At the Crossroads Between Neurodegeneration and Cancer: A Review of Overlapping Biology and Its Implications

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Abstract

Background: A growing body of epidemiologic evidence suggests that neurodegenerative diseases occur less frequently in cancer survivors, and vice versa. While unusual, this inverse comorbidity is biologically plausible and could be explained, in part, by the evolutionary tradeoffs made by neurons and cycling cells to optimize the performance of their very different functions. The two cell types utilize the same proteins and pathways in different, and sometimes opposite, ways. However, cancer and neurodegeneration also share many pathophysiological features.

Objective: In this review, we compare three overlapping aspects of neurodegeneration and cancer.

Methods: First, we contrast the priorities and tradeoffs of dividing cells and neurons and how these manifest in disease. Second, we consider the hallmarks of biological aging that underlie both neurodegeneration and cancer. Finally, we utilize information from genetic databases to outline specific genes and pathways common to both diseases.

Conclusions: We argue that a detailed understanding of the biologic and genetic relationships between cancer and neurodegeneration can guide future efforts in designing disease-modifying therapeutic interventions. Lastly, strategies that target aging may prevent or delay both conditions.

Keywords

Aging; neurodegeneration; carcinogenesis; trade-offs; hallmarks; neurons; dividing cells

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1. INTRODUCTION

Neurodegenerative diseases and cancers are often considered to be uniquely distinct but have a complex and intriguing interrelation. Both Alzheimer's (AD) and Parkinson's diseases (PD) are less frequent in survivors of many cancers (and vice versa), suggesting that a propensity towards one family of diseases may decrease the risk of the other [1–5]. In contrast, cancer survivors have a higher risk of other agerelated diseases, including non-neurodegenerative dementia, stroke, macular degeneration, and osteoarthritis [2, 6]. However, the inverse association is not consistent across all cancer types; the increased risk of malignant melanoma in patients with PD is the most notable example [7–9]. Cancer treatment may also modify the relationship; with some studies suggesting that chemotherapy treated breast cancer survivors may have lower white matter organization and connectivity when compared to healthy controls [10], and others associating chemotherapy with a lower risk of subsequent AD [6]. Thus, the epidemiologic association is complex and challenged by the difficulty of accounting for the ways in which diagnosis, treatment, and survival from one disease influence the risk of another [11].

While the epidemiologic data may be muddy, there is abundant evidence of a complex biological connection. An expanding body of literature describes genes, proteins, and pathways dysregulated in both cancer and neurodegenerative disease— often in opposite directions. For example, the expression of p53, a known tumor-suppressor gene, is upregulated in AD, PD and Huntington's disease (HD) [12–15], but downregulated in the large majority of cancers [16]. Pin1, a multifunctional gene hypothesized to function as a molecular timer, is notably upregulated in a number of cancers but is downregulated in AD [17, 18]. On the other hand, there is substantial positive pathophysiological overlap, with oxidative stress, DNA damage, inflammation, metabolic deregulation, and aberrant cell cycle activation playing a central role in both diseases [19]. This rich overlap has spurred substantial interest, especially among researchers hungry for new ways of understanding and treating age-related neurodegeneration [20].

In this article, we further examine the biological and genetic overlap between cancer and neurodegeneration and develop two lines of thought in an effort to elucidate the mixed signals that make up this complex relationship. The first is that inverse associations, such as regulation of the same gene or pathway in opposite directions, or differential use of the same protein, have their origins in teleology – the profoundly different purpose of cycling cells and neurons. The second is that positive biological overlap between sporadic AD and late-onset cancers is generally driven by the common ground of aging on which they occur. These two axes of association are illustrated in Fig. (1). We then provide an overview of the overlapping genes and biological pathways involved in cancer and neurodegeneration, followed by a discussion of ways in which this comparative biology is leading to a broader understanding of both diseases and the development of new therapeutic and preventive strategies.

1.1. A Tale of Two Cells: Insights from Evolutionary Bioiogy

The survival of living things, whether cells or species, depends on preserving the structure and function of genetic material and passing it on with fidelity, meeting energy needs, and maintaining bodily systems in the face of entropy and other forces [21]. Evolutionary tradeoffs, defined as a benefit in one context necessitating a cost in another, have occurred on both the genotypic and phenotypic level over millions of years [22]. Disease risks associated with evolutionary tradeoffs are often diametric; vulnerabilities to one family of diseases can be protective against another [23]. Examples of diametric disease pairs include affective disorders and autism, osteoporosis and osteopenia, and, as we discuss, cancer and neurodegeneration.

The survival strategy for most tissues in the body is an ongoing replacement. Blood cells have a lifespan of days to months, while the epithelial cells lining organs can live up to two years. Individual cells are interchangeable and can meet their own energy needs; the tissue will survive as long as the cell population is adequate. The tradeoff for this strategy is the risk of cancer. DNA integrity and careful cell-cycle control are thus the overarching priorities of dividing cells, as a single rogue cell can threaten the entire organism. With respect to meeting energy needs, dividing cells are generally self-sufficient. Under typical conditions, dividing cells undergo the more efficient process of oxidative phosphorylation, but can also perform anaerobic glycolysis in the absence of oxygen, or aerobic glycolysis during proliferation. Dysregulation of energy metabolism has been linked to both cancer and aging. A comparison of the tradeoffs made by neurons and dividing cells are listed in Fig. (2).

A neuron's purpose is to form networked connections with other neurons and maintain them for the life of the organism, but tradeoffs required for long-term survival make it particularly vulnerable to cell death. While there is evidence that neurogenesis can occur from neural stem cells in the dentate gyrus of the hippocampus, the subventricular zone, and the olfactory bulbs, most neurons in the brain are permanent [24–27]. Because they do not divide, they do not retain all the requisite enzymes to complete mitosis and repair only the DNA they use [28]. As a tradeoff for the specialization required to transmit information, neurons have lost the ability to independently meet many basic survival needs. They rely on nearby astrocytes, pericytes and microglia to perform a variety of critical maintenance tasks. Neurons use an enormous amount of energy and rely on glial cells to create energy precursors for oxidative phosphorylation [29]. These factors make neurons uniquely vulnerable to aging-related changes in energy metabolism.

1.2. Overlap Between Cancer, Neurodegeneration, and Hallmarks of Aging

It is well-accepted that aging is a manifestation of the time-dependent accumulation of cellular damage [30]. A review published in 2013 further proposed nine key cellular and molecular hallmarks of physiologic aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [31]. As further discussed below, each of these hallmarks of aging is significant with respect to both carcinogenesis and neurodegeneration, as seen in Fig. (3).

1.2.1. Genomic Instability—Cells can experience thousands of potentially toxic molecular lesions every day and have a variety of mechanisms to correct them [32]. A number of human DNA repair gene mutations, most famously BRCA1 and BRCA2, have been shown to strongly increase cancer risk [33, 34]. Most of these mutations precipitate a reduced efficacy of DNA repair processes. Within the past two decades, it has become apparent that epigenetic alterations play a significant role in silencing or reducing DNA repair protein expression [35–37]. Single-strand breaks can block transcriptional elongation by RNA polymerase II [38], and the accumulation of singlestrand breaks has been theorized to contribute to aging and neuronal dysfunction [39].

A seminal paper entitled "The Hallmarks of Cancer" has set the standard for defining the biological basis of cancer [40]. The overlap between the hallmarks of cancer and those of aging is striking; perhaps none is more obvious than genomic instability. Defects in DNA repair are strongly linked to cancer, and many progeroid syndromes are associated with an increased risk of developing both cancer and central nervous system (CNS) disorders [41]. Genomic instability is similarly related to neurodegeneration. A large number of progeroid syndromes are associated with neurodegeneration and/or mental retardation [42]. There is mounting evidence that neurons in patients with AD and other neurodegenerative diseases aberrantly attempt to re-enter the cell cycle as a response to DNA damage. Cell culture and animal models have demonstrated that abnormal activation of the cell cycle precedes the formation of tangles, plaques, and eventual cell death [43, 44]. Defects in various aspects of DNA repair, including nuclear excision repair and base excision repair, have also been linked to neurodegeneration [45, 46].

1.2.2. Telomere Attrition—Telomeres are stretches of repetitive nucleotide sequences at the tail end of each chromosome that over time become truncated due to cellular division. Eventually, when telomeres become too short, the chromosome reaches a "critical length," after which it can no longer replicate; instead, the cell enters a senescent state. Telomere attrition is classically seen in normal organismal aging [31, 47]; moreover, pathologic alterations in telomeres are also seen in neurodegeneration and cancer. In AD, telomere shortening has been implicated in oxidative stress and inflammation, coupled with cognitive impairment, amyloid pathology, and tau hyper-phosphorylation [48]. Recently, peripheral blood analyses have shown a decrease in telomere length in peripheral blood leukocytes in AD patients, compared to agematched controls, highlighting a potential biomarker for AD [49, 50].

Telomere shortening has been described as "simultaneously a cancer protective mechanism and a pro-aging mechanism" [51]. When telomeres become critically short with aging, chromosomal material is unprotected, potentially leading to a genetic catastrophe from which cancer can arise. In a number of studies, early stages of carcinogenesis have demonstrated evidence of shortened telomeres [52–54]. However, by definition, all cancer cells eventually need to activate telomerase, an enzyme that synthesizes telomeres, in order to become immortal [55]. Thus, telomere attrition is recognized as a risk factor for both age-related carcinogenesis and neurodegeneration.

1.2.3. Epigenetic Alterations—An epigenetic trait was defined as a "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" during a recent consensus meeting [56]. There are three pillars of epigenetic mechanisms: DNA methylation, histone modification, and noncoding RNA species, all of which have been implicated in both aging and cancer [57]. Progeroid syndromes can be induced by epigenetic perturbations, and loss- or gain-of-function mutations of epigenetically relevant enzymes, such as the sirtuin SIRT6 have been shown to inversely affect longevity in mice [31, 58, 59]. Many other epigenetic mechanisms can be perturbed in cancer, including oncogene activation [60], histone modification [61], and DNA binding protein dysregulation [62].

The past decade has seen an increase in efforts to understand the epigenetics of neurodegenerative diseases. All three levels of epigenetic gene regulation are also implicated in neurodegeneration [63]. AD, for example, is marked by global hypomethylation and hypohydroxymethylation [64], alterations of histone proteins[65], and elevated expression of certain noncoding RNAs [66]. Several genes associated with amyloid–β processing and methylation homeostasis display significant inter-individual epigenetic variability, which is theorized to contribute to late-onset AD development [67]. There is a growing body of literature linking PD, HD, and many other neurodegenerative diseases to epigenetic alterations, and this will surely increase in coming years. Epigenetic therapy has already been suggested as a potential method for correcting expression levels of dysregulated genes in neurodegenerative disorders as well as cancers.

1.2.4. Loss of Proteostasis—The fourth hallmark of aging is the loss of protein homeostasis or proteostasis, especially in the heat-shock family of proteins [31, 68]. Protein regulators, such as molecular chaperones [69], and control systems, such as the autophagylysosomal system [70] and the ubiquitin-proteosomal system (UPS) [71], decline with aging. Neurodegenerative diseases are characterized by a decline in these systems leading to accumulation of distinctive proteopathies. For example, PD is associated with downregulation of the UPS and aggregation of α–synuclein into Lewy bodies [72], while AD is distinguished by impaired chaperone proteins and autophagy, with aggregation of abnormal amyloid–β and tau [73, 74].

Neoplastic cells display a loss of proteostasis, but often in the opposite direction. Because increased protein synthesis is required for unregulated cellular division [75], cancer cells upregulate the UPS and heat shock proteins [76, 77]. These pathways help to drive cellular proliferation, downregulate cell death, and modulate protein folding.

1.2.5. Deregulated Nutrient Sensing—The dysregulation of nutrient sensing is an additional hallmark of aging. Intriguingly, in organisms with constitutively decreased insulin and insulin-like growth factor signaling (IIS), as well as dietary restriction, longevity is extended. This can be attributed to lowered rates of cellular damage due to slower cellular growth and metabolism [31]. Aged cells often attempt to decrease IIS as a protective measure against cellular damage, but this can cross a minimal threshold where the costs of decreased nutrient signaling outweigh the benefits. Just as under typical conditions, where

decreased nutrient signaling increases lifespan, the opposite is true for anabolic signaling, which has been shown to accelerate aging [78].

Alterations in nutrient sensing are also characteristically seen in both neurodegeneration and cancer. Nearly 100 years ago, Otto Warburg first observed that cancer cells metabolize glucose differently than normal tissues, performing glycolysis even in the presence of oxygen— a phenomenon now known as the Warburg effect [79, 80]. Aerobic glycolysis, while less efficient than oxidative phosphorylation, is more rapid, allowing hungry cancer cells to outcompete their normal neighbors for energy precursors. It also produces the biomass needed for proliferating cells to meet their increased biosynthesis and redox needs. Altered vasculature provides tumor cells with a continuous supply of oxygen and nutrients for increased demands and liabilities [40, 81]. The PI3K pathway is commonly upregulated in cancers, and one downstream effector in this pathway, AKT1, stimulates ATP generation through a variety of mechanisms [82]. Numerous altered genes across all members of this pathway are associated with an increased risk of cancer [83]. Interestingly, many neoplasms also express mutations that allow them to systematically slow glycolysis, allowing carbohydrates to enter subsidiary pathways that support other necessary processes, such as biomass generation [84].

Neuronal functions are also tightly linked to glucose metabolism, and compromised levels of the nutrient sensor OGlcNAcylation have been shown in AD brains [85]. This corroborates findings from other studies showing that hyperphosphorylated tau is associated with a decrease in OGlcNAcylation [86]. Altered brain glucose metabolism and hyperglycemia have been suggested to contribute to the pathogenesis of AD, and AD has notably been touted as "type 3 diabetes" due to the striking reduction in the utilization of glucose, as well as extensive abnormalities in genes encoding insulin and its related growth factors [87, 88]. AD patients show reduced glucose energy metabolism in affected regions of the brain [89], and the AD brain also shows a marked reduction in GLUT3, the neuronal glucose transporter [90]. There is growing evidence that this hypometabolism may be preceded by a period of hypermetabolism in compensation for bioenergetic insufficiency [91, 92]. This metabolic upregulation may be a similar phenomenon to that seen in cancer and has been coined the "inverse Warburg effect." Elevated mTOR signaling has also been shown to promote tau pathology in AD and other tauopathies [93].

1.2.6.   Mitochondrial Dysfunction—As discussed in the previous section, neurons and dividing cells handle their energy needs in differing ways. Mitochondrial DNA is especially vulnerable to the inevitable loss of molecular integrity that accompanies aging, as well as to oxygen free radicals produced by normal cellular respiration. Mounting evidence suggests that age-related changes in bioenergetics and the metabolic compensation that ensues may be an important driver of both cancer and neurodegeneration, and a potential target for prevention and therapy.

Dysfunction of the mitochondria of dividing cells leads to disruption in DNA repair, and it is well known that these deficiencies increase cancer risk. Specifically, mutations in cell checkpoint genes and human DNA repair have been linked to malignancy [33, 34]. In addition to DNA repair, mitochondrial dysregulation of energy metabolism is also linked to

cancer. Cancer cells metabolize glucose via aerobic glycolysis, an inefficient but rapid process. Various other pathways involving the mitochondria are dysregulated in cancers as well, including the PI3K pathway, as discussed prior [82].

As energy metabolism is crucial in neurons, it is not surprising that energetic dysregulation has been linked to neurodegeneration [94, 95]. In a number of AD mouse models, mitochondrial dysfunction in both neurons and glial cells has been demonstrated before the onset of memory impairment or amyloid plaques [96]. Neurons are highly specialized and recruit nearby glial cells for many survival functions, and because neurons are permanent, they accumulate DNA damage over time, and it has been theorized that the accumulation of single-strand breaks contributes to neuronal dysfunction [39]. Recent studies have shown that deleted mitochondrial DNA (mtDNA) is associated with reduced respiratory chain efficiency, and this increases with aging, and the prevalence of mtDNA deletions is particularly high in neurodegenerative disorders such as PD [97, 98]. Astrocytic dysfunction has also been demonstrated in a number of neurodegenerative diseases, including AD [99, 100].

1.2.7. Cellular Senescence—Cellular senescence, the phenomenon by which normal diploid cells cease to continue dividing, was first described in the 1960s when Hayflick and colleagues demonstrated the limited ability of dividing cells to proliferate in culture [101]. Though senescence is canonically associated with loss of replicative capabilities, its phenotype is in reality much more diverse, involving alterations in gene expression, epigenetic regulation, and cellular metabolism [102]. Cellular senescence most notably results from telomere attrition, and can also be induced via non-telomeric DNA damage and derepression of the INK4/ARF locus [51]. The removal of senescent cells in transgenic progeroid mice, as well as nonpregeroid mice, causes an increased resistance to age-associated symptoms, further providing evidence of the association between senescence and aging [103, 104]. Overall, senescence is thought to be a survival response to protect the organism from cancer; ultimately, it leads to the buildup of senescent cells, which in turn can be a driver of age-related disease.

Although neurons are non-dividing cells, senescencelike phenotypes, such as p38MAPK activation, elevated beta–galactosidase, and secretion of interleukin-6, have been noted in Purkinje and cortical neurons following DNA damage [102, 105]. Moreover, senescence of glial cells, namely astrocytes, microglia, and oligodendrocytes, is observed in aging and neurodegeneration and is commonly characterized by dystrophy followed by altered cell functionality [43, 106–109]. These senescent cells in the mammalian brain have been shown to secrete pro-inflammatory senescence associated secretory phenotype (SASP) factors and disrupt cell-cell contacts, thereby leading to neurodegeneration [110–112].

On the other hand, cellular senescence protects against cancer by preventing oncogenic cells from dividing, and abnormalities in senescence have been linked to neoplasia. Of note, inactivation of tumor suppressor proteins p53 (primarily) and p16 (secondarily) causes the reversal of senescence and can trigger cells to re-enter the cell cycle [113]. The relationship between cellular senescence and the tumor microenvironment is complex; while cells may enter a senescent state to prevent pathogenesis, senescent cells can promote the development

of age-related cancer by stimulating leukocyte infiltration, tumor growth, and malignant phenotypes. Thus, cellular senescence is an example of antagonistic pleiotropy; a process that protects one from cancer early in life that actually becomes a risk factor for disease at older ages [114].

1.2.8.   Stem Cell Exhaustion—Stem cell exhaustion occurs physiologically during the aging process as stem cells decrease in number and slowly lose their ability to differentiate and replenish. The decline in stem cells seems to be an integrative result of multiple types of damage to both cells and their microenvironment [31, 115]. The attenuation of hematopoietic aging in mouse models has been demonstrated by stem cell rejuvenation [116].

Neural stem cells, which are associated with neurogenesis, as well as differentiation into various glial cells, are present in low numbers in isolated regions of the brain. The Wnt signaling pathway has recently been shown to play a critical role in neural stem cell proliferation, and alterations of this pathway are closely related to the pathologic development of AD [117]. Additionally, the neuronal microenvironment is significantly altered in neurodegenerative diseases [118]. This change in the extracellular milieu contributes to exaggerated inflammatory responses through the release of toxic factors, reducing neurogenesis [119]. In a similar vein to stem cell exhaustion, aberrantly regulated stem cells through pathways such as the Wnt signaling pathway have been linked to cancer [120]. Because cancer mutations occur in a series of steps, it is theorized that subsets of tumor cells are in fact malignant "cancer stem cells" [121].

1.2.9.   Altered Intercellular Communication—Neurohormonal signaling pathways are often affected in the physiological aging process in the face of globally diffuse increasing inflammatory reactions, decreasing immune responses, and environmental changes [31]. This includes the NF–κB signaling pathway, whose over-activation is a transcriptional signature associated with aging [122]. Inter–organ synchronization of aging has also been described, where senescent cells induce senescence in nearby fibroblasts through a "bystander effect," using gap junctions and processes involving reactive oxidative species [123].

Altered intercellular communication is also seen in both neurodegeneration and cancer. In cancer, molecular strategies allow for the reprogramming of existing physiological pathways, such as chemokine receptor pair pathways, to promote the survival of tumor cells [124]. Cancer cells have additionally been shown to emit a large number of microvesicles, which function as mediators of intercellular communication [125]. These structures transfer bioactive molecular content to recipient cells, aiding in pro-oncogenic events, such as tumor invasion, angiogenesis, metastasis, drug resistance, and cancer stem cell hierarchy [125].

Proper cell-to-cell communication is integral to the survival of neurons. Indeed, disruptions in this process have been invariably linked to the earliest stages of a number of neurodegenerative disorders, including AD [126], HD [127], and ALS [128]. Moreover, glutamate removal from the synaptic cleft is critical to the process of neurotransmission, and failure to eliminate can lead to glutamate excitotoxicity and, ultimately, neuronal death. This

has been demonstrated in ALS, hD, and spinocerebellar ataxia type 7 (SCA7) [129]. Additionally, an elegant review recently described a number of ways in which intercellular communication may be altered in a variety of neurodegenerative diseases by means of disrupted neuron-neuron communication, dysfunctional crosstalk between neurons and glia, and the transmission of pathogenic proteins between cells [130].

2. BIOLOGIC OVERLAP

Genetic diseases commonly have an early age of onset and lead to an early death; as a result, they remain rare in the population. In contrast, chronic age-related diseases such as cancer and neurodegeneration have complex causes that include small contributions from many genes, as well as aging- related changes, environmental, and lifestyle factors [131–136]. The connections between the genetics of PD and cancer are more obvious. In fact, while the familial PD genes are used by the neuron to control protein processing and clearance, in dividing cells, most play some role in development or cell cycle regulation. PARK2 (Parkin) and PARK5 are a critical part of the UPS, the main pathway by which proteins are degraded in cells. These genes have anti-proliferative properties and are often inactivated in cancers [137, 138]. PARK6 may also have anti-proliferative functions [139, 140]. Thus, these PD genes are both neuroprotective and tumor-suppressive. On the other hand, PARK7 (DJ–1) takes part in the UPS, but in the dividing cell antagonizes the tumor suppressor gene PTEN [141–143]. Rather than functioning as a tumor-suppressor, then, PARK7 is an oncogene. Thus, there are "mixed signals" in the overlap, and this may help explain why there are both positive and negative associations between PD and cancer.

Less is known about the shared genetic component between AD and cancer, as strongly AD–associated genes are not known oncogenes or tumor suppressors. Using summary statistics from large genome wide association studies, we have recently found evidence of a shared genetic component between AD and five cancers (colon, breast, prostate, ovarian, lung) [144]. Our results suggested that gene expression regulators play an important role in the genetic overlap, and that some shared variants modulate the risk of both diseases in the same direction, while others increase the risk of one disease while increasing the risk of the other. Here, we examine the genetic overlap between cancer and AD using publicly available databases. The NetAge database is an online biogerontological database for the study of aging, longevity, and age-related diseases, and it contains lists of genes implicated in cancer and AD [145]. To construct this database, genes were collected, compiled, and manually curated from a number of scientific and publicly available databases and selected according to three criteria: 1) mutations associated with disease frequency, 2) consistent positive or negative association with gene expression, and 3) gene polymorphisms associated with disease susceptibility or predisposition [145]. NetAge classifies each gene within a categorical function and creates a topologic map of other genetic interactions (Fig. 4). It is immediately evident that genes related to nucleotide metabolism are more prominent in cancer than in AD, reflecting the mitotic activity of these cells. General metabolism, protein metabolism, and transport are elevated in AD when compared with cancer, a reflection of the importance of waste clearance and maintenance of cellular structure and function in these long-lived cells.

We then sought to examine the genes most commonly associated with either AD or cancer. For this, we queried information on 20 genes from each family of disease using two databases. AlzGene is a database that lists genes associated with AD [146]. In its listing, it also ranks the top 10 genes associated with sporadic AD according to the HuGENet interim criteria for the cumulative assessment of genetic associations [147, 148]. This ranking is determined by the p– value of association with AD, derived using meta-analysis techniques. We were unable to find a cancer database that ranked cancer genes according to statistical association with the development of cancer and instead used Phenopedia, a component of the integrated knowledge base on human genome epidemiology (HuGE Navigator) [149, 150]. This comprehensive online database ranks genes by a total number of citations in peer-reviewed literature. We used Phenopedia to gather the top 20 genes linked to cancer, as well 10 more genes linked to the sporadic AD, and compared the function of these genes (Table 1). From these data, it is apparent that the genes most associated with either disease directly correspond to the evolutionary tradeoffs associated with their cells of origin. Genes most associated with AD are intimately linked with waste removal and neuroinflammation, while those associated with cancer are mostly implicated in DNA repair, cellular growth, and signaling. While this confirms much of what we already understand about the two disease families, it alone does not address the relation between them.

To compare the biological overlap between the two families of disease, we analyzed all cancer and AD genes cited at least two times, according to Phenopedia, and tabulated the total number of mutual genes (Fig. 5). From this database, 3006 genes were associated with cancer and 456 with AD. Of these genes, 286 overlapped between the two families of disease, many of which were in our "Top 20" gene category of one disease, but were located further down the list in the other disease. Notably, this links more than 60% of AD– linked genes to cancer. One drawback to Phenopedia, when compared to NetAge, is that it does not classify genes by function. And while NetAge does make these categorizations, the categories lack detail. Of the 286 overlapping genes from Phenopedia, we manually assigned each gene a more specific functional category, as shown in Figure 6. Interestingly, several of these genes, including AT–1, are implicated in the pathogenesis of both neurodegeneration and cancer, but through different mechanisms due to the multifunctionality of their proteins [151].

3. CLINICAL IMPLICATIONS

A number of important conclusions regarding preventive and therapeutic approaches to age-related cancer and neurodegeneration can be drawn from this review. First, interventions that slow the hallmarks of aging will decrease the risk of both families of diseases. It has already been shown that promoting healthy lifestyle and metabolism can decrease the risk of both cancer and cognitive decline [152, 153]. In addition to fostering healthy metabolism, these interventions are known to decrease markers of inflammation, improve mitochondrial health and decrease oxidative stress [154]. The FINGER trial, a randomized controlled trial (RCT) of regular exercise, modified Mediterranean diet, and cognitive training, either improved or maintained cognitive function at two years [155]. Medications that target various hallmarks of aging are also being explored in both fields. Metformin, a biguanide approved for the treatment of Type 2 diabetes, appears to decrease the risk of cancer, dementia, and other

age–related diseases through multiple mechanisms [156–158]. These include a decrease in insulin and IGF–1 levels, inhibition of the mTOR pathway, inhibition of mitochondrial function and decrease in oxidative damage and activation on AMP kinase [159–162]. The "Targeting Aging with Metformin" trial– a large randomized controlled trial for metformin for the prevention of age-related disease– is currently in its early stages [156].

Drugs that decrease inflammation have been tested in cancer field for years and are now being actively investigated for their possible role as neuroprotective agents. Similarly, a number of DNA–methylation and histone acetylation inhibitors are currently in various stages of the drug development process. Senescent cells are also a potential target for therapy because of their presence in many age-related diseases, including both carcinogenesis and neurodegeneration. Due to altered excretion of toxic metabolites caused by aberrant mutations in autophagy-associated genes such as AT– 1/SLC33A1, therapies targeting improved proteostasis involving these genes are being explored in animal models of AD [151, 163]. Senescent cells express unique proteins such as p16^{INK4a} that cause intriguing age-related deterioration and can be used as potential targets in new therapies [164]. Another proposed approach to combating cancer and other agerelated diseases is targeting select epitopes such as SASP on senescent cells [165].

Consideration of the horizontal axis in Fig. (1) that illustrates differentially regulated pathways common to the two diseases raises other therapeutic possibilities. Proteasome inhibitors such as bortezomib inhibit protein degradation, and their role as anticancer agents has been expanding on the past decade. If inhibitors of the proteasome are effective anti-cancer agents, then drugs that enhance proteasome function will likely be neuroprotective. Small molecules that increase proteasome 26S activity are currently being developed for this purpose [166]. However, proteasome activation would need to be carefully targeted to neurons, as it could theoretically promote cancer in other tissues. This is not unreasonable, as proteasome inhibitors should theoretically cause PD in humans, but thus far there is no evidence of this. Inhibitors targeting heat shock proteins have been in development for cancer for years; the effort to modulating the chaperone network of proteins as a strategy for neuroprotection has begun only recently [167, 168]. Modulating a single chaperone protein like Hsp90 has been proposed as a potential therapeutic for both cancer and neurodegeneration [169].

CONCLUSION

We have provided an overview of the complex and intriguing interrelation between age-related neurodegenerative disease and cancer. While some of the connections between the disorders could help explain the pattern of inverse comorbidity seen in epidemiologic studies, others would suggest that the diseases should co-occur. This mixed picture may help explain why an inverse association with neurodegeneration is seen in some cancers but not others. Both positive and inverse associations in the overlapping biology provide new potential directions for developing effective prevention and treatment. The strong overlap between the processes of neurodegeneration, cancer and aging suggests that interventions that target hallmarks of aging, such as metformin, are likely to prevent both diseases.

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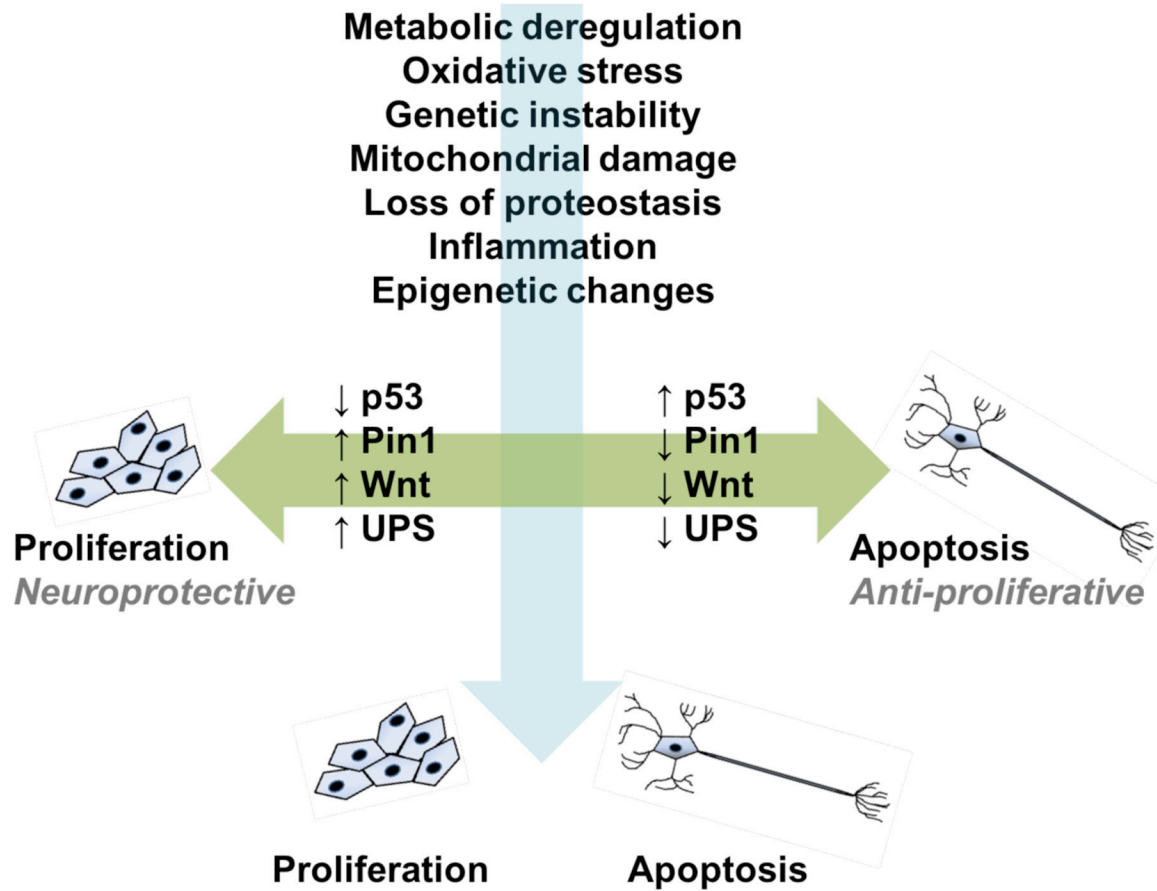
Fig. (1).

Two patterns of association between cancer and neurodegeneration, as depicted in the figure as "proliferation," and "apoptosis," respectively. The horizontal axis denotes specific genes, proteins, and pathways that are inversely regulated in cancer and neurodegeneration. The vertical axis shows age-associated pathophysiologic features that are directly associated with both families of diseases.
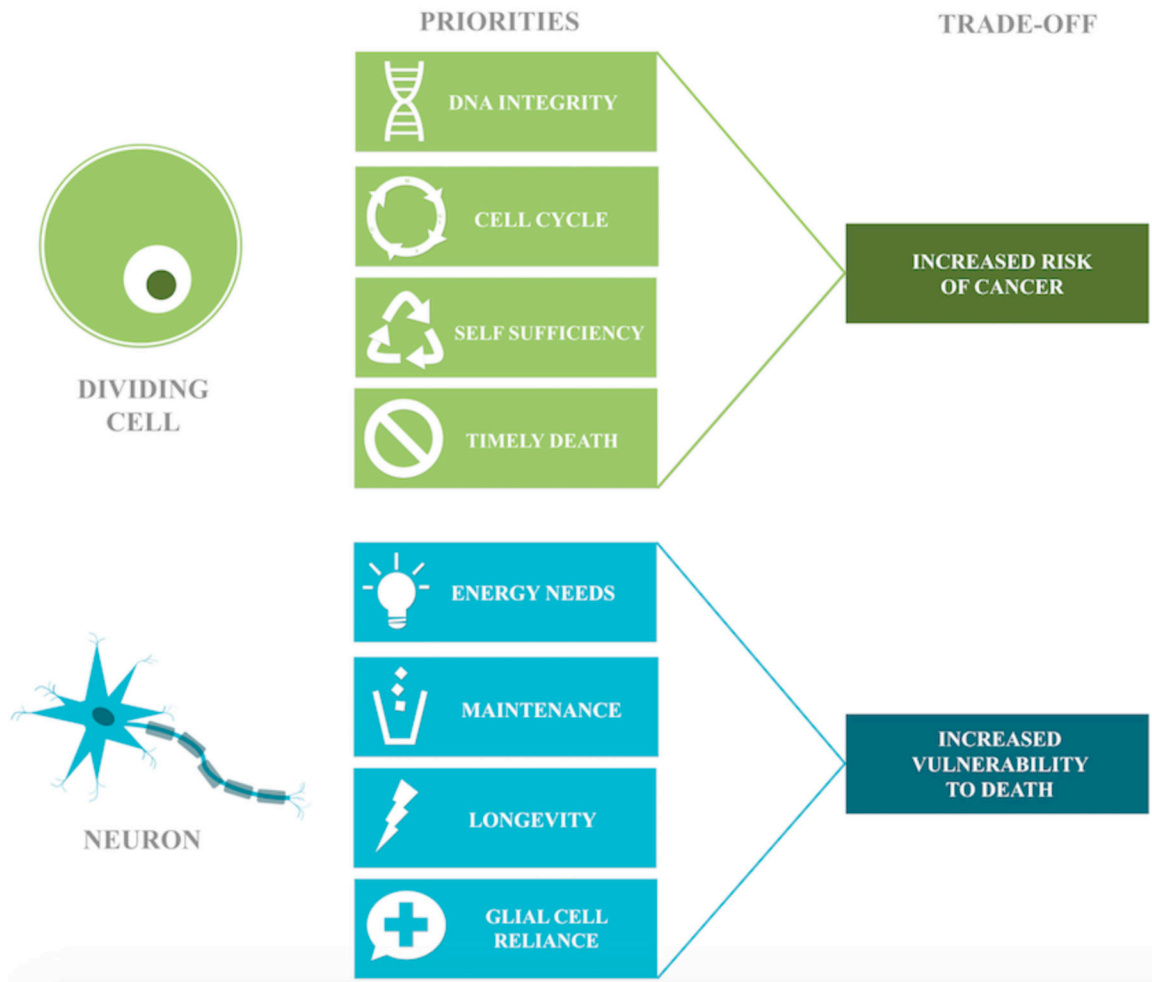
Fig. (2).
The differential priorities of dividing cells and neurons. Dividing cells prioritize DNA integrity, frequent self-replacement, and bioenergetic self-sufficiency but need to die on time to avoid cancer. The mission of neurons requires longevity and maintenance of networked connections. Their complexity, dependence, and high performance come at the cost of vulnerability to cell death.

Fig. (3).
Overlap between hallmarks of aging and cancer and neurodegeneration. The nine hallmarks
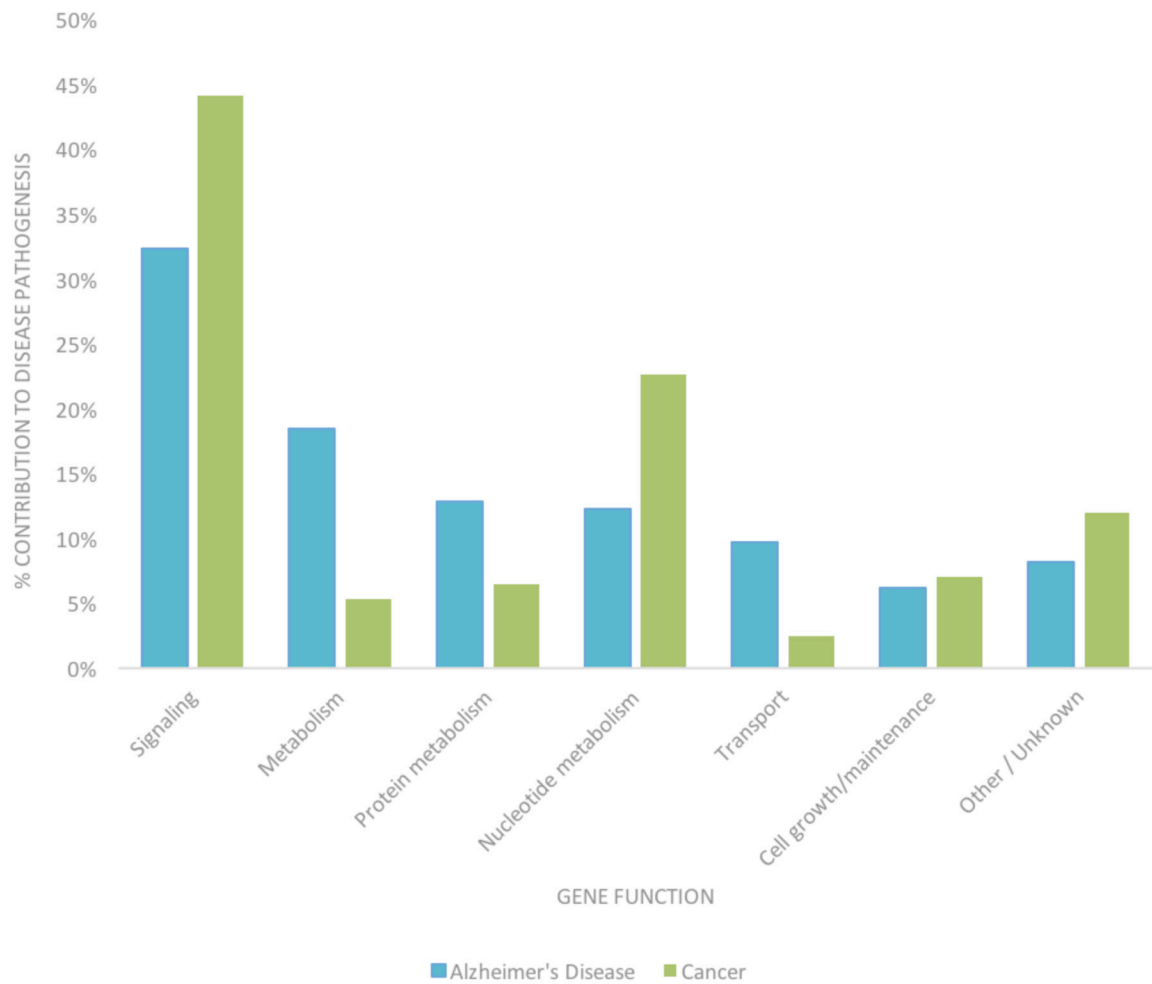of aging are shared by carcinogenesis and neurodegeneration [31].

Fig. (4).

NetAge gene categorization of AD and cancer. In both cancer and AD, the majority of classified genetic contributors are associated with signaling activities. Compared to cancer, in AD, a disproportionate number of genes involved in general metabolism (18.46% *vs.* 5.28%), protein metabolism (12.82% *vs.* 6.44%), and transport (9.74% *vs.* 2.50%) are mutated. Compared to AD, in cancer, a disproportionate number of genes involved in nucleotide metabolism (22.67% *vs.* 12.31%) are affected.
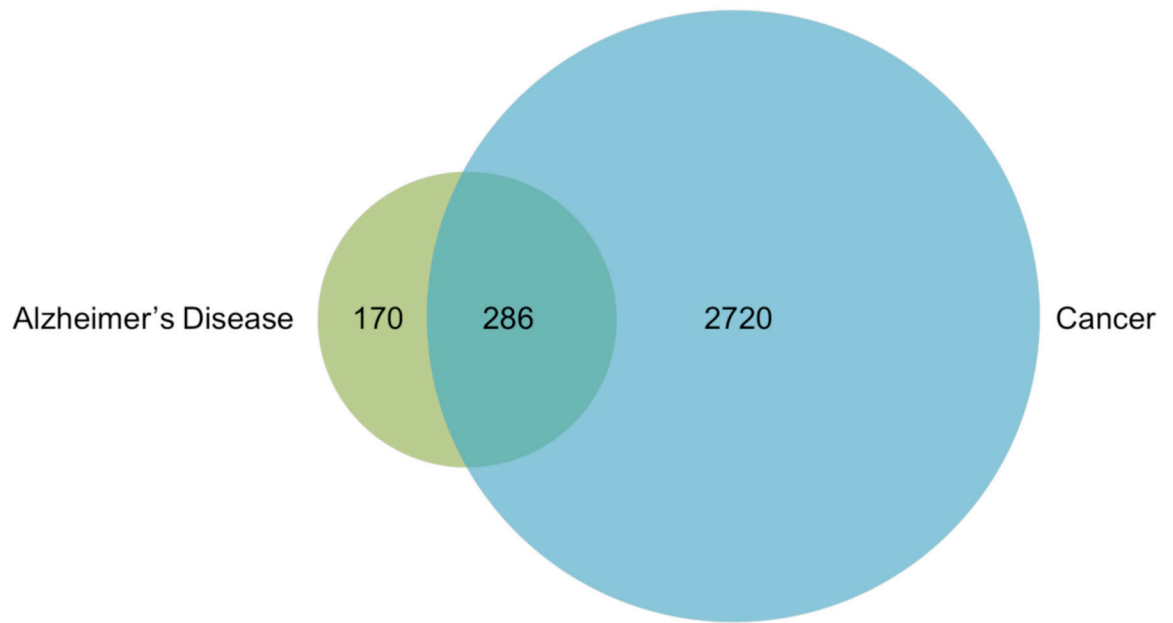
Fig. (5).

Overlap between genes associated with AD and cancer. Of the 456 genes associated with AD and the 3006 genes associated with cancer, 286 overlap between the two diseases.
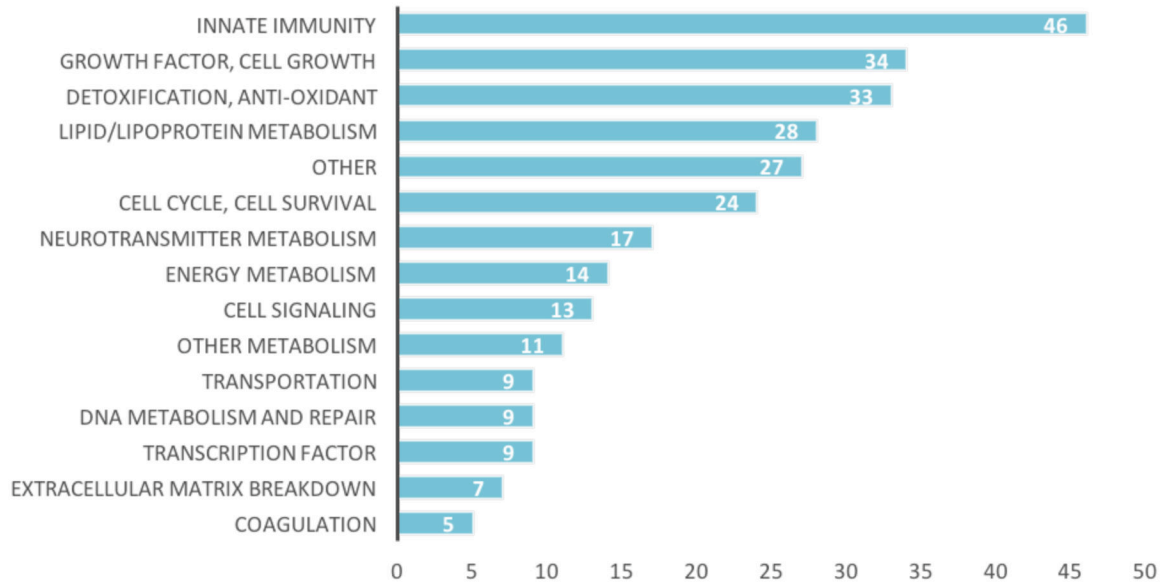
Fig. (6).

Functions of the overlapping genes between AD and cancer. It is evident that genes regulating innate immunity, cell growth, and detoxification are most commonly implicated in both diseases.

Table 1.

Top 20 genes linked to AD and cancer. (A) Genes most associated with AD are mainly involved in waste removal and neuroinflammation. (B) Genes most associated with cancer are mainly involved in DNA repair, cellular growth, and signaling.

A)

Alzheimer's Disease	
Gene	**Function**
APOE	Cholesterol packaging
BIN1	Modulates tau pathology
CLU	Unknown (chaperone protein)
ABCA7	Unknown (transporter protein)
CR1	Neuroinflammation
PICALM	Waste removal
MS4A6A	Unknown (immune-mediated function)
CD33	Immunoregulation
MS4A4E	Unknown (immune-mediated function)
CD2AP	Actin cytoskeleton regulation
MAPT	Encodes tau
ACE	Blood pressure regulation and waste removal
BDNF	Neuroprotection
SORL1	APOE receptor
MTHFR	Unknown (protein production)
IL1A	Neuroinflammation
IL6	Neuroinflammation
A2M	Neuroinflammation
IL1B	Neuroinflammation
SLC6A4	Serotonin transport

(B)

Cancer	
Gene	**Function**
TP53	Tumor suppressor
KRAS	Signaling
EGFR	Growth factor
GSTM1	Detoxification
BRCA1	Tumor suppressor
BRAF	Signaling
BRCA2	Tumor suppressor
GSTT1	Detoxification
XRCC1	DNA repair
GSTP1	Drug metabolism
ERCC2	DNA repair
CYP1A1	Drug metabolism
PIK3CA	Signaling
TNF	Innate immunity - cytokine
ABCB1	Detoxification, transportation
XRCC3	DNA repair
IL10	Neuroinflammation
NAT2	Drug metabolism
ERCC1	DNA repair
VEGFA	Growth factor