanisms [11, 12]. Epidemiological evidence suggests a notable inverse relationship between neurodegenerative diseases (NDs) and cancer, with patients frequently exhibiting reduced incidences of malignancies such as colorectal, lung, and liver cancers [13, 14]. Notably, while Alzheimer's disease (AD) and Parkinson's disease dementia (PDD) are both associated with decreased cancer risk, PDD shows an even lower incidence particularly in colorectal cancer compared to AD. However, exceptions exist; for example, melanoma as well as breast and prostate cancers occur more frequently in patients with Parkinson's disease [15]. Several large cohort and case–control studies highlight how differential detection can bias an apparent PD–cancer inverse association. For example, Freedman et al. analyzed SEER–Medicare data (N≈743,779 cancer patients vs 419,432 controls in cohort; 836,947 cancer cases vs 142,869 controls in case–control) while adjusting for physician visits. They found no significant association between prior cancer and subsequent PD (HR≈0.97, 95%CI 0.92–1.01). In their case–control analysis, PD patients had lower odds of subsequent cancer (OR=0.77, 95%CI 0.71–0.82), but a similar inverse association emerged for an implausible outcome (auto-accident injuries followed by cancer; OR=0.83, 95%CI 0.78–0.88), suggesting a generalized surveillance/detection bias [16]. In a Medicare case–control study, Gross et al. found that adjusting for healthcare utilization markedly attenuated PD–cancer associations: all odds ratios decreased by ~8–58% with use-of-care adjustment, and smoking-related cancers switched from a positive association to a negative one when physician visits were controlled [17]. Earlier, a U.S. population cohort (Olmsted County, 196 PD vs 185 controls) reported higher cancer incidence after PD (overall RR=1.64, 95%CI 1.15–2.35; skin cancer RR=1.76, 95%CI 1.07–2.89) (18), but the authors noted that this likely reflected surveillance bias. Likewise, a recent Korean cohort (8,381 PD patients vs 33,524 matched controls) found much lower cancer incidence in PD (adjusted HR≈0.63, 95%CI 0.57–0.69 for all cancers), though the authors cautioned that increased clinical monitoring of PD patients may partly explain reduced cancer diagnosis [19]. Together, these studies illustrate that when healthcare utilization is taken into account, the apparent "protective" association often attenuates, indicating detection bias rather than a true biological effect. Similar bias concerns apply in dementia, a recent meta-analysis (19 cohort studies, 3 case–controls; total N≈9.6 million) found only a weak inverse link: history of cancer was modestly associated with lower Alzheimer incidence (cohort pooled HR≈0.89, 95%CI 0.79–1.00) and with lower odds of AD in case-control data (OR≈0.75, 95%CI 0.61–0.93). Crucially, studies with poorer confounder adjustment or greater diagnostic bias had risk estimates closer to null (e.g. one analysis reported HR≈0.94 versus 0.73 depending on bias level) [20]. This suggests that uncorrected biases tend to mask rather than create the inverse effect. In an insurance-claims study of dementia (1.69 million cases, 3.37 million controls), researchers compared 10-year cancer prevalence trajectories and concluded that selective survival and underdiagnosis of cancer in dementia (and vice versa) partly explain the inverse cancer–dementia pattern [21]. For instance, cognitive impairment can delay cancer detection, yielding fewer recorded cancers among dementia patients. In sum, while epidemiological estimates often show fewer cancers in people with PD or AD, quantitative analyses consistently find that adjusting for healthcare utilization or detecting bias greatly attenuates these inverse associations [16, 20]. These patterns imply that predisposition to one condition may, in some contexts, confer relative protection against the other, though notable exceptions exist. Moreover, therapeutic interventions such as chemotherapy further shape this relationship, at times inducing structural alterations in the brain but also being associated with a decreased risk of Alzheimer's disease [14, 22]. At the molecular level, critical regulators including Parkin, Pink1, p53, and PIN1 exhibit distinct expression profiles in neurodegenerative diseases compared to cancer, driving opposing cellular fates [23]. Additionally, non-coding RNAs play a modulatory role in determining whether cells undergo degeneration or unchecked proliferation. Elucidating these shared and contrasting mechanisms enhances our understanding of the complex interplay between neurodegeneration and cancer and provides avenues for identifying prognostic biomarkers and designing targeted therapies that leverage common pathways while minimizing adverse effects on either condition [23-25]. Neurodegenerative diseases (NDs) encompass a heterogeneous group of disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), which are marked

by progressive, selective neuronal loss leading to cognitive, motor, and behavioral impairments [26]. While each condition exhibits distinct pathological hallmarks such as amyloid-β and tau deposition in AD, dopaminergic neuron degeneration in PD, and motor neuron loss in ALS they converge on shared molecular mechanisms, including protein aggregation, neuroinflammation, oxidative stress, mitochondrial dysfunction, and impaired protein clearance [27, 28]. Proteins associated with these diseases, such as tau, alpha-synuclein, SOD1, and TDP-43, not only define disease-specific neuropathology but also serve as biomarkers across NDs; for example, cerebrospinal fluid levels of tau and α-synuclein correlate with both cognitive decline and disease progression in AD and PD, highlighting overlapping mechanisms with potential prognostic and diagnostic value [29, 30]. Increasing evidence indicates that these molecular pathways also intersect with those involved in cancer and microbial diseases, revealing shared regulatory networks that govern cellular survival, inflammation, and protein homeostasis [31, 32]. Although factors such as inflammation, oxidative stress (ROS), genetic mutations, and aberrant cell death have been proposed to account for the frequently observed reduced cancer risk in neurodegenerative diseases (NDs), these pathways ultimately converge on mitophagy, the selective elimination of damaged mitochondria. Oxidative stress exerts opposing effects in cancer stem cells (CSCs) and NDs: while elevated ROS in CSCs drives genomic instability and tumor progression, in NDs it accelerates neuronal loss and compromises cellular repair mechanisms [33]. Consequently, shared disturbances in redox balance, signaling cascades, and mitochondrial dynamics underscore common molecular mechanisms that could be exploited as therapeutic targets in both cancer and neurodegenerative disorders [33, 34]. Cancer is characterized by resistance to cell death, whereas neurodegenerative diseases (NDs) involve progressive neuronal loss. Interestingly, epidemiological studies reveal an inverse relationship between these conditions: cancer survivors exhibit a lower risk of developing Alzheimer's disease (AD) and Parkinson's disease (PD), while patients with AD or PD generally show reduced incidences of cancer [35]. This inverse comorbidity may be driven by shared molecular regulators, including TP53, PIN1, PARK7, Tau, and specific microRNAs, as well as overlapping pathways such as Wnt signaling and protein degradation systems [35, 36]. These common molecular players suggest that divergent cellular outcomes survival in cancer versus degeneration in NDs underlie the observed reciprocal association, although the precise biological mechanisms remain to be fully elucidated [36, 37]. Interestingly, proteins commonly implicated in neurodegenerative diseases such as Tau, amyloid-β, α-synuclein, SOD1, and TDP-43 have been increasingly recognized for their roles in cancer biology, where they influence cell proliferation, apoptosis, chemoresistance, and tumor progression. These findings not only highlight shared molecular pathways between neurodegeneration and cancer but also suggest that these proteins may serve as valuable biomarkers and potential therapeutic targets in oncology [15, 38]. The DNA damage response (DDR) and the unfolded protein response (UPR) are central cellular mechanisms that maintain homeostasis and protect against disease, yet dysregulation in each can contribute to distinct pathologies [39]. DDR preserves genome integrity, with defects leading to cancer in proliferating cells and neuronal loss in the nervous system, illustrating its critical role in balancing cell survival and death. Insufficient DDR activity predisposes cells to tumorigenesis, whereas excessive DDR signaling in neurons can trigger apoptosis and drive neurodegenerative processes [40]. Similarly, the UPR, mediated by endoplasmic reticulum stress sensors such as PERK, IRE1, and ATF6, manages protein misfolding and is implicated in neurodegenerative diseases including Alzheimer's, Parkinson's, ALS, and prion disorders. Although UPR modulation is being investigated as a therapeutic strategy, variability across disease models underscores the need for further studies, particularly in human brain tissue, to fully elucidate its role in neurodegeneration [40, 41]. Emerging evidence directly links DDR/UPR pathways with the hallmark proteins. For example, intraneuronal Aβ accumulation induces oxidative stress and DNA double-strand breaks, and defective DNA repair promotes tau pathology, while α-synuclein aggregation is likewise associated with nuclear DNA damage [42-44]. Conversely, Aβ and tau aggregates trigger ER stress and UPR activation in AD models, and mislocalized TDP-43 provokes ER stress/UPR signaling in ALS/FTD [45, 46]. These findings directly connect DDR and UPR with tau, Aβ, TDP-43 and α-synuclein, emphasizing their mechanistic interplay in neurodegenerative disease. Collectively, these overlapping molecular pathways spanning protein homeostasis, mitochondrial quality control, DNA repair, redox balance, and key signaling networks underscore the complex interplay between neurodegenerative diseases and cancer, offering potential avenues for prognostic biomarkers and therapeutic interventions that target shared mechanisms without exacerbating either condition (Figure 1).

Genetic Modifiers of Cancer Susceptibility in Neurodegeneration

Several genetic variants implicated in neurodegenerative diseases (NDs) also influence cancer risk, either increasing or decreasing susceptibility. Key genes such as LRRK2, PARK2, MAPT, APOE, SOD1, and TARDBP exhibit both oncogenic and tumor-suppressive roles, shaping cancer outcomes in ND patients (Table 1).

LRRK2 (PD): The G2019S mutation is the most common genetic cause of PD and is associated with increased cancer risk (RR≈1.26), especially for brain, breast, colon, and hematologic tumors. Its kinase overactivity may enhance cellular proliferation [47].

PARK2 (AR-PD): Parkin, a known tumor suppressor, is often deleted or mutated in solid tumors. While its mutations cause early-onset PD, Parkin loss promotes tumor growth, and overexpression inhibits it. Mouse models confirm increased cancer susceptibility in Parkin-deficient states [48].

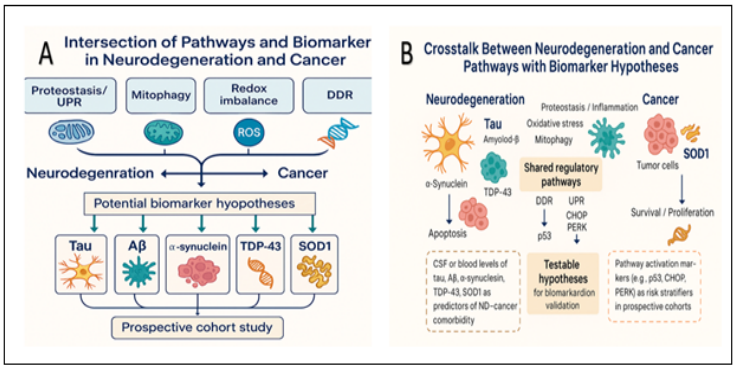

Figure 1. Schematic Representation of the Molecular Crosstalk between Neurodegeneration and Cancer. (A) Overlapping cellular pathways proteostasis/UPR, mitophagy, redox imbalance, and DNA damage response (DDR) influence disease progression in opposite directions, with shared biomarker proteins (Tau, Aβ, α-synuclein, TDP-43, and SOD1) offering potential for cross-disease monitoring in prospective cohort studies. (B) Integration of these pathways suggests testable hypotheses for biomarker validation, where central proteins and pathway markers (e.g., CHOP, PERK, p53) may stratify risk or predict ND–cancer comorbidity.

MAPT (Tau, AD/FTD): Tau mutations contribute to dementia and may affect cancer through DNA damage pathways. Loss of Tau impairs p53 stability, while elevated Tau expression improves survival in cancers like gliomas. MAPT mutation carriers have shown ~3.7-fold higher cancer risk [49-51].

APOE (AD): Though APOE ε4 is the major AD risk allele, most meta-analyses find no strong link between APOE variants and overall cancer risk. Some small studies report minor changes in breast or colorectal cancer susceptibility, but findings are inconsistent [52].

SOD1 (ALS): SOD1 mutations cause familial ALS but wild-type SOD1 is overexpressed in many cancers and supports tumor survival by neutralizing ROS. Inhibitors like LCS-1 selectively kill SOD1-dependent cancer cells, revealing its dual role in neurodegeneration and oncogenesis [53].

TARDBP (TDP-43, ALS/FTD): TDP-43 regulates cancer-related transcripts (e.g., MALAT1) and is mislocalized in tumor tissues. Its dysregulation is linked to altered splicing and immune evasion in cancers, suggesting functional overlap with neurodegeneration mechanisms [54].

Huntington's disease

Research consistently shows that individuals with Huntington's disease (HD) have a lower overall risk of developing cancer compared to the general population, even though smoking is more common among gene carriers [55]. One large cohort study reported a reduced cancer risk, and further work indicated that polyglutamine disorders in general are linked to lower cancer incidence, independent of CAG repeat length though very large expansions may increase the likelihood of certain cancers, such as breast cancer [56]. Another investigation found far fewer cancers than expected in HD patients, although skin cancers occurred at a higher rate [57]. Likewise, data from the REGISTRY study involving thousands of participants confirmed decreased cancer rates in HD patients, supporting the inverse relationship between HD and cancer [58]. The lower incidence of cancer observed in Huntington's disease (HD) may be partly attributed to underdiagnosis, since clinical attention often centers on neurological decline, but molecular evidence also points to protective mechanisms [59]. Trinucleotide repeat (TNR) expansions can produce RNA fragments that act as toxic siRNAs, eliminating cancer cells through RNA interference and the DISE (death induced by survival gene elimination) pathway [60]. Polyglutamine proteins activate several cell death mechanisms, and the huntingtin-associated protein HAP1 has tumor-suppressive properties in breast cancer by limiting cell growth, migration, and invasion [61]. Moreover, transcriptional dysregulation in HD alters stress-response gene expression: factors such as Sp1 modulate oncogenes and tumor suppressors, while p53 influences huntingtin expression, underscoring the molecular connections between HD and cancer [62, 63].

Parkinson's disease

Multiple studies have reported an inverse relationship between Parkinson's disease (PD) and overall cancer risk, with patients showing fewer cancer cases and lower mortality from malignancies compared to the general population, even after adjusting for smoking [64]. A decreased incidence of colorectal cancer has also been noted, with some cohorts indicating up to a 21% reduction in risk. Nevertheless, notable exceptions exist: PD is consistently associated with a higher likelihood of melanoma, in some cases nearly doubling the risk, and a modestly elevated risk of breast cancer [65]. Genetic factors, including specific PD subtypes such as those linked to LRRK2 mutations, may further shape cancer susceptibility, reflecting a complex and heterogeneous connection between PD and malignancy [66]. Aging promotes both cancer and neurodegeneration through overlapping mechanisms, including genomic instability, epigenetic alterations, mitochondrial dysfunction, and disrupted protein homeostasis [67]. Parkin (PARK2), a major familial Parkinson's disease gene with tumor-suppressive properties, is central to protein degradation, mitophagy, and cell survival, and its mutations contribute to early-onset PD as well as cancer [68]. In addition to its well-known role in mitophagy, Parkin restrains necroptosis by regulating

Table 1. The Table Summarizes These ND-associated Genes and Their Reported Impacts on Cancer

Gene (Protein)	Neurodegenerative Context	Cancer Association (Risk/Effect)
LRRK2 (kinase)	PD (familial; e.g. G2019S)	↑ Overall cancer risk in carriers. LRRK2-G2019S PD patients: RR≈1.26 for any cancer, notably ↑brain (RR≈2.4), ↑breast (2.6), ↑colon (1.8), ↑hematologic (2.0) vs idiopathic PD. (LRRK2 kinase GOF may drive proliferation.) [5]
PARK2 (Parkin) (E3 ligase)	PD (juvenile, AR)	Tumor suppressor. PARK2 is often deleted/mutated in cancers (breast, lung, colorectal, glioma, etc.); loss promotes tumor cell proliferation. Parkin-null mice have ↑tumor incidence. No strong evidence that heterozygous PD mutation carriers have higher cancer, but PARK2 deficiency clearly aids cancer progression [6].
MAPT (Tau) (microtubule-binding)	FTD/Tauopathy, AD, PD	Multifunctional: Tau variants (FTD mutations) appear to increase cancer risk (one study: HR≈3.7) [8, 9]. Tau loss impairs DNA repair and destabilizes p53, reducing apoptosis. In cancer patients, high MAPT expression often correlates with less invasiveness and better survival (e.g. in glioma) [7]. Thus Tau influences tumor cell stress responses and therapy sensitivity.
APOE (lipid transporter)	AD risk (ε4 allele)	Largely neutral for cancer. Meta-analysis of ~12 000 cases found no significant overall association between APOE genotype and cancer incidence [10]. (APOE alleles may still modulate specific tumor microenvironments, but no large effect size is established.)
SOD1 (antioxidant enzyme)	ALS (familial)	Pro-tumor role. SOD1 is commonly overexpressed in multiple cancers (e.g. lung, breast) and is essential for cancer cell survival under oxidative stress [11]. Inhibiting SOD1 kills tumor cells by allowing toxic ROS buildup. Thus, wild-type SOD1 supports tumor progression, although SOD1 mutations cause neurodegeneration.
TARDBP (TDP-43) (RNA-binding)	ALS/FTD	Emerging link. TDP-43 is abnormally regulated in some tumors and may promote oncogenesis via altered RNA splicing/transport. Computational analyses identify TARDBP as a biomarker of tumor progression and immune evasion [12]. Definitive clinical data on TARDBP variants affecting cancer risk are still lacking, but mechanistic overlap is noted.

the RIPK1–RIPK3 pathway. This effect is strengthened by AMPK-dependent phosphorylation, which stabilizes RIPK3 polyubiquitylation and suppresses inflammatory cell death. Together, these functions position Parkin as a molecular link between neuroprotection and tumor suppression [69-70].

Alzheimer's disease

Research indicates an inverse association between Alzheimer's disease (AD) and cancer, as multiple studies have reported a lower cancer incidence in individuals with AD compared to healthy controls [71]. For instance, one study detected cancer in only about 8% of dementia cases versus 14% among controls, while another showed a roughly 61% reduction in cancer risk in probable AD. Similarly, additional findings demonstrated around a 60% decrease in the likelihood of developing cancer in AD patients even after adjusting for other variables [72]. Recent studies suggest that cancer and Alzheimer's disease (AD) share genetic and metabolic pathways that may confer risk in opposite directions [71]. For instance, the inverse Warburg effect links altered energy metabolism to either cancer growth or neurodegeneration, while overlapping genes, such as p53, influence apoptosis differently in both diseases. Pin1, crucial for cell cycle regulation, is overexpressed in cancers but downregulated in AD, where it may also suppress tau and amyloid β deposition [73]. Similarly, Tau/MAPT genes connect neurodegeneration and gliomas through roles in microtubule stabilization and genomic integrity. Moreover, β-amyloids have been shown to inhibit cancer cell growth through mechanisms varying by tumor type, highlighting how the cellular environment can differentially shape cancer and AD pathogenesis [74].

Amyotrophic Lateral Sclerosis (ALS)

ALS (Lou Gehrig's disease) is a progressive neurodegenerative disorder that affects motor neurons, causing muscle weakness and eventual paralysis [75]. Over 50 genes have been implicated in ALS, with key mutations in SOD1, TARDBP, and FUS/TLS, which encode proteins essential for cellular functions. These proteins are involved in pathways such as mitochondrial function, autophagy, RNA metabolism, DNA repair, inflammation, and intracellular trafficking, all contributing to neurodegeneration [76, 77].

Neurological Biomarkers in Cancer

The roles of five major neurological biomarkers Tau, Amyloid-beta (Aβ)/APP, Alpha-synuclein (α-syn), SOD1, and TDP-43 in cancer biology.

Originally associated with neurodegenerative diseases such as Alzheimer's and Parkinson's, these proteins are now increasingly recognized for their involvement in tumor progression, metastasis, and resistance to therapy across various cancer types.

Tau

Tau is a microtubule-associated protein primarily found in neurons, where it stabilizes the cytoskeleton and participates in pathways regulating cell proliferation, differentiation, and motility [78]. The MAPT gene produces six isoforms of tau through alternative splicing, maintaining a critical 3R:4R ratio in healthy adult brains [79]. Disruption of this balance, along with post-translational modifications (PTMs) such as hyperphosphorylation, destabilizes microtubules and contributes to neurodegenerative disorders [80]. Beyond the nervous system, tau is increasingly implicated in cancer. It is abnormally expressed in gliomas and various

peripheral tumors including breast, ovarian, gastric, colorectal, and prostate cancers, where it influences tumor progression, prognosis, and therapy response [49, 81, 82]. In gliomas, hyperphosphorylated tau appears to preserve microtubule stability, limiting mitotic activity and tumor cell migration contributing to more favorable clinical outcomes [83, 84]. Conversely, in breast and ovarian cancers, excessive tau phosphorylation disrupts microtubule architecture, impairs taxane–microtubule binding, and promotes microtentacle formation, facilitating tumor cell reattachment and resistance to chemotherapy [85-87]. These context-specific effects suggest that tau PTMs modulate microtubule dynamics in a cell-type dependent manner, either stabilizing or destabilizing the cytoskeleton to influence proliferation, migration, and drug sensitivity [78]. Tau's expression is not limited to neurons but is also found in glial cells and tumor cells, affecting survival and metastatic potential [88]. In colorectal and prostate cancers, tau promoter methylation, phosphorylation, and isoform shifts influence therapy resistance and cell-cycle regulation [82, 89]. Collectively, these findings underscore tau's potential as both a diagnostic and prognostic biomarker and a therapeutic target in cancer, with ongoing efforts to therapeutically modulate its post-translational states.

Aβ

Amyloid-beta (Aβ), generated through sequential cleavage of amyloid precursor protein (APP), is a defining feature of Alzheimer's disease (AD) and contributes to the formation of senile plaques, though its precise function remains unclear [90]. Both Aβ and APP undergo various post-translational modifications that influence their structure, localization, and activity. While primarily studied in neurodegeneration, APP and Aβ are increasingly recognized for roles in cancer [91]. APP is frequently overexpressed in tumors such as breast, pancreatic, prostate, colon, and brain cancers, promoting proliferation, migration, and metastasis, whereas certain non-toxic Aβ oligomers can trigger tumor cell death, indicating a context-dependent effect [92]. In breast cancer, APP enhances invasiveness and interacts with pathways including MAPK, with its expression regulated by estrogen and androgen receptors, making it a potential therapeutic target [93]. In gliomas and glioblastoma, both APP and Aβ are associated with tumor progression and inflammation, while amyloid precursor-like protein 2 (APLP2) drives proliferation, invasion, and metastasis in cancers such as pancreatic and lung. In prostate cancer, APP modulates androgen-responsive genes, promoting tumor growth and migration [94]. APP is also implicated in colorectal, nasopharyngeal, hepatocellular, and non-small cell lung cancers, affecting proliferation, migration, and epithelial–mesenchymal transition [95]. Certain drugs, including carbamazepine and valproic acid, reduce APP levels in colon cancer, and APP silencing in nasopharyngeal cancer inhibits EMT via MAPK pathway downregulation. In hepatocellular carcinoma, APP is regulated epigenetically, and phosphorylated APP serves as a prognostic marker in non-small cell lung cancer, highlighting its broad potential as a biomarker and therapeutic target across multiple tumor types [29].

Alpha-Syn

Recent studies have highlighted roles for α-synuclein (α-syn) beyond neurodegeneration, showing its involvement in cancer development. Elevated α-syn levels have been detected in pancreatic ductal adenocarcinoma (PDAC), particularly in tumors with perineural invasion, suggesting a link to tumor aggressiveness [96]. Melanoma cells also exhibit high α-syn expression, and its inhibition reduces tumor growth, alters iron metabolism, and affects autophagy, indicating an active role in cancer progression rather than a passive presence. Importantly, α-syn is absent in non-melanocytic skin cancers and normal tissue, with its Ser129-phosphorylated form contributing to pathogenic processes in melanoma [97, 98]. Beyond melanoma and PDAC, α-syn promotes malignant meningioma progression through activation of the Akt/mTOR pathway, reinforcing its role in tumor aggressiveness. These observations point to α-syn as both a potential biomarker and a therapeutic target, warranting further research into its mechanisms in cancer biology and therapy [99]. Other Parkinson's disease–associated proteins, including UCHL1 (PARK5) and DNAJ/HSP40 chaperones, also play roles in cancer [100]. UCHL1, primarily neuronal, can function as either a tumor suppressor or an oncogene depending on context. Its promoter methylation is associated with cancers such as hepatocellular, nasopharyngeal, gastric, breast, ovarian, and pancreatic, while restoring its expression can regulate cyclins like p53, inhibit proliferation, and trigger apoptosis [101]. Conversely, its oncogenic activity involves PI3K/Akt and MAPK/Erk signaling, promoting invasion and metastasis. Similarly, DNAJ/HSP40 proteins, especially DNAJC14, interact with Hsp70 to regulate ATPase activity, and their upregulation in cancers like osteosarcoma suggests a contribution to tumorigenesis [102].

SOD1

Mutations in the SOD1 gene, which encodes the Cu/Zn superoxide dismutase enzyme responsible for neutralizing cytoplasmic superoxide radicals, were first linked to ALS in 1993 [103]. SOD1 is highly conserved, broadly expressed, and regulated by post-translational modifications such as phosphorylation, lysine and redox changes, and nitration. Beyond its role in neurodegeneration, SOD1 is frequently altered and overexpressed in cancers, including non-small cell lung and breast cancers, where it contributes to tumor growth and metastasis. Inhibition of SOD1 with compounds like LCS-1 reduces tumor proliferation and induces apoptosis, highlighting its therapeutic potential, while CSF-1 has been reported to suppress SOD1 overexpression and slow tumor progression [104, 105]. Studies in transgenic breast cancer models confirm that SOD1 inhibition slows tumor growth, and mechanistic work indicates that mTORC1-mediated regulation of SOD1 supports cancer cell survival and chemoresistance under stress [106]. Other agents, such as the copper chelator ATN-224, are being

evaluated in clinical trials, particularly for prostate cancer, although conclusive results are still pending. Ongoing research into SOD1's functions in cancer is essential for developing new therapies and understanding its dual role in neurodegeneration and tumor biology [107].

TDP-43

TDP-43, initially identified as a TAR DNA-binding protein, is a highly conserved RNA-binding protein encoded by the TARDBP gene on chromosome 1 and primarily localized in the nucleus [108]. It regulates gene transcription, splicing, and mRNA stability, with its activity modulated by post-translational modifications such as phosphorylation, ubiquitination, acetylation, and SUMOylation. While abnormal aggregation or mislocalization of TDP-43 is linked to neurodegenerative diseases, emerging evidence also implicates it in cancer, underscoring its relevance in both neurology and oncology [109]. Studies indicate that TDP-43 promotes tumor progression across various cancers. In glioblastoma, its overexpression activates autophagy and inhibits apoptosis through HDAC6, with HDAC6 inhibition mitigating these effects [110]. In glioblastoma models, cytoplasmic aggregation of TDP-43 elicits endoplasmic-reticulum stress and a maladaptive UPR most notably PERK→eIF2α→ATF4/CHOP and IRE1α→XBP1s signaling while pharmacologic HDAC6 inhibition reduces TDP-43 aggregation and attenuates CHOP/ATF4 induction, partially restoring proteostasis [111]. TDP-43 is also upregulated in hepatocellular carcinoma, melanoma, and triple-negative breast cancer, where it enhances proliferation, metastasis, and poor clinical outcomes, and silencing the protein reduces tumor growth [112]. Mechanistically, TDP-43 influences pathways such as Wnt/β-catenin signaling and modulates alternative splicing of oncogenic factors, including CD44 in breast cancer stem cells. Despite these insights, further investigation is required to clarify TDP-43's role in cancer and assess its potential as a therapeutic target [113].

Blood-Based Biomarkers

Early detection and monitoring of cancer remain major challenges, as conventional approaches such as imaging and tissue biopsies often identify disease only at later stages and can be invasive, expensive, or limited in availability. Blood-based biomarkers have emerged as a promising alternative, offering a minimally invasive and cost-effective means to track cancer progression in real time. These biomarkers including proteins, nucleic acids, exosomes, and metabolites can provide insights into tumor biology and treatment response, enabling earlier intervention and potentially better patient outcomes. Proteins commonly linked to neurodegenerative diseases such as Aβ, tau, α-synuclein, SOD1, and TDP-43 have also been implicated in cancer and may serve as useful blood-based biomarkers. Elevated levels of Aβ, tau, and α-syn are found in various tumors, affecting apoptosis, proliferation, metastasis, and drug resistance. Similarly, dysregulated SOD1 and TDP-43 contribute to tumor growth, oxidative stress, and gene regulation. Incorporating these biomarkers into clinical practice, along with standardized detection methods and multi-modal diagnostic strategies, could improve early cancer detection, enable effective disease monitoring, and guide therapeutic decisions [114].

Discussion

Cancer has long been at the forefront of probing biological mechanisms and uncovering new pathways, and a rigorous interpretation of these data is of particular importance [115-119]. Repurposing neurodegeneration (ND) therapies for cancer is promising but fraught with risk, because many ND-targeting agents (e.g., autophagy enhancers for Parkinson's) act on core cellular programs and lack strict specificity; applied in oncology without careful tailoring, they can injure healthy neurons [120]. Preclinical PD data illustrate this double edge: non-selective autophagy induction can worsen neuronal damage, whereas blocking excessive autophagy (e.g., with N-acetylcysteine against 6-OHDA toxicity) protects dopaminergic neurons implying that "more autophagy" is not universally beneficial [121]. At the same time, genetic and molecular crosstalk reveals tangible opportunities: restoring parkin (PARK2) expression suppresses tumorigenicity in lung carcinoma models, and trinucleotide-repeat (TNR)–derived siRNAs from CAG repeats in Huntington's disease selectively kill cancer cells via RNAi/DISE without harming normal tissue, nominating TNR-based therapeutics for future cancer trials. More broadly, the epidemiology often suggests an inverse ND cancer association (varying by tumor type), underpinned by shared mechanisms mutations and epigenetic regulation, oxidative stress, mitochondrial dysfunction, impaired vs. heightened proteostasis, abnormal protein trafficking and converging nodes such as Parkin, p53, PTEN, HAP1, PDE10A, LRRK2. Notably, autophagy modulation remains a context-dependent lever: it may clear toxic aggregates in PD yet sustain established tumors. Consequently, translational strategies should prioritize pathway specificity and targeted delivery (e.g., dose optimization, tissue-selective carriers) to exploit overlaps that curb malignancy without exacerbating neurodegeneration [120, 121].

Future Study and Conclusion

To address these concerns, we have refocused the Future Studies section on oncology-specific innovations and removed unrelated references. In particular, advanced drug-delivery technologies are now a priority [122-124]. For example, engineered nanoparticles have demonstrated the ability to overcome biological barriers and improve targeting of therapeutics [125]. A concrete case is the potential for nanoparticle-mediated delivery of TDP-43 inhibitors to tumors: TDP-43 is a protein implicated in many cancers (e.g. breast, lung, liver, glioblastoma, melanoma), and studies show that silencing TDP-43 in triple-negative breast cancer markedly reduces tumor growth and metastasis [126]. By encapsulating anti-TDP-43 RNA or small molecules in tumor-targeted nanoparticles, one could inactivate this oncogenic driver

while sparing normal neurons. This approach leverages precision nanomedicine: as summarized by Mitchell et al., increasingly refined nanoparticle designs can be optimized for personalized drug delivery, improving tumor specificity and safety [125]. In future work, we therefore emphasize the development of nanocarrier systems for ND–cancer therapy and other cancer-tailored modalities (e.g. targeted gene editing, immune-oncology combinations) rather than generic ND-repurposing strategies. To advance the field, several high-impact research gaps must be addressed through coordinated efforts across molecular biology, oncology, and neuroscience. First, there is an urgent need to develop selective autophagy and proteostasis modulators that can distinguish between tumor and neuronal contexts. Current autophagy-targeting drugs, while promising in cancer, risk off-target neurotoxicity by disrupting essential neuronal homeostasis, underscoring the need for highly specific modulators or combination regimens that selectively suppress tumor autophagy without impairing neuronal survival [126]. Second, the creation of targeted delivery platforms, particularly nanoparticle-based systems, represents a critical step toward minimizing systemic toxicity. Advanced nanocarriers capable of co-delivering chemotherapeutics and TDP-43 inhibitors directly to tumors guided by tumor microenvironment cues could achieve precision targeting and avoid unintended effects on the brain [125, 127]. Third, biomarker and diagnostic integration remains underdeveloped: the discovery of blood- and imaging-based biomarkers that reveal subclinical neurodegenerative signatures in cancer patients (and vice versa) could revolutionize early detection and enable personalized screening strategies [128, 129]. Fourth, preclinical comorbidity models are required to mechanistically probe the ND–cancer interface. Mouse models combining oncogenic mutations with neurodegeneration-associated genes, along with organoid co-culture systems that mimic neuron–tumor interactions, would allow for testing of dual-action therapeutics and toxicity profiles [130]. Finally, clinical and epidemiological studies must systematically explore how neurodegenerative and cancer pathologies co-exist in patients, tracking long-term neurological outcomes of cancer therapies and establishing guidelines for comorbidity management, including dose adjustments and neuroprotective co-treatments [15]. Addressing these multidimensional gaps through integrative, precision-driven research will enable the safe and effective translation of shared ND–cancer mechanisms into next-generation diagnostics and therapeutics.

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Conflict of interest

Authors declare no conflict of interest.

Author contribution

All authors have contributed to implementation of this research.

Originality Declaration for Figures

All figures included in this manuscript are original and have been created by the authors specifically for the purposes of this study. No previously published or copyrighted images have been used. The authors confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research or designed uniquely for this manuscript.

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