Review

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Review

Association of Parkinson's Disease and Cancer: New Findings and Possible Mediators

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Abstract: Epidemiological evidence points to an inverse association between Parkinson's disease (PD) and almost all cancers except melanoma, for which this association is positive. Epidemiological evidence indicates an inverse association between PD and almost all cancers, except melanoma, where this association is positive. The results of multiple studies have found that patients with PD are at reduced risk of the majority of neoplasm occurrence and death. Several potential biological explanations exist for the inverse relationship between cancer and PD. Recent results identified several PD-associated proteins and factors mediating cancer development and cancer-associated factors affecting PD. Accumulating data points to the role of genetic traits, members of the synuclein family, neurotrophic factors, the ubiquitin-proteasome system, circulating melatonin, and transcription factors as such mediators. Accumulating data points to the role of genetic traits, members of the synuclein family, neurotrophic factors, ubiquitin-proteasome system, circulating melatonin, and transcription factors as potential mediators. Here, we present recent data about shared pathogenetic factors and mediators that might be involved in the association between these two diseases. We discuss how these factors, individually or in combination, may be involved in pathology, serve as links between PD and cancer, and affect the prevalence of these disorders. We also discuss how these factors, whether acting individually or in combination, may play a role in pathology. They serve as potential links between PD and cancer and can influence the prevalence of these disorders. Identification of these factors and investigation of their mechanisms of action would lead to the discovery of new targets for the treatment of both diseases.

Keywords: Parkinson's disease; cancer; malignant melanoma; neurotrophic factors; ubiquitin-proteasome system; melatonin; transcription factors; synucleins; BAP1

1. Introduction

A growing number of studies demonstrate that patients with PD have a lower risk of developing most types of cancer compared to the control group [1]. A major exception from this rule is melanoma, the incidence of which positively correlates with cancer [2,3]. Experimental results demonstrating that PD and cancer might have several identical or similar genes and signaling pathways give a basis for the hypothesis that people predisposed to PD may have some mechanisms protecting them from cancer development [4]. New findings provided experimental evidence that the negative correlation between PD and cancer may be explained by the fact that these two seemingly divergent diseases are connected by molecule linkers, which provide possible targets for their treatment [4]. Both conditions apparently can involve the same set of genes; however, in affected tissues, the expression is inversely regulated: genes down-regulated in PD are up-regulated in cancer and vice versa. Several candidates in both diseases may be considered links connecting their pathogenesis. It is well established that accumulation of α-synuclein in PD causes some of the typical signs of this disease, while in malignant melanoma, elevation of α-synuclein may increase the proliferation of tumor cells [4,5]. Other factors

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that may be mediators between cancer and PD pathogenesis are neurotrophic factors, members of the ubiquitin-proteasome system, circulating melatonin, transcription factors, and mutations or polymorphisms in genes involved in the pathogenesis of these diseases. Additional factors that may act as mediators between cancer and PD pathogenesis include neurotrophic factors, members of the ubiquitin-proteasome system, circulating melatonin, transcription factors, and mutations or polymorphisms in genes involved in the pathogenesis of these diseases. Below, we discuss the data supporting the role of these factors in more detail.

2. Inverse association between cancers and PD

Many epidemiological studies have indicated an inverse association between the risk of developing cancers and PD [1,6–8]. For example, Bajaj and coauthors conducted a meta-analysis of 29 studies, including 107598 PD patients (2010) [1]. The combined analysis demonstrated that the diagnosis of PD was associated with an overall 27% reduced risk of all cancers and 31% diminished risk after the omission of melanoma and other skin tumors. In another study a meta-analysis showed a 17% decreased cancer risk in PD patients [9].

Although this correlation is found in most studies, some exceptions are also described. For example, in some investigations, leukemia, stomach, and uterine cancers do not show significance for an undisputed and clear inverse association. Moreover, a positive association in certain cancers, including skin, breast, and brain, was described in several studies [8]. Therefore, a more standardized approach with better criteria for enrollment and a higher number of patients is required to have an unbiased conclusion about this association.

3. Differences and similarities in the pathogenesis of cancer and PD

To better understand the reason for these controversies, it may be helpful to compare the mechanisms of cancer and PD development, to reveal the differences and similarities in their pathogenic pathways, and to disclose the role of the main players in these diseases. Cancer and neurodegenerative processes are two main leading causes of morbidity and mortality worldwide [1,4,7]. At first glance, their pathogenesis is based on two apparently opposite biological processes. Cancer is characterized by aberrant and uncontrolled cellular multiplication and proliferation, whereas neurodegenerative diseases are associated with the progressive loss of structure or function of neurons. However, there are some analogies between carcinogenesis and neurodegenerative diseases that may explain the controversies described above. Indeed, both diseases are caused by abnormal regulation of cell survival, and some data point to overlapping pathways associated with these two disorders [10]. Other similarities include a) Age-specific incidence rises sharply with age. b) Clinical signs emerge late in the course of these diseases. c) Marked geographical and environmental variations abound. d) Events or exposures much earlier in life may underlay the later expression of the disease. e) Both cancer and PD develop due to the interaction of genes and environmental factors. f) Both diseases display a significant imbalance in the ubiquitination/deubiquitination processes.

In order to find new medications against these two devastating diseases, it is essential to identify the reasons for the inverse association between the risk of developing cancers and PD and to identify underlying mechanisms.

4. Processes, mechanisms, pathways, and factors that can explain the inverse relationship between cancer and PD

4.1. Processes controlling functions of mitochondria and endoplasmic reticulum

Mitochondria are important for all cellular activities and mutations in genes controlling these subcellular structures affect tumorigenic process and neurodegeneration. Cancer and PD cancer share common mutations in several mitochondrial proteins, e.g., Parkin and PINK1. As shown by Kalyanaraman and coauthors, mitochondria-targeted substances possess both neuroprotective properties and inhibit tumor cell proliferation (2020) (11).

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Polyphenolic compounds, antioxidants, and other substances ensure the maintenance of cellular energy essential for neuronal cell survival. In contrast,energy conservation inhibits the proliferation of cancer cells by depriving the source of energy needed for cancer cell growth.

Mitochondria-targeted drugs containing triphenylphosphonium (TPP+) group attached through alkyl chains linked to a naturally occurring molecule (11). These findings propose a drug repurposing strategy based on mitochondria-targeted drugs with low toxicity.

A region located between mitochondria and endoplasmic reticulum, termed the mitochondria-associated membranes, plays a role in Ca^{2+} homeostasis and lipid synthesis. This structure requires an optimal distance between the endoplasmic reticulum and mitochondria for best function. A diminished distance has been described in PD and during cancer treatment (12). The authors assume that the mitochondrial permeability transition pore is a key cell death signaling structure indirectly regulated by the spatial characteristics of mitochondria-associated membranes.

4.2. Mutations in genes controlling apoptosis

One mechanism that might explain this relationship between cancer and PD is associated with gene mutations controlling the efficiency of apoptosis. Mutations increasing the efficiency of apoptosis might raise the risk of PD and decrease the probability of cancer. Polymorphic variations in the genes possessing such effects may also play some role [2,13,14].

The examination of published data may also explain the association between PD and melanoma. This analysis shows that the changes in several genes increase the risk for both PD and melanoma, i.e., α-synuclein, Parkin, and LRRK2 [3]. Similar analysis identified some low-penetrance genes, e.g., cytochrome p450 debrisoquine hydroxylase locus, glutathione S-transferase M1, and vitamin D receptor, which also raise the risk for both PD and melanoma. The association between PD and melanoma may also be explained by impaired autophagy in both PD and melanoma. Changes in PD-related genes such as Parkin, LRRK2, and α-synuclein may increase the risk of melanoma [3].

4.3. Ubiquitin-proteasome system

A common pathway in PD and cancer is the ubiquitin proteasome system (UPS), which controls protein degradation and cell cycle [15]. UPS is an essential regulatory mechanism in cells, fundamental for supporting cellular homeostasis, controlling signaling transduction, and affecting cell fates. The study of mutations in the gene encoding PARK2 made an essential contribution to our understanding of the connection between PD and cancer. PARK2 encodes an E3 ubiquitin ligase, is the most common cause of early-onset PD. Veeriah and coauthors demonstrated that the PARK2 mutations in cancer occur in the same domains as the germline mutations causing familial PD [16]. Cancer-specific mutations abolish the growth-suppressive effects of the PARK2 protein. Furthermore, PARK2 mutations in cancer reduce PARK2's E3 ligase activity, compromising its capability to ubiquitinate cyclin E, resulting in mitotic instability. These findings point to PARK2 as a tumor suppressor. The results also show that PARK2 is a gene that causes neuronal dysfunction when mutated in the germline, may also contribute to oncogenesis when altered in non-neuronal somatic cells [16].

Disturbances in this system are described in cancer, where the system is overactive [15,17,18], and with PD, where the UPS pathway is impaired [19–21]. UPS inhibitors are considered low-invasive chemotherapy medications drugs and are progressively used to relieve symptoms of various cancers in malignant states. There are two ways to synthesize a scaffold of UPS inhibitors and change it. The first approach uses the biology-oriented synthetic method to produce structurally novel molecules. The second approach is fragment-biased compound design in which several fragments are used to generate a scaffold by conjugating with each other [15]

Tian et al. (2021) investigated the genetic linkage between PD and gastric cancer using the barcode algorithm [23]. The method allows to analyze overlapped differentially expressed genes in two diseases. This approach revealed that the ubiquitin-conjugated enzyme E2 M protein (UBE2M) is linked to both diseases. In addition to UBE2M, three other candidates were identified: cathepsin D

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(CTSD), glutathione peroxidase 3 (GPX3), and casein kinase 1 delta (CSNK1D). Further analysis will show the exact mechanism of their involvement.

Another potential link between PD and cancer is ubiquitin C-terminal hydrolase BRCA1-associated protein 1(BAP1), a tumor suppressor and a known genetic risk factor for PD [24,25].

BAP1 is a ubiquitin C-terminal hydrolase with a wide array of biological activities.

4.4. Circulating melatonin

Accumulating data point to the role of circulating melatonin in the association of PD with cancer. Schernhammer et al. assumed that elevated circulating melatonin levels in patients with PD cause reduced cancer risk (2006) [26]. There is significant laboratory data and some epidemiological evidence that melatonin is important in carcinogenesis. The findings of elevated morning melatonin levels in patients with PD compared to healthy controls partially support this hypothesis. However, the evidence about melatonin's role in PD and other neurodegenerative diseases is not conclusive and needs to be further investigated.

4.5. Transcription factors

A growing number of experimental results show that transcription factors (TFs) are involved in the modulation of age-related disorders, including cancer and neurodegenerative diseases. They play a crucial role as regulators of many important cellular processes, including mitochondrial biogenesis, energy metabolism, oxidative stress, DNA repair, inflammation, nutrient homeostasis, vascular development, and cell regenerative capacity [27]. For example, transcription factor EB (TFEB) participates in the regulation of DNA damage and epigenetic modifications, inducing autophagy and proteostasis, regulating mitochondrial quality control, linking nutrient-sensing to energy metabolism, regulating pro- and anti-inflammatory pathways, suppressing senescence, and stimulating cell regeneration. Safe and effective strategies for activating TFEB might be considered a therapeutic approach for cancer and neurodegenerative disease treatment and for extending longevity [27].

Another TF playing a pivotal role in cancer and neurodegeneration is HIF1A- a hypoxia-inducible factor considered the master transcriptional regulator of cellular and developmental response to hypoxia [28]. This TF responds to the reduction in available oxygen in the cellular environment and can be modified by E3 ubiquitin ligase (Parkin). Liu et al. demonstrated that HIF1A ubiquitinated by Parkin (E3 ubiquitin ligase) on lysine 477 (K^{477}) became susceptible to degradation, which in turn reduces metastasis of breast cancer cells [28]. On the other hand, Parkin plays a critical role in mitochondrial quality control, and mutations in the Parkin gene cause a form of autosomal recessive juvenile PD [29].

Other proteins with TF-activity are implicated in both cancer pathogenesis and neurodegenerative diseases, which may play a role in linking pathogenic pathways in these two disorders. For example, DJ-1, cancer- and PD-associated protein, stabilizes the antioxidant transcriptional master regulator Nrf2 (nuclear factor erythroid 2-related factor), a master regulator of antioxidant transcriptional responses [30,31]. DJ-1 stabilizes Nrf2 by preventing association with its inhibitor protein, Keap1, and Nrf2's subsequent ubiquitination. Without intact DJ-1, the Nrf2 protein is unstable, and both its basal and induced transcriptional responses are decreased. DJ-1's effect on Nrf2 and the following impacts on antioxidant responses can explain how DJ-1 can affect both cancer and PD. DJ-1/Nrf2 functional axis represents a therapeutic target in cancer treatment and confirms the role of DJ-1 as a tumor biomarker [30,31].

4.6. Amyloidogenic substances

Naskar and Goar combined and analyzed published data and proposed a generic amyloid hypothesis, considering that amyloidogenic proteins may be responsible for the etiology of a plethora of diseases, including PD and cancer [32]. The hypothesis assumes that traditional amyloids are formed not only by proteins or peptides, but also by metabolites, including single amino acids,

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nucleobases, lipids, and glucose derivatives. They all have a propensity to form amyloid-like toxic assemblies. For example, phenylalanine can generate amyloid-like nanofibrillar structures under millimolar concentrations [33]. The authors assume that common therapeutic interventions for these diseases can be developed by designing drugs that act as generic amyloid inhibitors.

4.7. Neurotrophic factors

Neurotrophic factors possess protective effects on neurons, including their influence on the differentiation and survival of dopaminergic neurons. For example, glial cell line-derived neurotrophic factor (GDNF) is a member of the transforming growth factor β (TGF-β) superfamily. GDNF plays the role of a survival factor, acting on different neuronal activities, and is at present an established therapeutic target in PD [34].

On the other hand, accumulating evidence demonstrates that GDNF is abundantly expressed in gliomas, especially in glioblastomas, and is a potent proliferation factor involved in the development and migration of gliomas. For example, it is highly expressed in Glioblastoma Multiforme (GBM) due to the epigenetic regulation of its gene expression. This epigenetic mechanism includes DNA methylation and histone H3K9 acetylation of the promoter and silencer regions of the GDNF gene, stimulating its transcription. GDNF also modulates microtubule-associated proteins and actin-associated proteins in cellular migration. Due to these activities, GDNF may acquire pro-oncogenic activity and deprive cells of their apoptotic activity. As a result of high GDNF activity, microglia are attracted to tumor microenvironments to promote glioma progression. Thus, GDNF may contribute to glioma migration and invasion [34], and play the role of a potential molecular link in the association between PD and glioma.

The expression of another neurotrophic factor - Brain-derived Neurotrophic Factor (BDNF) is downregulated in PD and other neurodegenerative disorders and upregulated in various types of cancers. The lower level of BDNF in PD is related to cognitive and other neuropsychological deficiencies. At the same time, its high concentrations are associated with tumor growth, metastasis, and poor survival in cancer patients [35]. The authors assume that BDNF level is essential in establishing the program of cellular pathophysiology, being a critical factor in regulating homeostasis and the development of cancer or neurodegenerative disorder.

4.8. Chronic inflammation

Another link between cancer and PD is chronic inflammation in neurons and tumors, which contributes to microenvironmental changes that cause the accumulation of DNA mutations and eases disease development [36]. This hypothesis is based on considering the crucial role of microglia and the genetic involvement of COX2 and CARD15 in PD and cancer. If the main findings of this article are confirmed, it will explore preventive and therapeutic measures for both disorders [36].

4.9. microRNAs

microRNAs may play a role as a link between PD and cancer. Saito and Saito reported that microRNAs miR-9, miR-29, and miR-34 are differentially expressed in Parkinson's disease and some other neurodegenerative diseases and act as tumor suppressors during human carcinogenesis [37]. Hu and coauthors found that miR-148a is a potential tumor suppressor that reduces gastric cancer metastasis and also involved in neurological development and several functions [38]. For example, the expression of miR-148a is decreased in patients with PD compared to that in the control group.

5. α-Synuclein at the crossroad of PD and cancer

Synucleins are a family of three small, conserved proteins (α-, β-, and γ) expressed primarily in neural tissue and some tumors [39]. Despite a lack of clear understanding of their physiological role, their association with neurodegenerative diseases and cancer has been attracting the attention of researchers for many years.

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5.1. α-Synuclein in PD and other synucleinopathies

α-synuclein in PD and other synucleinopathies. It is well established that α-synuclein plays a fundamental role in PD and other synucleinopathies. Accumulation of misfolded α-synuclein oligomers and larger aggregates raises the vulnerability of neurons to dopamine-induced cell death [40–42]. Furthermore, α-synuclein is the major protein component of Lewy bodies and Lewy neurites [42,43]. The association of α-synuclein with PD and other synucleinopathies is proven by various experimental approaches, including genetic, biochemical, and immunochemical, and summarized in these reviews [39–43], so we will not discuss their details here.

5.2. Synucleins in cancer

The association of synucleins with cancer was first documented for γ-synuclein in breast cancer [44] and later in several other types of cancer [15,45,47]. Accumulating data indicates that two other members of the synuclein family (α, β) are also associated with tumorigenesis (reviewed in [46]. For example, both β-synuclein and γ-synuclein are highly expressed in stage III-IV of breast ductal carcinomas, while all three types of synucleins are expressed in ovarian carcinomas [47].

α-Synuclein is expressed in certain types of cancer, i.e., its expression is described in breast cancer, melanoma, and ovarian cancer [46–49]. The expression of α-synuclein was also reported in medulloblastomas [50], colorectal cancer [48], acute erythroid leukemia and acute megakaryoblast leukemia [51], osteosarcoma cells [52]. As described by Kawashima et al., α-synuclein is expressed in various brain tumors showing neuronal differentiation (2000) [53].

The data about the changes in α-synuclein expression level depends on the type of cancer. An increased expression of α-synuclein is described in pancreatic adenocarcinoma [54] and melanoma [55]. On the other hand, α-synuclein expression is reduced in some tumor tissues, and its down-regulation is related to poor prognosis and overall survival [56]. There is a substantial decrease in α-synuclein expression in colon adenocarcinoma; however, in colorectal cancer, α-synuclein level is increased [46]. In some studies, it was demonstrated that upregulation of α-synuclein suppresses tumorigenesis [15].

New results recently published by Yang suggest a mechanism of α-synuclein involvement in cancer development. α-Synuclein acquires this activity after combining with two other proteins implicated in tumorigenesis, i.e., metabotropic glutamate receptor 5 (mGluR5) and another member of the synuclein family - γ-synuclein (2023) [15]. mGluR5 receptor activity is essential for the proliferation and survival of cancer cells [57]. These new findings demonstrate that mGluR5 and γ-synuclein are tumor-promoting factors stimulating cancer cells migration, proliferation, and metastasis. Thus, α-synuclein can be associated with mGluR5 and γ-synuclein, contributing to the inhibitory effect on cancer progression [15]. The involvement of α-synuclein in various types of cancer is summarized in a recent review by Zanotti et al. (2023) [46].

Synuclein's role in cancer is associated with its involvement in various cancer-related cell signaling processes and pathways. For example, α-synuclein is implicated in autophagy, mitochondrial metabolism, and the generation of ROS in cancer and in the same processes in neurodegenerative diseases [46].

5.3. α-Synuclein and melanoma

The association between PD and malignant melanoma was found not only in epidemiological studies, as discussed above (Section 2), but it is also proven by biochemical studies. This relationship is due, at least partially, to α-synuclein's role as a regulator of pro- and antiapoptotic processes [58]. The accumulation of the α-synuclein oligomers has been described both in PD, being a hallmark of this disorder, and in malignant melanoma, which increases the proliferation of tumor cells [5,59–61].

Furthermore, in cultured B16 melanoma cells, α-synuclein overexpression caused increased cell proliferation [62]. Significantly, knocking out α-synuclein in melanoma cells suppresses tumor growth [63]. Accumulating data point to the epigenetic mechanisms, which play a critical role

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regulating of α-synuclein expression and affect its involvement as a mediator linking cancer and neurodegeneration [4,64,65].

The data showing that α-synuclein expression influences tumorigenesis [62,66] points to the existence of a common pathogenic mechanism between cancer and neurodegenerative diseases.

Additional evidence in favor of such a mechanism is the effect of a higher risk for malignant melanoma in PD patients [67–69].

Filippou and Outeiro reported that increased levels of α-synuclein in PD patient's melanocytes reduced tyrosine hydroxylase levels, thereby reducing melanin synthesis and increasing the risk of melanoma. Therefore, increased levels of α-synuclein raise the risk for both PD and melanoma (2020) [13]. The authors expressed hope that insights from one disease might lead to improved management of both diseases.

According to the majority of data, the inverse correlation between α-synuclein expression and melanin production suggests that α-synuclein disturbs the activities of tyrosine hydroxylase and tyrosinase - enzymes involved in melanin biosynthesis [2,4,13]. Dean and coauthors proposed an alternative explanation of α-synuclein and melanin interplay (2021) [70]. Based on epidemiological findings and molecular interaction data, they assume that α-synuclein binds and controls the aggregation of Pmel17, a functional amyloid that serves as a scaffold for melanin synthesis.

Thus, the disruption of melanin biosynthesis by α-synuclein in melanoma cells may involve the two amyloid-forming proteins, α-synuclein and Pmel17, affecting the pigmentation in melanoma cells (2021)[70].

Lee et al., found a physiological significance of α-synuclein phosphorylation on serine-129(2013) [71]. These researchers demonstrated that such phosphorylation causes α-synuclein translocation to the cell surface with its subsequent vesicular release in melanoma cells. The authors hypothesize that α-synuclein release from melanoma cells plays a role in the pathogenesis or progression of PD, since it might propagate into neuronal cells. This hypothesis is partially supported by a finding that α-synuclein is transmitted from human melanoma cells to neuroblastoma cells when these two types of cells are co-cultured [72]. Interestingly, Ser129-phosphorylated α-synuclein is abundantly found in melanoma cells but not in normal skin [2].

Role of α-synuclein phosphorylation. α-Synuclein post-translational modifications change its properties and affect the involvement in diseases, including PD and cancer. Currently, the most thoroughly studied post-translationally modified α-synuclein is phosphorylated in Serine129 form [73]. Almost all α-synuclein in Lewy bodies in Parkinson disease brains is phosphorylated on Serine-129 [74–77]. Phosphorylation of α-synuclein on serine-129 also affects its role in melanoma. According to Inzelberg and coauthors, the mechanisms underlying the high prevalence of cutaneous malignant melanoma in PD involve common pathways in which phosphorylated in serine-129 plays a major role [2] (2016). This post-translationally modified form of α-synuclein is abundantly expressed in cutaneous malignant melanoma but not in normal skin [78]. The authors also showed that α-synuclein phosphorylated on Ser-129 is abundantly found in melanoma cells but not normal skin [78].

A new regulatory role of Ser129-phosphorylated α-synuclein was found by Inzelberg and coauthors, who showed that this form of α-synuclein can modulate Pmel17 functional amyloid formation [2].

6. Molecular mechanisms underlying α-synuclein role in the association with PD and cancer

In another recent study, Hou et al.] examined the potential role of α-synuclein in the link between PD and liver cancer and found that exosome-delivered α-synuclein inhibited the growth, migration, and invasion of cultured hepatocellular carcinoma cells (2023) [10]. Integrin αVβ5 in exosomes enhanced this effect. Importantly, in vivo experiments with rat models confirmed that exosome-delivered α-synuclein inhibited liver cancer. These findings show the critical role of α-synuclein in the inhibition of hepatoma, suggesting a new mechanism underlying the link between these two diseases.

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Data discussed above suggest the role of epigenetic mechanisms, which play a critical role in the regulation of α-synuclein expression and affect its involvement as a mediator linking cancer and neurodegeneration [4,64,65].

Synuclein's role in cancer is associated with their involvement in cancer-related cell signaling processes and pathways. For example, α-synuclein is implicated in autophagy, mitochondrial metabolism, and the generation of ROS in cancer and in the same processes in neurodegenerative diseases [46].

6.1. Chemical reactivity of α-synuclein amyloids

Recent studies point to a new gain-of-function property of α-synuclein amyloids that may affect the pathogenesis of human diseases. α-Synuclein amyloid fibers possess enzyme-like catalytic properties, for example, esterase and phosphatase activity. α-Synuclein monomers had little or no enzymatic activity [79]. In another recent article, Horvath &Wittung-Stafshede demonstrated that α-synuclein amyloid caused alterations in metabolites: the amount of four of them increased, while the amount of seventeen decreased (2023) [80]. The exact nature of these findings deserves further investigation, but they may open a new era dealing with unexplored pathological pathways associated with amyloids in human diseases.

6.2. Irisin is at the crossroads between cancer and PD

Irisin ameliorates the course of both cancer and PD. Irisin is an adipomyokine that is involved in the regulation of metabolic processes. It is an exercise-induced polypeptide secreted by skeletal muscle. Irisin is at the crossroads between cancer and PD, being able to ameliorate the course of both diseases. It has been confirmed that irisin inhibits in vitro proliferation, migration, and invasion. It also influences inflammatory processes, including cancer, decreasing the expression of cancer markers [81,82]. On the other hand, irisin prevents pathologic α-synuclein-induced neurodegeneration in PD. It causes a decrease in the formation of pathologic α-synuclein, prevents the loss of dopamine neurons, and lowers striatal dopamine. Irisin also reduces motor deficits and decreases the formation of phosphorylated serine-129 in α-synuclein [83].

7. Role of two other members of the synuclein family β and ɣ-synuclein

7.1. β-Synuclein

β-Synuclein is closely related to α-synuclein [39] and often coexpressed with α-synuclein [84]. β-Synuclein acts as a molecular chaperone to inhibit α-synuclein aggregation [85]. Recent reports suggest that β-synuclein promotes neurotoxicity, indicating that β-synuclein is implicated in other cellular pathways independent of α-synuclein. β-Synuclein is involved in neurodegenerative diseases [86], and $P^{123}H$ and $V^{70}M$ mutations in β-synuclein are associated with dementia with Lewy bodies [85]. β-Synuclein also attracts attention in the neuro-oncological area since its high expression in glioma tissues [87] in erythroid leukemia and acute megakaryoblastic leukemia [88].

7.2. ɣ-Synuclein

ɣ-Synuclein is a predominately neuronal protein that is also overexpressed in various types of human cancer. High levels of ɣ-synuclein proteins have been revealed in many types of cancer, notably in advanced stages of the disease [89]. Furthermore, overexpression of ɣ-synuclein compromises normal mitotic checkpoint controls, causing multinucleation and accelerated cell growth. ɣ-Synuclein stimulates invasion and promotes metastasis in in vitro assays and animal models. In addition, ɣ-synuclein promotes phosphorylation of transforming growth factor-β-induced p38 mitogen-activated protein kinase (MAPK) phosphorylation [90]. These findings point to the essential role of p38MAPK promoting cancer metastasis by ɣ-synuclein and imply that p38MAPK inhibitors may serve as potential medications for ɣ-synuclein-overexpressed cancer [90].

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Motor neurons contain a significant amount of γ-synuclein, especially in axons, where it presumably regulates the organization of the axonal cytoskeleton [91–93]. Accumulation of γ-synuclein in distinct profiles within the dorsolateral column has been described in amyotrophic lateral sclerosis (ALS) cases [89]. Histopathological pathological structures containing abnormal γ-synuclein have been reported in several other neurodegenerative diseases [94–96]. Although γ-synuclein role in several types of cancer and neurodegenerative diseases is well documented, there is no precise data about its role in the association of these two types of pathologies.

8. Common protective factors for PD and cancer

Reduced levels of cancer mortality or incidence in PD patients have generated an assumption about the existence of protective factors common to both diseases. It is important to identify these factors to understand the mechanisms of both pathologies better and to find approaches for their treatment. One such factor which may play a protective role in both PD and cancer is the serine-threonine mitochondrial protein kinase PINK1. PINK1 possesses a neuroprotective effect since it prevents mitochondrial damage and apoptosis in response to stress factors. Cell protection of PINK1 is due to phosphorylation of Bcl-xL and regulation of its pro-apoptotic cleavage [97].

On the other hand, PINK1 has some protective effects for some types of cancer, and its loss results in elevated proliferation of glioma cells, decreased oxygen consumption and raised glycolysis [98]. In certain types of malignancy, e.g., ovarian and breast cancer, PINK1 plays the role of tumor suppressor [99].

Another protein that may protect against cancer and PD is Parkin (Park2), a multifaceted E3 ubiquitin ligase. It is an important tumor suppressor, and at the same time, it inhibits apoptosis and promotes survival in neuronal cells, potentially being protective against cancer and PD. Such protective Parkin activity may be associated with its regulatory action toward p53 [14].

Inhibition of p53-mediated apoptosis is a mechanism that causes the neuroprotective effect of Parkin [100].

9. Conclusion

Multiple clinical and epidemiological studies have shown that patients with PD have a lower risk of developing cancer. However, the mechanisms of their association are still not completely understood.

PD and cancer are intricate diseases with multiple cellular changes. An intriguing aspect of the inverse association between PD and cancer that merits thorough investigation is their different pathophysiological time frames. PD is characterized by gradual neuronal loss, being a chronic and generally slow-progressing neurodegenerative disease. In contrast, cancer usually exhibits rapid progression with the fast proliferation of glial cells over a much shorter duration. This disparity suggests that in PD, neuronal loss can be compensated for over an extended time, whereas the aggressive nature of cancer, driven by highly infiltrative and metastasizing cells displaying considerable heterogeneity, leads to a rapid disease progression. Common pathogenic mechanisms underlie both PD and cancer, encompassing inversely deregulated pro-survival and immune signaling, DNA damage, mitochondrial dysfunction, cell cycle defects, metabolic alterations, and chronic inflammation. Recent data points to neurotrophic factors and members of the synuclein family as signaling molecules involved in both diseases.

10. Future Directions

Advancements in understanding the pathogenesis of PD and cancer have the potential to catalyze the development of novel diagnostic methods with practical clinical applications. Insight into the potential mechanisms underlying these pathologies and their interdependencies could be the foundation for effective targeted therapies, modifying and enhancing the course and prognosis of both diseases. Increasing knowledge about the involvement of common pathways, mechanisms, and molecules in these two diseases will aid in devising strategies to combat the challenges on both fronts

and decipher the molecular connections between PD and cancer. Advancing our understanding of the common pathways, mechanisms, and molecules involved in these two diseases will help devise strategies to address challenges on both fronts and unravel the molecular connections between PD and cancer. The rapid progress in CRISPR technology holds promise for treating genetic forms of these diseases, while the development of artificial intelligence will uncover existing associations and identify new ones.

Author Contributions: AS - wrote the manuscript; made analysis and interpretation of data; made a final approval of the version to be published; and agreed to be accountable for all aspects of the work. AAS – participated in writing and editing of the manuscript and interpretation of data; made substantial contributions to the conception of the work; made a final approval; and agreed to be accountable for all aspects of the work.

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