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REVIEW ARTICLE

Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence

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Abstract Growing evidence suggests an unusual epidemiologic association between cancer and certain neurological conditions, particularly age-related neurodegenerative diseases. Cancer survivors have a 20–50 % lower risk of developing Parkinson's and Alzheimer's disease, and patients with these neurodegenerative conditions have a substantially lower incidence of cancer. We review the epidemiologic evidence for this inverse co-morbidity and show that it is not simply an artifact of survival bias or under-diagnosis. We then review the potential biological explanations for this association, which is intimately linked to the very different nature of dividing cells and neurons. The known genetic and metabolic connections between cancer and neurodegeneration generally fall within two categories. The first includes shared genes and pathways such as Pin1 and the ubiquitin proteasome system that are dysregulated in different directions to cause one disease or the other. The second includes common pathophysiological mechanisms such as mitochondrial dysfunction, oxidative stress and DNA damage that drive both conditions, but with different cellular fates. We discuss examples of these biological links and their implications for developing new approaches to prevention and treatment of both diseases.

Keywords Cancer · Neurodegeneration · Alzheimer's disease · Parkinson's disease · Epidemiology

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The curious cancer pattern in certain neurological conditions has drawn increasing attention as converging evidence suggests that one family of diseases may provide protection against the other. Over 50 years ago, it was anecdotally noted that patients with Parkinson's disease (PD) seem to have a lower than expected rate of most cancers (Doshay 1954). Since then, more than 30 studies have confirmed this observation (Driver et al. 2007a; Driver et al. 2007b; Elbaz et al. 2005; Elbaz et al. 2002; Fois et al. 2010; Olsen et al. 2006; Olsen et al. 2005). It has been less than a decade since Beherens and Roe noted a similar inverse association between cancer and Alzheimer's disease (AD), and hypothesized it might be due to an

increased propensity toward apoptosis (Behrens et al. 2009). There is now convincing evidence of an inverse relationship between cancer and AD (Catala-Lopez et al. 2014; Driver et al. 2011; Musicco et al. 2013; Roe et al. 2005; Roe et al. 2010). There is also limited data to suggest an abnormal cancer pattern in Huntington's disease and some non-degenerative neurological conditions, including schizophrenia and multiple sclerosis, but the relationship is less clear (Catala-Lopez et al. 2014). While positive correlations between diseases are common in an aging population, "inverse comorbidity" is quite unusual (Tabares-Seisdedos and Rubenstein 2013). Many factors might account for this "mutual protection," both biological, such as opposing genes and pathways, and non-biological, such as behaviors, diagnostic patterns or medication effects.

Because of its biological plausibility, the inverse association between cancer and neurodegeneration has captured the imagination of a growing number of researchers. Cancer is characterized by unlimited cellular proliferation, while neurodegeneration is a process of premature cell death. In this sense, the diseases appear to be opposing ends of the same spectrum. In fact, they share many genes and biological pathways, and these are often regulated in different directions (Behrens et al. 2009; Plun-Favreau et al. 2010). My colleagues and I first started investigating the link between cancer and AD over 10 years ago because of the critical but opposite role that the enzyme Pin1 plays in both conditions (Driver and Lu 2010). It is but one of a number of proteins whose role is quite different in neurons and peripheral cells. Furthermore, the neuron and the dividing cell meet their energy needs in dramatically different ways. Both diseases are characterized by metabolic dysregulation and a compensatory increase in metabolic rate, but with very different outcomes (Demetrius and Simon 2012; Demetrius and Simon 2014). The fundamental teleological, genetic and metabolic differences between neurons and other cells give credence to the idea that a history of cancer might decrease the risk of neurodegenerative disease, and vice versa.

However compelling these proposed mechanisms may be, the inverse epidemiologic association between cancer and neurological conditions cannot be assumed to have a biological explanation. Investigating the relationship between two diseases is inherently complex and requires careful consideration of a number of potential biases and non-biological factors. For example, cancer survivors might be "protected" from future disease of any type simply because they are at higher risk of death from recurrence or complications of therapy. Patients with cognitive or functional impairment from neurological disease may be less likely to be screened for cancer or report symptoms, leading to lower cancer rates that are due to under-diagnosis. Diagnosis with one disease might influence the risk of being diagnosed with the other, thus "masking" its true incidence. Finally, treatment for one disease might decrease the risk of contracting the other. In this article, we will review the epidemiologic evidence for the strange cancer pattern in neurodegenerative diseases and determine the strength of the evidence for a true inverse association. We will also look at the evidence for a lower risk of cancer in non-degenerative neurological diseases. Finally, we will discuss the possible explanations for this link, and explore its therapeutic possibilities.

Cancer and Parkinson's disease

Parkinson's disease is a movement disorder characterized by the degeneration and death of dopaminergic neurons in the *substantia nigra*. The cause of neurodegeneration in PD remains obscure in most cases, and there is still no known curative therapy. Overall, epidemiologic studies show a decreased risk of most cancers in PD patients, but they have been of variable size and design. The largest studies have used the Danish National Hospital Register. From 1977 to 2006, 20,000 people were diagnosed with PD and were followed for the subsequent diagnosis of cancer (Rugbjerg et al. 2012). Compared to the general population, the standardized incidence rate of overall cancer in people with PD was 0.86 (95 % CI 0.83–0.90). Decreased rates of both smoking-related (SIR = 0.65; 95 % CI 0.60–0.70), and non-smoking related cancer (SIR = 0.79; 95 % CI 0.71–0.86) were found. The few cancers for which there was an increased association included malignant melanoma, non-melanoma skin cancer, and breast cancer. We found similar results in the Physician's Health Study, a well-defined prospective cohort of over 21,000 US physicians. Men with PD had a decreased risk of overall cancer both before (Driver et al. 2007a) and after (Driver et al. 2007b) their diagnosis, as well as a

decreased risk of cancer death (Driver et al. 2008). In a meta-analysis of 29 studies including 107,598 patients with PD, we found a decreased aggregate risk of overall cancer (relative risk (RR) = 0.73; 95 % CI 0.63–0.83), smoking-related cancer (RR = 0.61; 95 % CI 0.58–0.65) and non-smoking-related cancer (RR = 0.80; 95 % CI 0.77–0.84) (Bajaj et al. 2009). The decreased risk of lung cancer (HR = 0.46), hematologic malignancies (RR = 0.76), colorectal cancer (HR = 0.77) and prostate cancer (HR = 0.80) were all statistically significant. The lower cancer risk was seen both before and after the diagnosis of PD, and the only cancer type for which there appeared to be an increased risk was melanoma (RR = 1.41; 95 % CI 0.90–2.19). A more recent meta-analysis including 55,304 patients with PD confirmed our findings and reported an overall pooled effect size of 0.83 (Catala-Lopez et al. 2014).

There are a number of potential explanations for the inverse association. One is the fact that people who develop PD tend to be lifelong non-smokers (Hernan et al. 2002). While this could explain the stronger negative correlation with smoking-related cancers, it does not account for the decreased risk of non-smoking-related cancers. A second possibility is that patients with PD have an increased mortality rate and may be less likely to survive to develop cancer than reference subjects. However, we found the same inverse pattern in our prospective cohort study, which accounts for survival time and loss to follow-up (Driver et al. 2007b). Treatment for PD might also influence cancer risk, but the evidence suggests that cancer rates are decreased both before and after PD diagnosis. The only cancer type for which there is a well-documented increased risk in PD is malignant melanoma. This is interesting, as melanocytes and neurons of the *substantia nigra* are both pigmented cells. A number of theories have been proposed to explain this correlation, which likely represents a separate mechanism from that driving the inverse association (Paisan-Ruiz and Houlden 2010).

Cancer and AD

Little was known about the relationship between cancer and AD, the most common neurodegenerative disease of aging, until recently. The first evidence came from autopsy studies. Patients with histologically confirmed AD were noted to have less incidental cancer on autopsy than those without AD (Corsellis 1962; Tirumalasetti et al. 1991). This is surprising, since those who cannot report symptoms might be expected to have a higher rate of undiagnosed disease. In a study of people at increased risk for cancer (Japanese atomic bomb survivors), those with clinically diagnosed AD had 70 % less cancer prior to their AD diagnosis than age-matched controls without dementia. Interestingly, people with a diagnosis of vascular dementia had a 60 % *higher* risk of prior cancer than controls (Yamada et al. 1999).

Over the past few years there have been a number of carefully conducted cohort studies confirming these initial observations. In a longitudinal memory cohort, Roe and Beherens found that people with AD had a 61 % decreased risk of incident cancer compared to reference subjects (Roe et al. 2005). In follow-up work using the cognition cohort of the Cardiovascular Health Study, they showed that people with prevalent cancer at baseline had a lower risk of probable AD (HR = 0.57; 95 % CI 0.36–0.90), and those with prevalent AD had fewer cancer hospitalizations (HR = 0.31; 95 % CI 0.12–0.86) (Roe et al. 2010). In contrast, there was no inverse relationship between cancer and vascular dementia. In the Framingham Heart Study, a cohort with very long follow-up in which both AD and cancer are carefully defined, we found that participants with a history of confirmed cancer had a lower risk of incident AD (HR = 0.67; 95 % CI 0.47–0.97), and exclusion of those who died before age 80 did not diminish the association (HR = 0.68; 95 % CI 0.47–0.99) (Driver et al. 2011). A study using claims data from Northern Italy found a 35 % lower risk of AD in patients with a history of cancer and a 50 % lower risk of cancer in those with AD (Musicco et al. 2013). In this analysis the authors carefully demonstrated that the inverse association was present both before and after the diagnosis of each disease. They also convincingly showed that the inverse association was present in those who died as well as those who survived.

The consistency of the findings across these studies is striking. Together they suggest that the decreased risk of AD in cancer survivors is not primarily due to the fact that they are more likely to die than reference subjects, since the effect is seen in both survivors and non-survivors. Furthermore, if the decreased risk of AD in cancer survivors is due to their earlier mortality,

the incidence of *any* late onset disease should be reduced. However, the incidence of vascular dementia and stroke are both substantially increased in this population. Similarly, the lower risk of cancer diagnosis in patients with AD is not simply due to underdiagnosis or under-reporting in the setting of cognitive impairment, since the same pattern is not seen in patients with vascular dementia. Furthermore, a number of studies document that the decreased risk precedes the onset of AD. Although bias, confounding and treatment may still play a role in this complex relationship, the weight of the epidemiological evidence points to a true inverse comorbidity.

Cancer and other neurodegenerative diseases

Other neurodegenerative conditions such as Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) are much less common than AD and PD, and epidemiologic studies investigating their co-occurrence with cancer are sparse. HD is an autosomal dominant genetic disorder caused by a mutation in the HTT gene which codes for the protein huntingtin. As in familial AD, the protein is processed into toxic smaller fragments that are thought to cause the neurodegeneration. Two large studies have looked at cancer risk in patients with HD, and both find an inverse association. One used the Danish National Cancer Registry between 1943 and 1993 and identified 694 incidence cases of HD (Sorensen et al. 1999). Compared to the general population, the overall standardized incidence ratio for cancer was 0.60 (95 % CI 0.50–0.80). The SIRs were lower than expected for all cancer subtypes, but none were statistically significant. Using the Swedish Cancer Registry, another group found a lower than expected cancer incidence in HD (SIR = 0.47; 95 % CI 0.38–0.58) as well as two related neurodegenerative diseases, spinobulbar muscular atrophy (SIR = 0.65; 95 % CI 0.45–0.91), and hereditary ataxia (SIR = 0.77; 95 % CI: 0.70–0.85).

Although ALS is a neurodegenerative disease, unlike the previously discussed diseases, it primarily affects motor neurons. A study using hospital and mortality data from southern England compared the risk of cancer before and after the diagnosis of motor neuron disease (MND) in 838 cases and matched reference subjects (Fois et al. 2009). The RR for cancer diagnosed after MND was 0.98 (95 % CI 0.75–1.26), while the RR for MND after cancer was 0.84 (95 % CI 0.66–1.07). The risk of Hodgkin's lymphoma and brain tumors were significantly increased in those with MND, but only within a year around MDN diagnosis. A study using the Surveillance, Epidemiology and End Results (SEER) cancer registry with over 16 million person-years of follow-up looked at death rates from ALS among people who survived at least one year after cancer diagnosis (Freedman et al. 2014). There was no overall association (standardized mortality ratio (SMR) = 1.00) but a reduced rate of death from prostate cancer and an increased risk of melanoma and tongue cancer were noted. Another SEER-Medicare study of ALS incidence in patients 65 and older found no association overall (HR = 0.99; 95 % CI 0.81–1.22) (Freedman et al. 2014). The only significant association was an increased risk in the year following leukemia diagnosis. Although limited, these results do not suggest an inverse association between MND and cancer.

Cancer and other neurological conditions

A recent meta-analysis combining data from 8 studies and 54,929 patients with multiple sclerosis (MS) found a slightly reduced incidence of overall cancer RR = 0.91; 0.87–0.95, primarily driven by a lower risk of lung (RR = 0.72; 95 % CI 0.62–0.84) and prostate (RR = 0.74; 95 % CI 0.59–0.94) cancer. Once considered a neurodegenerative condition, MS is primarily an autoimmune disease. Other autoimmune conditions have been associated with unusual cancer patterns. For example, patients with rheumatoid arthritis tend to have an increased risk of lymphoma and a lower risk of colon cancer than the general population (Huang et al. 2014). However, whether this association is due to underlying biological factors or anti-inflammatory therapy is unclear.

Some studies have reported an inverse association between cancer and schizophrenia, a devastating neuropsychiatric syndrome that generally begins in young adulthood. A meta-analysis of 16 studies including 427,843 people with schizophrenia found no overall association with cancer (RR = 0.98; 95 % CI 0.90–1.07) (Catala-Lopez et al. 2014). Schizophrenia was associated with substantially lower rates of prostate cancer (RR = 0.55; 95 %CI 0.45–0.67) and melanoma (RR = 0.72; 95 %CVI

0.62–0.83) in this meta-analysis, but a higher risk of breast cancer (RR = 1.25; 95 % CI 1.10–1.42).

In summary, the epidemiologic evidence of a mutual protection between cancer and certain neurodegenerative diseases is strong, especially for the age-related forms of AD and PD. More work is needed to clarify if this inverse comorbidity extends to other types of neurological conditions, and which factors help to explain it. We will spend the remainder of the article focusing on the intriguing biological links between neurodegeneration and cancer.

Cellular teleology, cancer and neurodegeneration

Long-lived organisms require robust mechanisms of tissue renewal and cell survival. For most cell types in the human body, the solution is interval renewal of the cellular population through mitosis. In tissues with proliferative potential, no individual cell is indispensable–any number of cells can take its place. The danger of this approach is the possibility of malignancy, and thus mitotic signals and proteins must be tightly controlled. A system of careful checks and balances has evolved to protect organisms from cells that have potential to escape control, with senescence or apoptosis as fail-safe mechanisms. The cell cycle affords an opportunity to review and repair the genome and thus maintain its integrity.

In contrast, the purpose of a neuron requires that it survive and maintain its connections with other neurons for as long as possible. Some individual neurons are indispensable; for example, those involved in memory. In keeping with their mission, once fully differentiated, neurons can no longer divide and are actually missing some enzymes needed to complete mitosis (Ackman et al. 2007). They do retain functional apoptotic pathways, however, so that irreparably damaged neurons can undergo programmed cell death (Staropoli 2008). Neurons have a close collaboration with surrounding astrocytes, which serve as support cells and provide energy and antioxidant precursors (Stobart and Anderson 2013).

While capable of great feats such as processing enormous amounts of information at lightning speed, the super-specialized neuron is vulnerable in a number of important ways. It cannot meet its own metabolic needs and does not efficiently and regularly remove DNA damage by means of the cell cycle, only repairing the DNA it actually uses. As it is so long lived, the neuron is more susceptible than most cell types to damage from age-related entropy which particularly affects its mitochondrial DNA and results in declining cellular energy metabolism (Demetrius and Driver 2013; Drachman 2006). This helps to explain the striking overlap between age-related changes and AD/PD, as well as the neuron's selective vulnerability and sensitivity to oxidative stress. For example, hippocampal cells require more energy than any other cell type in the brain, and AD is characterized by hypometabolism and atrophy beginning in the medial temporal lobe and extending along networked areas (Bakkour et al. 2009; Dickerson et al. 2009). In short, while safe from cancer, neurons must struggle against the ravages of time and its effect on cellular metabolism. The striking differences between post-mitotic neurons and regular mitotic cells, which are summarized in Table 1, thus provide insight into the inverse association between cancer and neurodegeneration.

Table 1 Comparison of dividing cells and neurons

Characteristic	Dividing cell	Neuron
Function	Various functions	Information processing, communication with other neurons
	Cells of the same type can be replaced	The individual cell is irreplaceable
Tissue survival	Interval mitosis renews cell population	Individual cell must survive as long as the organism
	Response to growth and mitotic factors regulated carefully	Unable to complete mitosis
		Normally unresponsive to mitogens
DNA repair	Ongoing focal repair	Ongoing focal repair of necessary genes only
	Careful checking and repair of entire genome during cell cycle	No cell cycle
Energy production	Can meet its own needs	Dependent on astrocytes for glycolysis and antioxidant production
	Normal mode is oxidative phosphorylation but also uses glycolysis during hypoxia and proliferation	Neuron uses oxidative phosphorylation almost exclusively

Differential regulation of common genes and pathways

The few studies that have looked for genetic overlap between cancer and neurodegeneration have found two patterns of association, as illustrated by Fig. 1 (Holohan et al. 2012; Ibanez et al. 2014; Tabares-Seisdedos et al. 2011). In one axis, genes and pathways associated with proliferation, cell survival and apoptosis tend to be differentially regulated by neurons and peripheral cells. Promotion of cell survival is neuroprotective but may increase cancer risk, while lowering the threshold for apoptosis may prevent cancer but promote neurodegeneration. On the other axis, pathways and genes involved in bioenergetics, inflammation, and DNA damage repair are positively associated with both diseases. Analysis of the NetAge database, a network-oriented platform for research on the genetics of longevity and age-related diseases, found a significant overlap between cancer- and AD-associated genes and protein–protein interaction networks (Wolfson et al. 2009;Tacutu et al. 2010). Overlapping genes/proteins included those involved in signal transduction, cellular metabolism, cellular growth or maintenance, immune response and apoptosis.

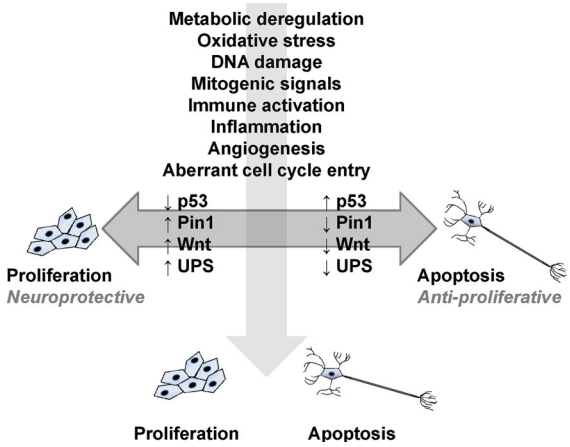

Fig. 1 Cancer and AD/PD can be seen as extremes along the same axis (horizontal axis). If proliferative pathways (e.g. Pin1 and the ubiquitin proteasome system (UPS) are upregulated they may promote cancer but provide neuroprotection. If p53 function is upregulated, it will promote apoptosis but protect against cancer. Cancer and neurodegenerative disease also share many pathophysiological features in common (*vertical* axis). Due to the very different nature of the two cell types, these forces promote cancer in the peripheral cell but apoptosis in the neuron. Age-related metabolic deregulation and metabolic reprogramming may be an initiating event for both carcinogenesis and neurodegeneration

Differential regulation of common genes in AD and cancer is well exemplified by Pin1, a unique enzyme that changes the 3-D structure of target proteins, thereby having profound effects on their function (Yaffe et al. 1997). The reversible phosphorylation of specific sites on target proteins is a major signaling mechanism used to control key cellular processes such as transcription and splicing, the cell-cycle, DNA damage response, and neuronal survival (Lu and Zhou 2007). In the dividing cell, Pin1 is tightly regulated as it is used to coordinate mitosis. As the adult neuron has no need to divide, Pin1 can be expressed at high levels and is used to restore tau and amyloid precursor protein to a functional shape, thus preventing the buildup of the toxic tau and beta-amyloid species associated with AD. Many human tumors overexpress Pin1, while it is inactivated by oxidation in the brain tissue of people with AD (Bao et al. 2004). Inhibition of Pin1 causes tumor regression, while its upregulation in postnatal neurons reverses neurodegeneration in mouse models. Pin1 promoter single nucleotide polymorphisms (SNPs) that inhibit its expression are associated with an increased risk of AD (Segat et al. 2007) but a decreased risk of cancer (Lu et al. 2009). Another gene that is regulated differentially in cancer and AD is the tumor-suppressor protein p53, which induces cell-cycle arrest or apoptosis in the face of DNA damage. While protecting the body from cancer, p53 promotes the aging phenotype through cellular loss and senescence. A genetic propensity against apoptosis might protect an individual from cancer while increasing the risk of neurodegeneration, as seen in some p53 polymorphisms (van Heemst et al. 2005). Finally, the Wnt signaling pathway, which promotes cellular survival and proliferation, is upregulated in many cancers, but inactivated in AD (Inestrosa and Toledo 2008). Each of these pathways and their relation to cancer and AD is reviewed in detail elsewhere (Behrens et al. 2009; Driver and Lu 2010).

A number of the genes associated with familial PD, such as *PARKIN* and ubiquitin C-terminal hydrolase (*UCHL1*), are used for protein processing and clearance in neurons, but are involved in cell-cycle regulation in dividing cells (Devine et al. 2011; Driver 2012). While mutation in the genes associated with familial PD are not thought to be the cause of the sporadic form, their differential regulation in cancer again illustrates the principle that neurons and peripheral cells may use the

same pathways to very different ends, and dysregulation of these pathways, whether due to a genetic mutation or age-related damage, can lead to one disease or another depending on its direction.

The ubiquitin–proteasome system (UPS), the primary pathway by which intracellular proteins are degraded, also plays an opposite role in PD and cancer. Effective management of cellular waste is a critical issue for the neuron. Dysfunction of the UPS leads to the accumulation of intracellular proteins and the formation of Lewy bodies, the pathological hallmark of PD (Sherman and Goldberg 2001). UPS dysfunction is also seen in AD and HD. In contrast, upregulation of the UPS is commonly seen in cancer, and proteasome inhibition is used to treat a growing number of malignancies (Crawford et al. 2011).

There are a number of additional biological factors that might help explain the decreased co-occurrence of cancer and neurological disease including those that regulate the immune system and circadian rhythm. A broader discussion of the intersection of central nervous system function and cancer biology has been reviewed elegantly elsewhere (Tabares-Seisdedos and Rubenstein 2013).

Common pathogenesis with diverse outcomes

On the vertical axis, cancer and neurodegeneration share many pathophysiological processes including aging, mitochondrial dysfunction, oxidative stress, DNA damage, abnormal mitotic signaling, inflammation, and aberrant cell-cycle activation. Increased DNA damage can prompt cell-cycle entry not only in peripheral cells, but also in neurons. The strong similarities between oncogenesis and neurodegeneration have led to cell-cycle theories of the origin of AD and PD. The "two-hit hypothesis" of neurodegeneration proposes that both oxidative stress and abnormal mitotic signaling are required to prompt neuronal cell-cycle entry (Zhu et al. 2007; Lombardi et al. 1999; Xiang et al. 2002). While the cancer cell is able to escape cell-cycle checkpoints and begin uncontrolled proliferation, the neuron attempts mitosis but cannot complete it (Folch et al. 2012; Raina et al. 2000). At some point after S-phase, neurons become stuck in a dysregulated mitotic state which causes tau hyperphosphorylation leading to tangle pathology, and mitochondrial stasis, promoting oxidative damage and apoptosis. These similarities between the pathology of cancer and AD/PD would suggest a positive epidemiologic association, and yet an inverse association is observed. One explanation for this may be the different way that neurons and dividing cells solve their energy crisis in the face of age-related changes in energy metabolism.

The incidence of AD, PD and non-familial forms of cancer increases exponentially after age 70. An emerging concept is that age-related changes in cellular energy production may be the primary driving force behind older-onset diseases, while a much smaller and complex genetic component helps to explain differential vulnerability to this force (Demetrius and Driver 2013). Aging is characterized by progressive mitochondrial dysregulation due to loss of molecular fidelity and oxidative stress. Mitochondrial DNA is especially vulnerable to damage as it is exposed to higher levels of oxygen free radicals than nuclear DNA. It has long been known that cancer cells meet their energy needs by upregulating glycolysis even in aerobic conditions, a form of metabolic "reprogramming" known as the Warburg effect (Vander Heiden et al. 2009). This may be driven both by a response to dysfunctional mitochondria and in an effort to increase biomass needed for cell growth. The reprogrammed cells have a higher metabolic rate and out-compete their normal neighbors for energy precursors, thus giving them a survival advantage.

As neurons have such high energy demands, they are particularly vulnerable to age-related mitochondrial dysfunction. Oxidative stress and DNA damage have been shown to be the earliest events in sporadic AD (Nunomura et al. 2001). Similarly, decreased expression of genes involved in oxidative phosphorylation and glucose transport can be seen in people with preclinical sporadic PD and Lewy Body disease (Zheng et al. 2010). Cortical neurons have weak glycolytic enzymes and are thus forced to upregulate oxidative phosphorylation to compensate for insufficient energy production (de la Monte et al. 2000; Manczak et al. 2004; Nagy et al. 1999). This metabolic upregulation has been called the "inverse Warburg effect" (Demetrius and Simon 2012). It is pathological, as the reprogrammed cells compete with healthy neurons for energy precursors while increasing their own level of oxygen free radicals and DNA damage. According to this model, neuronal loss can occur both as the result of metabolic exhaustion and progressive

DNA damage, leading to neurodegeneration and apoptosis, as described above. In summary, a propensity towards more robust glycolysis might protect neurons from degeneration while increasing the risk of cancer. A particular strength of this bioenergetic model is that it explains the epidemiological and demographic features of age-associated cancer and neurodegenerative disease as well as its underlying biology.

Implications and conclusions

As we have seen, epidemiologic evidence supports the existence of a true inverse comorbidity between cancer and the most common age-related neurodegenerative diseases. The biology we have reviewed immediately suggests new avenues of treatment. One approach is to focus on pathways that are differentially regulated between the diseases. If proteasome inhibitors are effective anti-cancer therapy, then proteasome activators might help prevent the progression of neurodegenerative disease (Huang and Chen 2009). In PD, neurons with more proteasome activation are spared from neurodegeneration (McNaught et al. 2010). Overexpression of the cellular proteasome activator PA28 has been shown to promote survival in neuronal models of Huntington's disease (Seo et al. 2007). A few candidate proteasome activators have been identified, including olive oil (Katsiki et al. 2007), antioxidants (Kwak et al. 2003), and resveratrol (Marambaud et al. 2005). Identification of proteasome activators would have a large clinical impact and should be a target for drug development. Such agents could theoretically increase cancer risk in other cell types, and so would need to be carefully targeted to neurons.

The other approach is to prevent both families of diseases by targeting shared pathophysiology. In addition to a healthy diet and exercise, targeted bioenergetic interventions could be very effective. Delivery of energy precursors or upregulation of glycolysis in neurons and astrocytes might prevent the need for upregulation of oxidative phosphorylation. On the other hand, inhibition of glycolytic enzymes on tumor cells should have strong anti-cancer effects. Type II diabetes is a strong risk factor for AD and many malignancies, including colon, breast, prostate, endometrial, pancreatic and bladder cancer. A number of abnormalities characteristic of DM can promote both carcinogenesis and neurodegeneration, including hyperinsulinemia (insulin is a mitogen), increased oxidative stress, and inflammation. Insulin may also specifically accelerate AD pathology (de la Monte 2009). Intranasal insulin improves memory and attention in patients with mild cognitive impairment (Benedict et al. 2008; Craft et al. 2012; Shemesh et al. 2012) and is currently being evaluated as treatment for early PD. Metformin is a particularly attractive candidate for chemoprevention, as it decreases levels of insulin and suppresses proliferative pathways both by activating AMP-activated protein kinase and inhibiting mTOR (Aljada and Mousa 2012; Jalving et al. 2010). In a meta-analysis of studies of cancer incidence in regular metformin users that included 210,892 patients, the pooled risk ratios of cancer incidence and mortality were 0.68 (0.53–0.88) and 0.66 (0.49–0.88) respectively (Noto et al. 2012). These decreased risks were not associated with insulin or other diabetes treatments. A recently published abstract found a 20 % reduction in dementia risk among new users of metformin in a large prospective cohort (Whitmer et al. 2013). Finally, drugs that have anti-oxidant and anti-inflammatory effects might also be effective chemoprevention for both diseases.

A deeper investigation into the curious relationship between cancer and neurodegenerative diseases will undoubtedly yield further insights into the treatment and prevention of both conditions.

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