Published online: March 30, 2020

Mini-Review

Neurodegenerative diseases and cancer: sharing common mechanisms in complex interactions

Natalia González Rojas[1], Martin Cesarini[1], José Luis Etcheverry[1], Gustavo Andrés Da Prat[1,2], Valeria Antico Arciuch[3] and Emilia Mabel Gatto[1,2,*]

[1] *Instituto Neurociencias Buenos Aires (INEBA), Guardia Vieja 4435, CABA, Argentina*

[2] *Sanatorio de la Trinidad Mitre, Bartolomé Mitre 2553, CABA, Argentina*

[3] *Conicet, Godoy Cruz 2290, CABA, Argentina*

*Correspondence: emiliamgatto@gmail.com (Emilia Mabel Gatto)

DOI:10.31083/j.jin.2020.01.3

Several epidemiological studies support low cancer rates in patients with neurodegenerative disorders, including Parkinson's disease, Huntington's disease, and Alzheimer's disease. Different mechanisms were raised as possible causes, from mutated tumor suppressor genes (PARKIN, PINK1) to small interfering RNA based on the CAG trinucleotide repeat expansions located in introns or untranslated regions. However, as every rule has an exception, some tumors have an increased incidence in these neurodegenerative diseases such as breast and skin cancer (melanoma). This mini-review aims to establish the epidemiology between these neurodegenerative disorders and cancer to determine the possible mechanisms involved and therefore set eventual therapeutic applications. According to our findings, we conclude the presence of an inverse relationship among most cancers and the aforementioned neurodegenerative disorders. However, this concept needs to be considered cautiously considering specific genetic and extra-genetic linkage factors for particular tumors.

Keywords

Parkinson's disease; Huntington's disease; Alzheimer's disease; neurodegenerative disorders; cancer; mechanisms

1. Introduction

Parkinson's disease (PD), Huntington's disease (HD), and Alzheimer's disease (AD) are neurodegenerative disorders from different etiologies, involve different mechanisms of neurodegeneration and have different prognoses (Lane et al., 2018; McColgan and Tabrizi, 2018; Nutt and Wooten, 2005). On the other hand, they do share certain pathophysiological mechanisms that rely on the inclusion of intracellular proteins, leading to neurodegeneration and cell death, as well as the fact that the entire disease process begins many years before clinical symptomatology, with subtle symptoms, in general, non-motor ones (Morales-Briceño et al., 2011).

Cancer, otherwise, represents an assembly of proliferative disorders characterized by malignant transformation, dysregulation of mitosis, invasion, and metastasis. At first sight, the relation between neurodegenerative diseases and cancer seems moot; while cancer is characterized by uncontrolled cell growth, neurodegenerative disorders are caused by untimely cell death. However, recent molecular and biological findings support an interplay between both conditions (Plun-Favreau et al., 2010).

Many reports establish an inverse relation among these pathologies and the incidence of certain cancers, such as colorectal, lung, and liver cancer, compared to groups matched with age and gender (Coarelli et al., 2017; Driver et al., 2012; Engel, 2016). Gene mutations, transcriptional, protein, and mitochondrial dysregulation in opposite directions play a substantial role in these disorders. In this sense, a tumor-suppressor gene with a transcriptional role, p53, is downregulated in several tumors and upregulated in PD, AD, and HD (Houck et al., 2018). Therefore, a link between cancer and neurodegeneration is plausible as they share several genes and biological pathways, including inappropriate activation and deregulation of the cell cycle, resulting in opposite endpoints.

The proposed mechanisms vary according to the underlying disease, from molecular changes that include genes as Parkin, Pink1, P53, translation of siRNA in no-coding regions that may be toxic to cancer cells, to mechanisms that involve replacement treatments like L-DOPA in Parkinson disease which is known to reduce the angiogenesis within the tumor. Although the association between neurodegeneration and cancer remains unproved, some genes manifest a prevalent role in both entities, involving cell cycle control, DNA repair, and kinase signaling. On the other hand, some reported cancers increase their incidence among these diseases, like breast and skin tumors.

Over the past few years, evidence has steadily emerged regarding possible relationships between cancer and neurodegenerative diseases. A better understanding of the biological links is already opening new therapeutic horizons. The usefulness of knowing these aspects is to be able to propose different therapeutic options for the different types of cancer without affecting or worsening the underlying disease.

Journal of Integrative Neuroscience

2. Epidemiology

Different epidemiologic studies reported a low incidence of malignant neoplasm in neurodegenerative conditions. After database research strategy, using the words "cancer," "Parkinson," "Huntington," "Alzheimer," "neurodegenerative disorder," "prevalence," "incidence," "mechanisms," "treatments" in PubMed and Embase, we analyzed twenty articles, from 2007 to 2019. Nine were about the association between PD and cancer (colorectal, melanoma, breast, lung, bladder, thyroid and prostate), six between HD and cancer (breast, skin, bladder, thyroid, prostate, cervix, ovary, lymphoma, leukemia, lung, brain and colon) and five between AD and cancer (breast, skin, and prostate).

2.1 Parkinson disease

Hoehn and Yahr (2016) were the first authors describing the possible inverse association between PD and malignant neoplasm. The expected number of deaths by cancer in their general population was estimated at 41 individuals, while the number identified in their PD sample was 24 ($P < 0.001$). Subsequently, many reports arose supporting that theory. Jansson and Jankovic (1985) reported 18 new diagnoses of cancer in 406 PD patients concerning the 41.9 estimated cases in the general population ($P < 0.0001$). One of the most extensive studies was conducted by Vanacore et al. (1999) and included 10,322 PD patients. In this Italian population, the risk of cancer death estimated by standardized mortality ratio (SMR) was 44% lower concerning the expected SMR in the general population (Vanacore et al., 1999). To exclude potential confounders, such as smoking, the SMR was estimated in two groups PD smoking patients and PD non-smoking ones. In both cases, the SMR was decreased in PD patients concerning the general population with an SMR 51, 95% CI 42 to 60 in the smoking group, and SMR 58, 95% CI 52 to 65 in the non-smoking group, respectively. Another study identified 1,282 individuals with cancer over 14,088 PD patients with a 12% reduction concerning the 1,464 expected in the general population standard incidence ratio (SIR): 0.88 (95% CI 0.8 to 0.9) (Inzelberg and Jankovic, 2007).

A Japanese study found a reduction of 9% in the deaths by malignant neoplasms in PD patients versus the general population (10% vs. 19%, respectively) The difference was not significant ($P = 0.07$) due to the small sample of patients with Parkinson's disease (n = 50) (Jansson and Jankovic, 1985).

We found two studies regarding PD and colorectal cancer (CRC) (Boursi et al., 2016; Xie et al., 2016). The first one included an extensive series of 22,093 CRC cases, in which PD was identified in 117 (0.5%). Moreover, a personal history of PD was associated with lower CRC risk (OR: 0.84; 95%CI 0.69-1.03). No association was demonstrated between anti-parkinsonian drugs and CRC risk. The second one is a review which included 11 cohort and 2 case-control studies comprising 343,226 PD patients, showing a reduction of 21% in the risk of developing CRC in PD patients. These findings contribute to supporting the inverse association between PD and the risk of CRC in the Western population.

Delving into the risk of cancer in the PD population according to its cause, we found a study that compares LRRK2 PD patients and idiopathic PD (Bjørg and Aasly, 2018). The authors report a higher incidence of non-skin cancers (17.5% vs. 15.1%) and early age of onset of non-skin cancer in LRRK2 positive PD patients concerning the idiopathic PD patients (60.5 years vs. 66.3 years, respectively). Although most cancers appear to be less common in this population, a few types, including malignant melanoma, breast carcinoma, and thyroid, have been reported to occur with increased rates in patients with PD (Pan et al., 2011). In this sense, a higher incidence of skin cancer (melanoma) was reported in the DATA TOP cohort with 5 cases concerning the 1.5 cases expected adjusted by age and gender (Constantinescu and Kieburtz, 2006).

Table 1. Observed cancer cases vs. expected ones in an HD population (Coarelli et al., 2017).

TYPE OF CANCER	CASES	EXPECTED
Breast	8	14.22
Skin	5	0.98
Bladder	2	4.52
Prostate	1	5.96
Cervix	1	4.48

The most extensive study conducted in the USA demonstrated a 2.2 fold higher prevalence of invasive melanoma in PD patients concerning the general population (Bertoni et al., 2010), according to the national Surveillance Epidemiology and End Results-US Cancer Statistics Review database. On the other hand, the occurrence of melanoma was associated with an increased risk of PD development (50%). In agreement with Bertoni et al. (2010) (Olsen et al., 2006), PD patients showed a two-fold increased risk for melanoma (Rugbjerg et al., 2013).

The second mentioned cancer with increased risk in PD patients is breast cancer. In this sense, a Danish study, including more than 20,000 PD patients showed an increased risk of breast cancer in PD patients compared with the general population (SIR: 1.17; 95% CI 1.02-1.34) (Rugbjerg et al., 2013).

2.2 Huntington's disease

Coarelli et al. (2017) examined 372 patients with HD and found a total of 23 malignant neoplasms vs. an expected number of 111 (Standardized incidence ratios (SIR) = 0.21, 95% confidence interval (CI)). Nevertheless, in patients with HD, skin cancers were more usually found than expected (5 vs. 0.98, SIR 5.11, 95% CI) (Coarelli et al., 2017). All types of cancer found in this paper are summarized in Table 1.

Turner et al. (2012) concluded in a remarkably reduced incidence of cancer in HD. The rate ratio for cancer in people with HD in the all-England cohort was 0.71 (95% confidence interval 0.61--0.83). Although smoking has been reported to be more frequent in presymptomatic HD gene carriers than in the general population, cancer incidence has been reduced in HD. Thion et al. (2016) made an interesting observation, asserting that polyglutamine diseases showed a lower incidence of cancer, independently of the CAG length (even if the CAG expansion does not reach the incomplete or complete penetrance range). They found that also though the frequency of cancer may be inversely correlated to the number of CAG repeats (nCAG), a large nCAG might favor the progression and local spreading of some cancers, particularly breast tumors (Thion et al., 2016). This was supported by McNulty et al. (2018) in their research report from 6540 subjects participating in the REGISTRY study of the European Huntington's Disease Network, one of the most extensive studies performed comparing

cancer incidence in HD patients with the general population, observing lower rates of malignancy in the former group.

2.3 Alzheimer's disease

Little data is available regarding a link between cancer and AD. Driver et al. (2012) studied 495 cases of any dementia, 49 of possible Alzheimer's disease, and 327 of probable Alzheimer's disease. Three healthy controls were paired with each case. On average, cancer was identified in 8% of cases vs.14% in the control group, showing in the age-matched group a considerable decrease of cancer occurrence in those patients with any dementia (mean 0.44, range 0.32-0.61) or probable AD (mean 0.39, range 0.26 -0.58).

Moreover, in this cohort, cancer survivors showed a reduced risk of developing AD (33%). On the other hand, a case-control study supports a 61% reduced risk of developing a malignant neoplasm in patients with probable AD (Roe et al., 2010).

Bennett and Leurgans (2010) examined the relation of prevalent dementia to incident cancer. Among 165 persons with prevalent dementia and 2,107 healthy persons, they found 376 cases of incident cancer. After appropriate adjustment for covariates, a 60% decreased risk of incident cancer was observed in AD.

3. Possible mechanisms

3.1 Parkinson's disease

Aging has been associated with cellular damage regarding a large number of similar mechanisms involved in carcinogenesis and neurodegeneration, leading to a common final path. Such mechanisms include genomic instability, telomere tearing, epigenetic alterations, dysregulation of biological pathways that control biogenesis, folding, trafficking, and clearance of proteins, altered nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell damage, and impairment in intercellular communication. (Fig. 1)

For example, causative genes of familial PD, such as PARK2 (Parkin) and PARK5, have a fundamental role in the ubiquitin proteasomal protein degradation. These genes possess antiproliferative properties that appear to be inactivated in neoplasms.

Ample evidence suggests that Parkin is a tumor suppressor gene, involved in a variety of cancers (Cesari et al., 2003; Denison et al., 2003; Picchio et al., 2004; Wahabi et al., 2018; Wang et al., 2004). Parkin is an E3 ubiquitin-protein ligase, which ubiquitinates a large number of proteins, including itself, to promote different pathways, including ubiquitin -proteasomal pathway, and mitophagy. Moreover, its phosphorylation may also alter its folding, solubility, and binding affinity of ligand or substrate (Ko et al., 2007; Yamamoto et al., 2005). PARK2 tumor mutations are the most common ones associated with juvenile and early-onset PD. Parkin possesses a neuroprotective role against a large number of cellular offenses, such as manganese-induced cell death, endoplasmic reticulum stress, α-synuclein toxicity, mitochondrial damage, and ligands accumulation for proteasomal impairment. Lee et al. (2016) investigated the suppression activity mediated by Parkin. The authors proposed an inhibitor role of Parkin in the programmed necrosis death pathway (necroptosis). Necroptosis is one of the regulated cell deaths, which could be activated by different factors. Regarding this, tumor necrosis factor (TNF) appears as the first step in this cascade. The TNF activation is

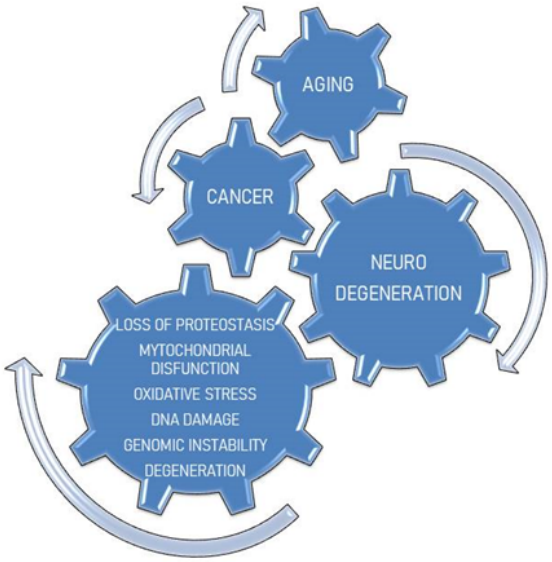

Figure 1. Aging results in increased levels of metabolic disturbances, loss of proteostasis, oxidative stress, and DNA damage leading to genomic instability. Many of these aging disturbances are involved in neurodegeneration and cancer and contribute to the development of both disorders.

followed by subsequent phosphorylation of receptor-interacting serine/threonine-protein kinases 1 (RIPK1) and 3 (RIPK3), which are recruited into a complex called the necrosome. RIPK3 phosphorylates the mixed lineage kinase domain-like protein (MLKL), leading to its activation and membrane permeabilization, favoring the pro-inflammatory molecules (damage-associated molecular patterns-DAMPs) release, and thereby inhibiting carcinogenesis (Cao and Tait, 2019; Lee et al., 2019).

Interestingly, the authors provide evidence that Parkin activation in necroptosis occurs independently of PINK1-Parkin-mediated mitophagy to remove damaged mitochondria. Beyond the classical role of parkin in mitophagy, they identified a role in the necroptosis inhibition mediated by AMP-activated protein kinase (AMPK) that increases RIPK3 polyubiquitylation affecting the RIPK1-RIPK3 interaction, one of the relevant steps for necroptosis (Lee et al., 2019).

The close link between AMPK and Parkin appears to be related to the presence of an AMPK phosphorylation site within the N-terminal ubiquitin-like domain of Parkin that is phosphorylated during necroptosis. AMPK dependent phosphorylation blocked the inhibition of the Parkin protective mechanism, mediated by blocking inhibition of RIPK3 activity. (Fig. 2)

Although anti-inflammatory and anti-tumor functions of Parkin are extensively recognized, PARK2 heterozygosity has been described to be associated with colorectal tumor progression in experimental models (Lee et al., 2019). Cancer cell survival might be explained by their capacity to impair the activity and expression of tumor suppressor genes, such as PTEN (phosphatase and tensin homolog) gene, which is known to be down-regulated in several cancers (Li et al., 1997). Interestingly, a PTEN inactivation mediated by Parkin deficiency has been described in human malignant neoplasms. Thus, these observations contribute to supporting

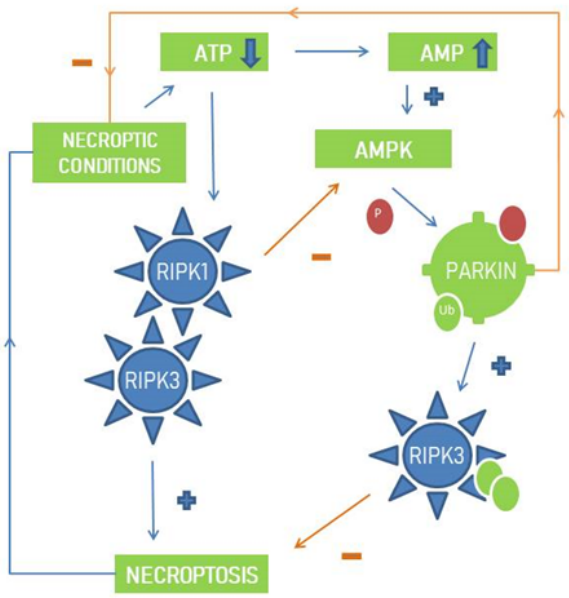

Figure 2. Schematic representation of the AMPK-Parkin pathway and the negative regulation of necroptosis and tumorigenesis via RIPK3 inhibition. Parkin reduces cancer-induced inflammation and leads to the inhibitory mechanism of necroptosis. Necrosome complex conformation requires the RIPK1 kinase activation to promote the binding to phosphorylated RIPK3. The complex RIPK1/RIPK3 induces AMPK activation that, in turn, phosphorylates and activates Parkin leading to RIPK3 ubiquitylation. This process inhibits necrosome conformation and prevents necroptosis and cancer-induced inflammation.

a clear Parkin-PTEN relationship in malignant transformation and cancer cell survival (Xu et al., 2014).

As mentioned previously, Parkin has been identified as a tumor suppressor gene, and in order with this characteristic, its expression has been reported to be decreased in a variety of tumor biopsies and tumor cell lines. Although the role of Parkin in other cancers, such as breast cancer, is still to be explored, reports are stating a loss of Parkin expression and increased Parkin methylation in those tumors with the worst prognosis related to metastasis and neoplasm growth (Wahabi et al., 2018).

Regarding transformed cell survival, a cancer cell requires the availability of nutrients and oxygen to last. To address these needs, the tumor cells develop neovasculature by a process called angiogenesis. Vascular endothelial growth factor (VEGF) is one of the most potent stimulators of angiogenesis identified so far, which affects endothelial cell proliferation, motility, and vascular permeability. Interestingly, it is observed that Parkin influences the expression of the VEGF receptor (VEGFR). In Parkin cells, expression of VEGFR is found to be reduced when compared with controls (Kerbel and Kamen, 2004; Sherwood et al., 1971; Wahabi et al., 2018; Waltenberger et al., 1994), through an unknown mechanism.

As we mentioned previously, inflammation plays a vital role in cancer development, and it represents a marker of tumorigenesis. An overexpression of pro-inflammatory markers, interleukin-1β (IL-1β), and TNF-α have been demonstrated in Parkin knockout cells, highlighting its anti-inflammatory function (Hussain and Harris, 2007; Lee et al., 2016). These findings suggest that inflammation plus Parkin deficiency (with PTEN inactivation, inflammatory response, and increased expression of VEGFR) might contribute to malignant neoplasm development (Rom et al., 2013).

In vivo and *in vitro* studies demonstrate microtubules involvement in the regulation of metastasis. Remarkably, Parkin increases microtubule stabilization. Therefore, the gene overexpression inhibits tumor cell migration. These observations agree with a negative effect of Parkin in cancer cell metastasis through microtubule-stabilization (Ren et al., 2009; Yang et al., 2005). (Fig. 3)

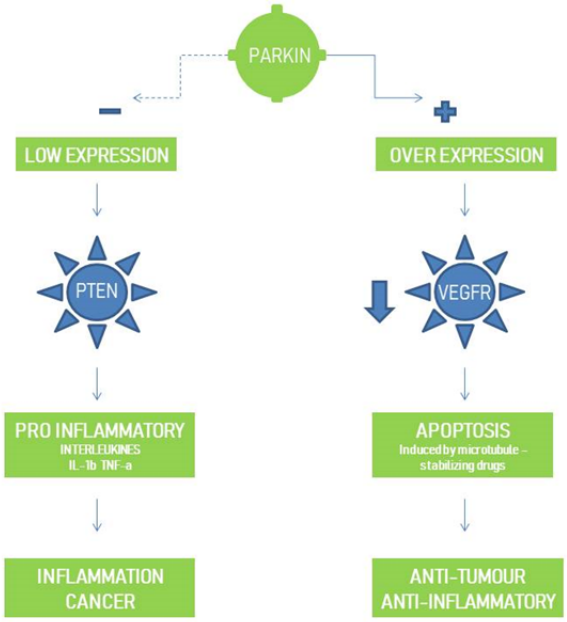

Figure 3. Parkinson's disease and cancer, Parkin mediated mechanisms. A scheme on the role of PARKIN in the development of cancer. The decreased expression of PARKIN lowers the expression of the tumor suppressor gene PTEN, leading to an increase in proinflammatory interleukins (IL-1b; TNF-a), increasing the rate of cancer development. On the other hand, the overexpression of PARKIN leads to a decreased expression of endothelial growth factor receptor (VEGFR), inducing the stabilization of microtubules and leading to an anti-inflammatory and antitumor effect.

Another analysis point involves mitochondria (Engel, 2016; Wahabi et al., 2018). Its dysfunction in oxidative phosphorylation may be viewed more as facilitating rather than causing idiopathic PD since energy failure backs up the influence of additional age-related, genetic and environmentally determining factors that lead to disease expression (Palacino et al., 2004; Schmidt et al., 2011). (Fig. 4)

According to Engel (2016), abnormal mitochondria biogenesis and function might regulate the development and proliferation of neoplasms (Bennett and Leurgans, 2010). They affirm that in idiopathic PD, the incapacity to adapt to the extreme metabolic demands added to other genetic and environmental variables results in punctual cell dysfunctions and, consequently, death. In the case of certain malignancies, the same deficit may offer pro-

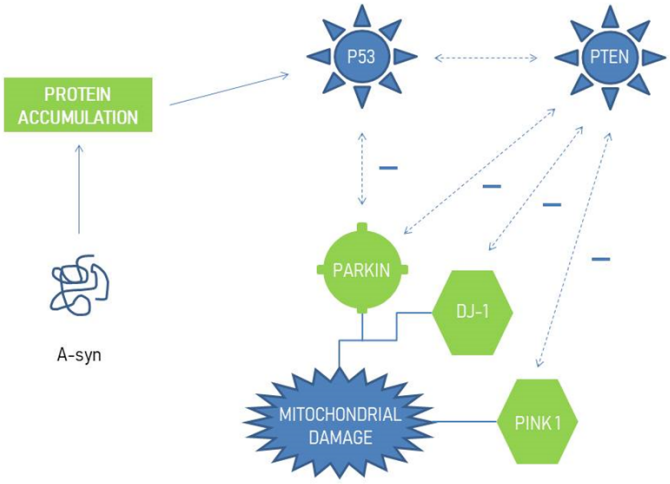

Figure 4. Overlapping biological pathways of PD and cancer mainly include protein accumulation, mitochondrial damage, oxidative stress response, chronic inflammation, and cell cycle control with flaws in DNA repair. This scheme shows how the three most common genes Parkin, DJ-1, and PINK1 involved in PD lead to dysregulation of both tumor suppressor genes, PTEN, and P53.

tection from tumor growth, invasion, and metastasis. These processes depend on dynamic metabolic reprogramming abilities and preserved mitochondrial competence for successful regulation of both glycolytic and oxidative phosphorylation routes.

We need to mention that PARK6 (PINK1) may also have a protective and anti-tumor function and that both genes, Park2 and Park6 (PINK 1), possess not only anti-inflammatory but also tumor-suppressive characteristics. On the other side, PARK7 (DJ-1) has been described as an oncogene, and this condition appears to be mediated by the inhibitor function on the PTEN, as mentioned beforehand, a known tumor suppressor gene (Houck et al., 2018).

Chan and Chan (2015) attributed a fundamental part to DJ-1 protein, known to be an oncogene, able to transform cells weakly on its own. DJ-1 protein has been mentioned as a positive regulator of the phosphoinositide-3-kinase--protein kinase B/Akt (PI3K/Akt) pathway, a signaling pathway involved in the regulation of the cell cycle. PI3K/Akt promotes a negative PTEN protein regulation as well as the p53 tumor suppressor activity (Haque et al., 2008; O'Flanagan and O'Neill, 2014; Thomas et al., 2011; Wu et al., 1998). In summary, in the presence of oxidative stress, DJ-1 downregulates PTEN, and induces PI3K/Akt pathway activation. Unfortunately, when these antioxidants were tested in an exogenous manner, they were not as useful as they thought they would be. Thereby, an alternative approach would be to activate the endogenous intracellular ones. A possible therapeutic pathway to explore is to increase the phosphorylation of PI3K/Akt complex to contribute cell survival through inhibition of proapoptotic factors (Kim et al., 2005, 2009).

On the other hand, in oxidative stress situations, DJ-1 contributes to the Pink1/Parkin pathway to maintain mitochondrial function. This process helps to the organelle quality control involving Parkin translocation to damaged mitochondria, favoring clearance by mitophagy. This way, increased function in mitochondrial DJ-1 by Pink1/Parkin may limit oxidative stress-induced damage to improve mitochondrial health (Alvin et al., 2012).

Regarding some particular tumors, Xie et al. (2016) studied the possible mechanisms related to colorectal cancer and PD. Different hypotheses have been proposed to explain the inverse association between both conditions (Louis et al., 2014). First of all, colorectal cancer and PD possess particular characteristics and different responses to cell proliferation. In order with this situation, apoptosis and dopaminergic neuronal death are the main features in PD, while colorectal cancer represents the opposite condition, with apoptosis inhibition and cell proliferation (Ong et al., 2014). Secondly, the PD therapy may provide another explanation, with dopamine acting as tumor angiogenesis and endothelial growth factor inhibitor (Sarkar et al., 2015). Although a pharmacological effect could be hypothesized, the study conducted by Boursi et al. (2016) and Elbaz et al. (2005) failed to show a relation between disease and therapy duration.

On the other hand, despite the low incidence of cancer in PD, many reports found a significant and direct relationship between PD and melanoma (Inzelberg and Jankovic, 2007; Pan et al., 2011, 2012). Various types of cells with a common neuroectodermal origin carry melanin pigment, including skin melanocytes, with the possibility of transforming into melanomas and the dopaminergic neurons in the substantia nigra, which can degenerate and lead to Parkinson's disease. There are some etiological hypotheses based on current and increasing evidence of a possible association between these different diseases. They are focused on a common vulnerability provided by different pigmentary genes, such as melanocortin 1 receptor (MC1R), and carried out thanks to the role of the enzyme tyrosinase (TYR) involved in the synthesis of both melanin and neuromelanin.

Taking these observations into account, it is likely to think that the origin of this association is related to the genes that regulate pigmentation, as are described below. The exact mechanisms of the involvement of pigmentation genes in Parkinson's disease and melanoma are not yet fully known, and it is a field still under in-depth investigation (Pan et al., 2011).

Some studies have suggested an increased risk of melanoma mediated by Levodopa (Pfützner and Przybilla, 1997; Przybilla et al., 1985; Sandyk, 1992; Skibba et al., 1972). However, subsequent studies raised some doubts about any possible link. More recent studies show a higher incidence of melanoma in PD patients at pre-clinical stages, and even before starting dopaminergic therapy, these observations argue against Levodopa-induced risks.

Based on an extensive review of evidence-based literature, Pan et al. (2011) conclude that Levodopa plays minimal or no role at all in the link between PD and melanoma. Genes related to pigmentation appeared to be involved in melanoma and PD association (melanin and dopamine (DA), respectively). At the onset, both pigments share a common initial pathway involving tyrosine and 3,4-dihydroxyphenylalanine (DOPA) (Pan et al., 2011).

Interestingly, monogenic PDs have shown a different pattern of association between PD and melanoma. Mutations of Parkin were demonstrated to be the most common cause of young-onset PD (Kitada et al., 1998). Chromosome 6 is frequently altered in a variety of human cancers including melanoma; ergo, Parkin mu-

tations that may cause changes in chromosome 6 regions could be risk factors for both PD and melanoma (Millikin et al., 1991).

Another gene involved is alfa-synuclein, markedly expressed in melanoma cells, primary and metastatic ones. This fact could indicate that alfa-synuclein plays a critical role in the pathogenesis of this tumor, increasing the risk for both diseases (PD and melanoma).

Pan et al. (2012) showed that ultraviolet (UV) light exposure increased melanin synthesis as well as tyrosinase activity. Their results showed that alfa-Syn expression reduced melanin synthesis induced by UV light and lower melanin content in those cells expressing alfa-Syn. This last finding could prove an inhibitory effect of alfa-Syn on melanin synthesis in melanoma cells. However, the melanin levels in alfa-Syn-over-expressed dopaminergic neurons were higher than those in non-alfa-Syn-expressed control cells. Therefore, they concluded that alfa-Syn could be one of the hinge points that link PD and melanoma through its different roles in melanin synthesis both in melanoma and dopaminergic neuronal cells (Maries et al., 2003; Polymeropoulos et al., 1997; Wakabayashi et al., 2007).

Another association consistent with these results was alfa-Syn over-expressed cells had less tyrosinase (TYR) activity compared to control cells, indicating that it may inhibit UV light-induced activation of the enzyme. The interaction between alfa-Syn and TYR could add roles to the former regarding melanoma (Tief et al., 1998; Xu et al., 1997). It can be concluded that α-synuclein affects the neuromelanin formation by interaction with tyrosine hydroxylase and TYR, and at the same time, it is expressed in melanoma cells.

In mutant LRRK2, a significant number of mutations occur in the kinase domain leading to a gain of function. This domain is homologous to other kinase domains involved in malignant melanoma. On the other hand, DJ-1 has been reported to be overexpressed in melanoma, while mutations accounted at this gene have been identified as causal familial PD. These findings allow us to hypothesize a protective role for skin neoplasm in PD (Leupold et al., 2019; Pan et al., 2011).

Finally, many studies have linked deficits in autophagy to neurodegenerative diseases such as PD, with rising evidence that correlates this process with tumors, showing how it promotes the survival of established neoplasms as they appear to use this mechanism to survive periods of metabolic or hypoxic stress. Studies have reported defective autophagy in melanoma (Alvarez-Erviti et al., 2010; Cheung and Ip, 2009; Pan et al., 2008, 2011). Additionally, PLA2G6 mutations, presenting with many phenotypes (among them parkinsonism -dystonia and early onset parkinsonism) has been reported to increase the risk of lung cancer (Hosgood et al., 2008; Paisan-Ruiz et al., 2009).

3.2 Huntington's disease

Coarelli et al. (2017) made their point by explaining that lower cancer occurrence in HD could be either attributed to the problematic follow-up of patients and decreased rate of cancer diagnosis by clinicians, possibly neglecting cancer screening because of the severe neurological underlying disease.

Murmann et al. (2018) found that the pathological mechanism in HD is not only a consequence of the mutant huntingtin but also by RNA generated from the trinucleotide repeat (TNR) expansions regions including small interfering RNA (siRNA) sized repeat fragments. One of the most outstanding findings is the fact that many of the repeats in TNR diseases are located in introns or untranslated regions (UTRs) (Nalavade, 2013; Nelson, 2013). These regions provide several siRNAs (non-coding RNAs, not translated to a protein), and many of them are toxic to cancer cells by targeting genes that contain long reverse complementary TNRs in their open reading frames (ORF). Therefore, siRNAs kill cancer cells using interfering RNA (RNAi) through modulation of critical genes by transcriptional inhibition or mRNA degradation (Goodwin, 2005; Krol, 2007; Murmann, 2018; Wojciechowska and Krzyzosiak, 2011).

Above a certain length, CAG/CUG repeats were found to be cleaved by Dicer (the ribonuclease crucial for microRNA biogenesis), to produce mature miRNAs from pre-miRNAs before they are incorporated into the RNA-induced silencing complex (RISC).

Death induced by survival gene elimination (DISE) was found to involve simultaneous activation of multiple cell death pathways, and cancer cells are vulnerable to this type of cell death (Murmann, 2018). The transfection of small inhibitor CAG/CUG in human cancer cells stopped them from growing a few hours later, and ultimately most of the leading cells died with outgrowth. In summary, CAG repeat-based siRNA may lead to cell death by inhibiting genes survival. (Fig. 5)

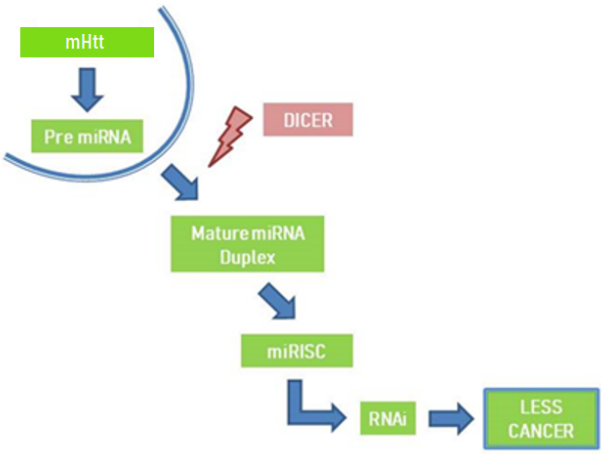

Figure 5. Flow charts of the canonical pathway of mutant Htt to miRNA. In the nucleus, primary microRNAs are cleaved by Drosha complex in precursor microRNA (pre-miRNA), The pre-miRNA is exported to the cytoplasm by Exportin-5. At the cytoplasm, pre-miRNA is processed by Dicer complex into double-stranded loop RNAs, mature microRNA (mature miRNA). The strand with the more unstable 5'-end is selected for loading onto miRNA-induced silencing complex (miRISC). RISC., -bound miRNAs to modulate miRNA activity (degradation and/or translational suppression). Finally, miRNA shows a regulatory role in different pathological pathways involving tumor cells.

PolyQ proteins induce cell death by different pathways such as apoptosis, autophagy, protease activation, and altered cellular stress response. Huntingtin-associated protein 1 (HAP1) is encoded by the HAP1 gene (Kalchman et al., 1997; Li et al., 1995).

The HAP1 protein binds to the mutant huntingtin protein (mHtt) proportionally to the nCAG repeats. It includes two cytoskeletal proteins, dynactin and pericentriolar autoantigen protein 1. This protein has been implicated in vesicular trafficking or organelle transport. HAP1 is localized in the mitotic spindle of dividing striatal cells and associated endosomes, microtubules, and vesicles in the basal forebrain and striatal neurons. (Fig. 6)

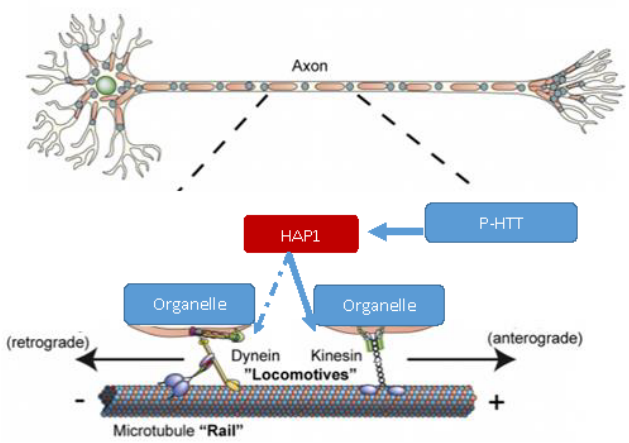

Figure 6. Role of the Huntingtin-associated protein 1 (HAP1) and mutant huntingtin interaction in traffic of organelles and protein regulation. Huntingtin is a scaffold protein with a capacity to bind to a HAP1 protein, which modulates the binding to dynactin or kinesin proteins (microtubule protein complex). The dynactin complex promotes retrograde trafficking, while kinesin promotes anterograde trafficking towards the synaptic area.

Zhu et al. (2013) demonstrated a decreased expression of HAP1 in breast tumors concerning the normal tissues. On the other hand, the over-expression of HAP1 reduced *in vitro* cell growth in breast cancer cell lines, suppressed migration, and invasion, and promoted the apoptosis of certain cell lines. Hence, this gene could be a future molecular target not only for diagnosis but also for the treatment of breast cancer.

Another theory of HD pathogenesis, which also intersects with cancer, has involved transcription deregulation. Kumar et al. (2014) suggest that HD represents a neurodevelopmental disorder, product of the pathological disruption of evolutionarily preserved adaptive gene programs to offset oxidative stress, mitochondrial dysfunction, and accumulation of misfolded proteins. Transcriptional deregulation of adaptive genes is even more exacerbated by repression of genes involved in normal synaptic activity or growth factor signaling.

Sp1 is a general transcription factor required for transcription of a vast number of genes in charge of metabolism, cell proliferation/growth, and cell death, called 'housekeeping genes.' It has become progressively clear over the years that many of these housekeeping genes play crucial roles, not only in neurodegenerative diseases but also in cancer initiation and progression. Its over-expression encloses many cancers and is associated with poor prognosis. Sp1 both activates and suppresses the expression of specific essential oncogenes and tumor suppressors, aside from genes related to critical cellular tasks, such as proliferation, differentiation, response to DNA insults, apoptosis, senescence, and angiogenesis (Qiu, 2006).

Interestingly, p53 represents a common regulatory pathway between neurodegenerative disorders and cancer, as was mentioned before in PD, it can regulate huntingtin (Htt) expression at a transcriptional level. (Fig. 7)

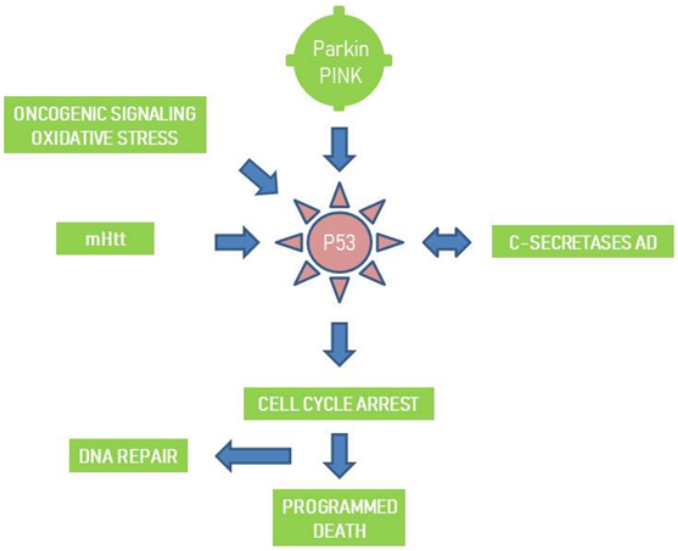

Figure 7. Common pathways to the three neurodegenerative diseases (Huntington's disease HD, Parkinson's disease PD and Alzheimer's disease AD) leading the activation of the P53 gene, with the consequent antioxidant effect and, as a final pathway, the apoptosis of neoplastic cells. P53, a transcriptional factor, has shown multiple functions in the crossroads among cancer and neurodegenerative disorders such as HD, PD, and AD. p53 demonstrates a central role in the balance of cell cycle arrest-DNA repair and programmed death, maintaining a delicate balance between cancer suppressive and age-promoting functions.

A review made by Wood (2015) focused on finding a possible biomarker in neurodegenerative basal ganglia disorders, such as HD and PD. They established by using functional imaging that phosphodiesterase 10A (PDE10A) levels were reduced even in early pre-motor stages of both disorders and may be used as a pathophysiological biomarker. PDE10A is an enzyme mainly expressed in the striatal GABAergic neurons, and its function is to regulate the cAMP-PKA-DARPP-32 signaling cascade, which also has a crucial role in controlling movement and promoting neuronal survival. (Fig. 8)

Brain regions rich in dopaminergic nerve terminals have high levels of cAMP-regulated phosphoprotein 32 kDa (DARPP-32), and high levels of this protein have been associated with more prolonged survival in some neoplasms. At the same time, lower expression, on the other hand, shortens survival time in other ones (Kotecha et al., 2019).

Recently, Zekeridou et al. (2019) reported a new paraneoplastic antibody specific against phosphodiesterase 10A. It is well known that PDE10A activity is increased in some cancers, such as lung,

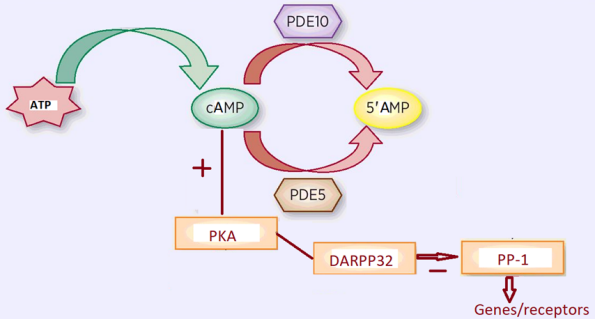

Figure 8. Role of Phosphodiesterase 10A (PDE10A) in the cAMP signaling cascade PDE10A mediated intracellular signaling by hydrolyzing the ATP to the cAMP. Increased levels of cAMP promote activation of protein kinase A (PKA) that, in turn, modulates Dopamine- and cAMP-Regulated Phosphoprotein, Mr 32 kDa (DARPP-32) phosphorylation leading the promotion of neuronal survival by genes regulation.

prostate, and colon, among others. Seven patients with a different type of cancers were included; four of them also developed movement disorders (hyperkinetic in 3 and parkinsonism in 1), before starting any kind of treatment. But the interesting thing is that two of them developed movement disorders after initiating immunological therapy, endorsing the inverse relationship between PDE10A levels regarding basal ganglia diseases and cancer.

The search for new PDE10A inhibitors is becoming an increasingly competitive field, and at present, about 180 patent applications have been published covering varying aspects of PDE10A drug discovery. Research has focused extensively on using PDE10A modulators as a novel therapeutic approach for dysfunction in the basal ganglia circuit, including Parkinson's' disease, Huntington's disease, addiction, obsessive-compulsive disorder, and schizophrenia. Curiously, this enzyme has demonstrated to be over-expressed in tumor cells of CRC (Li et al., 2015).

Ultimately, there's an upregulation of tumor suppressor gene p53 in multiple HD tissues. All these interactions between oncogenes and tumor suppressor genes with PolyQ proteins might account for diminished carcinogenesis in these neurodegenerative disorders (Bae et al., 2005).

3.3 Alzheimer's disease

Recent work from Okereke and Meadows (2019) suggests that a matrix of shared genetic factors may confer the risk of cancer and neurodegenerative disease in opposing directions. They have proposed an explanatory model in which age-associated metabolism and bioenergetics-balance differences may protect against neurodegeneration increasing the risk of cancer, or to the contrary, increase the risk of AD while decreasing the risk of cancer, through an inverse Warburg effect (even in aerobic conditions, cancer cells tend to favor metabolism via glycolysis rather than oxidative phosphorylation pathway) (Demetrius and Driver, 2015; Driver et al., 2012).

Additional studies have found 286 genes overlapping between cancer and AD. Interestingly, several of these genes produce proteins with different mechanisms in both entities mediated by the multifunctionality of the sequenced proteins. Driver et al. (2012) found that a genetic propensity against apoptosis might protect people from cancer while increasing their risk of neurodegeneration, as seen in some polymorphisms of the tumor suppressor gene p53 (Van Heemst et al., 2005).

A specific link between Alzheimer's disease and cancer is the protein Pin1, a unique enzyme that plays a part in protein folding as well as cell cycle control. As was mentioned before, Pin1 protein, a protein required for cell division, was over-expressed in individuals with cancer but decreased in the brain of AD patients, causing regression of tumors. As Pin1 is necessary for mitosis, its inhibition causes the regression of neoplastic cells (Segat et al., 2007).

This statement was supported by Ospina-Romero et al. (2019), who propose different mechanisms to the enzyme; PIN1 is upregulated in numerous human cancers but downregulated in AD (Driver et al., 2012; Ospina-Romero et al., 2019). Its function is to catalyze the isomerization of pSer/Thr-Pro motifs to influence several cellular processes, such as activation of telomerase and genomic repair by maintaining p53 functioning and regulating cell cycle processes. PIN1 is also believed to suppress tau and amyloid β deposition in AD (Gargini et al., 2019; Ma et al., 2012).

Curiously Tau/MAPT are two genes linked to neurodegenerative diseases and gliomas, as the stabilization of the microtubules is required in early glioma staging. Tau is implicated not only in microtubules stabilization but also in RNA/DNA integrity (Gargini et al., 2019).

The cellular habitat plays a fundamental role in the pathogenesis of both conditions; local or systemic signals promoting tumor cell growth in peripheral cells could translate into antiapoptotic signals in neurons.

Pavliukeviciene et al. (2019) demonstrated that β-amyloids inhibit the growth of hematological and solid cancer cells. The inhibition mechanism differs according to cell lines; therefore, it differs according to the type of cancer. It may involve interactions with the malignant cells membrane phospholipids or accumulation of amyloid species inside them.

4. Possible therapeutic applications

According to some genetic mechanisms mentioned above, one could expect them to be used as future therapeutic targets. For example, Picchio et al. (2004) examined the presence of parkin alterations in the coding sequence and changes in gene expression in 20 paired normal and non-small cell lung cancer samples. They found a common loss region in the parkin/FRA6E locus and observed parkin expression in three of nine (33%) lung tumors. Therefore, they worked at restoring the gene expression in the parkin-deficient lung carcinoma cell line using a recombinant lentivirus containing the wild-type parkin cDNA. This ectopic parkin expression could reduce *in vivo* tumorigenicity in mice.

We mentioned that defects in autophagy had been linked to PD. Therefore, a novel therapeutic strategy proposed for PD could be to increase autophagy, increasing the depuration of aggregated proteins and organelles. Innovative studies have suggested autophagy to be an essential factor for tumors, by demonstrating that increased autophagy plays a suppressive role in tumor initiation, but promoting the survival of tumors already set (Pan et al., 2008).

The precise functions of autophagy in both PD and melanoma

remain to be more fully explored. Still, autophagy deficits may explain mechanistic paths into the correlation between both diseases, and ergo could be used as a possible therapeutic target.

The codon ATG both codes for methionine and serves as an initiation site: the first ATG in an mRNA's coding region is where translation into protein begins. Concerning polyQ toxicity in HD, we alluded that repeat-associated non-ATG translation was discovered as another possible pathogenic mechanism of CAG repeat-containing mRNAs. It is well known that in some TNR the expanded triplets are located in non-coding or untranslated regions, UTRs, and as was mentioned before the CAG/CUG repeats could interfere by post-transcriptional mechanisms involving potentially noxious sRNA interfering with cellular splicing (Ho et al., 2016; Hosgood et al., 2008; Lin et al., 2016). Classically, an inverse correlation has been described among the number of CAG repeats and the malignant neoplasm in different organs. In this sense, Murmann et al. (2018) identified an entire family of siRNAs, in HD patients at least 10 times more toxic to cancer cells than any tested DISE-inducing si/shRNA. This fact suggests that this steered toxicity is caused by targeting multiple complementary TNR expansions present in the ORFs of many genes, rather than in their UTRs. One could argue that a cancer therapy based on delivering siCAG/CUG could be detrimental or harmful to patients as TNR expansion patients suffer as well from various pathologies.

Nevertheless, in an experimental model, specific siRNAs have demonstrated delayed tumor growth; this toxicity was restricted to the tumor cells without toxicity to normal cells. While the treatment with siCAG/CUG requires optimization, the available data on the toxicity mediated by siRNAs for malignant neoplastic cells, in addition to the low incidence for different types of cancer in patients with CAG expansions suggest that TNR-based siRNAs may be a useful tool for cancer therapy (Wakabayashi et al., 2007). So, henceforth, the purpose could be to develop super toxic TNR expansion-based siRNAs as a possible therapeutic option in humans.

5. Discussion

This mini-review contributes to supporting an inverse association between cancer and neurodegenerative disorders such as AD, PD, and HD. Nevertheless, this association is not consistent across all malignant neoplasm types.

These findings highlight the concept that neurodegenerative diseases and cancer are multifactorial etiological disorders. Even though many genes have been identified as a cause of AD, PD, and HD, other factors may contribute, modulate not only the phenotypes but also the potential link among other associated conditions, such as malignant neoplasms.

Different mutations, single nucleotide polymorphisms, epigenetic factors (non-coding RNA, histone conditions, DNA methylation), oxidative stress, protein degradation, mitochondrial function, cellular trafficking, abnormal proteins or oligomers protein spreading (propagation) among others factors determine multiple pathophysiological mechanisms implicated in the risk of developing some types of cancer in PD, HD, and AD.

The complicated relationship among multiple pathophysiological mechanisms represents a challenge for our best understanding and new therapeutic pathways relating to neurodegeneration and malignant neoplasms. This mini-review allows us to identify not only gene mutations, but also different pathophysiological pathways, that exert opposite roles in the development of cancer or neurodegeneration as we have mentioned in HD or AD, while others confer a protective role as we can observe between DJ-1 mutations in familial PD concerning melanoma. Although prima facie both entities appear dissimilar, substantial evidence supports common links. In both situations, aging has been identified as one of the main risk factors leading beyond the gene mutations, epigenetic alterations (related with the degree of acetylation, histone status, and ncRNA), DNA repair defect, oxidative stress, mitochondrial dysfunction, and abnormal protein degradations, among other mechanisms favoring carcinogenesis and neurodegeneration. There is a growing body of literature that has identified the same common aberrant pathways in AD, PD, and HD.

However, in the field of proteostasis, an opposite situation occurs between cancer and neurodegeneration. While a significant impairment of protein degradation via different pathways including ubiquitin proteasomal pathway (UPS), chaperone-mediated autophagy (CMA) and lysosome- autophagy pathway occur in neurodegeneration, in malignant neoplasms protein synthesis is increased and in many tumors UPS and CMA are upregulated contributing to cell survival and malignancy proliferation. This could be one of the mechanisms that support the inverse relationship.

Nevertheless, we need to mention other diverse factors considering the different origins and etiologies of PD, HD, and AD. Most of them involve genes related to the underlying disease, which, in contrast, interfere with the development of neoplasms in some way. Standard links could be hypothesized, including Parkin, P53, and ¨ PTEN genes, as well as HAP1 transcriptor.

Another interesting crossroads worth mentioning is the role that PDE10A plays. On the one hand, it is known that its level is decreased on the basal ganglia in certain neurodegenerative diseases such as PD and HD but increased in certain tumors such as lung and prostate. Therefore, it could be a possible pathway to developing some therapeutic applications. In this sense, it is well known the association of certain tumors with some monogenic PD such as LRRK2 mutations were a kinase increased activity constitutes the bridge among PD and breast cancer and melanoma. Moreover, some kinase inhibitors have very recently proposed as a potential therapeutic target for these specific PD patient's populations and certain cancers (Abdel-Magid, 2019).

Moreover, inhibitors of tyrosine kinase, Nilotinib, a drug approved for certain leukemias is now being tested in PD patients with alpha-synuclein mutations to avoid oligomeric aggregation (Pagan et al., 2019a,b).

The relevance of knowing these mechanisms lies in finding possible therapeutic applications guided at malignant cells without negatively affecting the rest of the tissues. Moreover, understanding the relationship between these neurodegenerative diseases and cancer may provide clues to the pathogenesis of both. Unraveling the role of specific genes in cell survival or cell death may improve our knowledge of the link between them and cancer and open a therapeutic window for both of them.

6. Conclusions

We report the complex interaction between two devastating disorders with a high impact on the quality of life and in public health in developed countries. Although epidemiologic studies and other biological explanations argue an inverse relation among cancer and neurodegeneration, the new knowledge in the field leads us to be cautious, taking into account that this inverse association is seen in some cancers but not in others. These findings provide new potential explorations and research in these directions and open new avenues for therapeutic targets.

Abbreviations

AMPK: AMP-activated protein kinase; CMA: chaperone-mediated autophagy; CRC: colorectal cancer; DA: dopamine; DARPP-32: Dopamine-and cAMP-Regulated Phosphoprotein, Mr 32 kDa; DOPA: 3,4-dihydroxyphenylalanine; DISE: death induced by survival gene elimination; HAP1: huntingtin-associated protein 1; IL-1β: interleukin-1β; MC1R: melanocortin 1 receptor; mHtt: mutant huntingtin protein; Htt: huntingtin; MLKL: mixed lineage kinase domain-like protein; ORF: open reading frames; PDE10A: Phosphodiesterase 10A; PKA: protein kinase A; PTEN: phosphatase and tensin homolog; RIPK1: receptor-interacting protein kinase 1; RIPK3: receptor-interacting protein kinase 3; RISC: RNA-induced silencing complex; SMR: standardized mortality ratio; SIR: standard incidence ratio; siRNA: small interfering RNA; TNF: tumor necrosis factor; TNR: trinucleotide repeat; TYR: tyrosinase; UPS: ubiquitin proteasomal pathway; UTRs: untranslated regions; UV: ultraviolet; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

Acknowledgment

We thank our team members for stimulating discussions

Conflict of Interest

The authors declare no conflict of interest.

Submitted: January 06, 2020
Accepted: March 27, 2020
Published: March 30, 2020

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