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A common biological mechanism in cancer and Alzheimer's disease?

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Abstract

Cancer and Alzheimer's disease (AD) are two common disorders for which the final pathophysiological mechanism is not yet clearly defined. In a prospective longitudinal study we have previously shown an inverse association between AD and cancer, such that the rate of developing cancer in general with time was significantly slower in participants with AD, while participants with a history of cancer had a slower rate of developing AD. In cancer, cell regulation mechanisms are disrupted with augmentation of cell survival and/or proliferation, whereas conversely, AD is associated with increased neuronal death, either caused by, or concomitant with, beta amyloid (Aβ) and tau deposition. The possibility that perturbations of mechanisms involved in cell survival/death regulation could be involved in both disorders is discussed. Genetic polymorphisms, DNA methylation or other mechanisms that induce changes in activity of molecules with key roles in determining the decision to "repair and live"- or "die" could be involved in the pathogenesis of the two disorders. As examples, the role of p53, Pin1 and the Wnt signaling pathway are discussed as potential candidates that, speculatively, may explain inverse associations between AD and cancer.

Keywords

Alzheimer; cancer; tumor suppressors; Pin1; Wnt signaling pathway

An inverse association between cancer and AD

While attending patients in nursing homes where most residents have some type of dementia, we were puzzled by the observation that a history of cancer was not a common finding among residents who were demented, whereas many residents that were cognitively normal had had cancer in the past. This anecdotal observation was followed by a longitudinal prospective study in which we found an inverse association between cancer and AD [1]. The study was done using archival data of longitudinal studies of memory and aging study at the Alzheimer's disease Research Center at Washington University School of Medicine in St Louis. In these studies, participants are cognitively evaluated annually with the Clinical Dementia Rating CDR [2], and a thorough medical history is obtained including a history of cancer, its type, treatment and date of diagnosis. Results showed an inverse association between cancer and AD. Specifically, we found that of the 594 participants, who at their first visit had no history of

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cancer, 395 had dementia of the Alzheimer type [DAT] and 199 were cognitively normal. Data from subsequent visits revealed that the rate of receiving a cancer diagnosis was significantly slower in the DAT group ($p < 0.001$). Conversely, of the 249 participants who were cognitively normal at study entry we found that 50 had a history of cancer and 199 did not. Those with a history of cancer had a slower rate of receiving a DAT diagnosis with time, although this result did not reach statistical significance at an alpha level of .05 ($p = 0.0600$). Cox proportional hazard models indicated that the inverse relationship between cancer and DAT was not accounted for by demographic factors such as age, sex and education [1]. These results are in accordance with previous cross-sectional and case-control studies which report a reduced prevalence of cancer among individuals with AD [3–8].

The incident cancers in the demented and non-demented groups were similar to those in the general US population [9]; 57% of all neoplasias in our study were skin cancers, most of them benign, ~80% basal or squamous cell with the analysis of carcinomas. The survival analyses were repeated examining the association between DAT at study entry and the development of skin cancer specifically. When skin cancer alone was analyzed as the dependent variable we found that, as with all cancers, the rate of skin cancer diagnosis was slower for participants with DAT compared to non-demented individuals in both the log-rank test ($p <0.001$) and the Cox proportional hazard models ($p < 0.005$; hazard ratios associated with DAT versus no dementia ranged between 0.22–0.26). Other cancer types were too infrequent in our sample to be analyzed separately. When combining all non-skin cancers into a single group, the rate of cancer diagnosis was slower with time for the DAT group, although the difference did not reach statistical significance (all $p>0.05$; hazard ratios associated with the DAT versus no dementia ranged between 0.65–0.83) [10].

The relationship of dementia to the different types of cancers individually (other than skin cancers) remains to be analyzed in detail, as well as the role of environmental factors. However, there is an interesting possibility that one or more biological mechanisms may link AD and cancer. If such a mechanism can be identified, it might lead to better understanding of these two disorders, as well as strategies to protect us from them. The purpose of this speculative review is to describe some potential biological links between the development of cancer and AD.

A common biological mechanism with opposing effects?

The neuropathological hallmarks of Alzheimer's disease include senile plaques, and neurofibrillary tangles. Senile plaques consist of extracellular deposits mainly composed of the beta amyloid (Aβ) peptide. Neurofibrillary tangles are intracellular deposits of an abnormally hyperphosphorylated tau, a microtubule-associated protein which is involved in axonal transport and other functions. In addition to amyloid plaques and neurofibrillary tangles, AD is characterized by extensive neuritic and synaptic degeneration and neuronal cell death. The type of cell death in AD is still controversial, but it is clear that in AD there is progressive atrophy of the brain due to cell and synaptic loss. The leading explanation for the pathologic changes associated with AD is the "amyloid hypothesis" which states that neuronal dysfunction and death, neurofibrillary degeneration, microglial activation and the full manifestation of Alzheimer pathology are initiated by Aβ deposition [11]. The abnormal phosphorylation of tau in AD and other neurodegenerative disorders induces a decreased capability of tau to promote tubulin polymerization and bind to microtubules [12], leading to a generalized loss of microtubule stability [13] and eventually retrograde neurodegeneration. Although the amyloid and tau hypotheses are the favored ones, apoptosis, synaptic loss, or neuronal dysfunction prior to cell death might also play a role in the physiopathology of AD [14,15].

Normal tissue function requires that the rate of cell loss is matched by the rate of renewal. The maintenance of tissue homeostasis is achieved by efficient mechanisms that control genomic stability to prevent aberrant proliferation [16,17,18]. After DNA damage, intracellular stress pathways which are able to recognize the damage are activated, and either recruit DNA repair factors to mend the damage, or induce apoptosis or senescence [19]. In cancer this reparative process is defective, leading to excessive cell growth. To simplify, cancer is a disorder typified by uncontrolled, excessive cell growth, whereas conversely, AD and other neurodegenerative disorders are characterized by progressive dysfunction and eventual loss of neuronal loss.

One possible explanation for why AD and cancer appear to be inversely associated is that both diseases arise via malfunction of an underlying common mechanism that regulates cell survival. This hypothetical mechanism could regulate the capability of the cells of switching the cell machinery from a prone-to-death state (AD phenotype) to a prone-to-survive/grow state (cancer phenotype). If cells are in the prone-to die state, then neurons will be more susceptible to cell death under stressors such as Aβ, tau hyperphosphorylation, oxidation, inflammation, or other unknown risk factors (the AD phenotype). At the same time, cells will respond to initiating cancer stimuli (UV radiation, for example) by death, reducing cancer susceptibility. Conversely, if cells are shifted to a survival/growth state, neurons would have a greater likelihood of surviving if subjected to stressors, while concomitantly becoming more susceptible to cancer development. Genetic polymorphisms in several key molecules that determine changes in their activity or variance in their DNA methylation could explain such opposing effects [20]. Here we discuss the possible involvement of the tumor suppressor p53, of Pin1 and the Wnt signaling pathway in the pathophysiology of both cancer and AD.

Tumor suppressors in cancer and aging

In tissues with the capability of renewal the repair or regeneration of cells has evolved as an advantage in terms of increased longevity compared to postmitotic tissues which lack this capability. However, this versatility to regenerate has the inherent risk of hyperproliferation, among which the most dangerous is cancer. Thus, together with the renewal capacity that poses increased longevity there evolved mechanisms to suppress tumor formation [21]. Tumor suppressors are the main actors of the surveillance mechanism to avoid aberrant proliferation under normal conditions. Tumor suppressors were given this name because, as regulators of diverse cellular activities, their loss enhances tumor formation. They regulate cell cycle checkpoint responses, detection and repair of DNA damage, protein ubiquitination and degradation, mitogenic signaling, cell specification, differentiation and migration, and angiogenesis [16]. Tumor suppressors can either eliminate potential cancer cells by inducing programmed cell death (apoptosis), or alternatively, they can induce permanent withdrawal from the cell cycle (cellular senescence). Apoptosis could give rise to a depletion of irreplaceable postmitotic cells in nonrenewable tissues; and in depletion of proliferating or stem cell pools in renewable tissues. In the same way, senescence could deplete tissues of proliferating or stem cell pools, resulting in the accumulation of senescent cells. Thus, tumor suppressor mechanisms may be an example of evolutionary antagonistic pleiotropy [21,22,23], that is, they promote early-life survival by preventing the development of cancer, but eventually limiting longevity.

The p53 gene is the prototypical tumor suppressor and its pathway is inactivated in most human cancers [18]. p53 is at the hub of numerous signaling pathways that are triggered in response to particular stresses and in this way is a major regulator of cellular stress. p53 can be described as a stress response gene; its product (the p53 protein) acts to induce apoptosis or cell-cycle arrest in response to DNA damage, thereby maintaining genetic stability in the organism by transcriptional and nontranscriptional mechanisms [18]. Mice engineered to be deficient in *p53* are developmentally normal, but susceptible to spontaneous tumors [24]. In addition, knocked out p53 mice ($p53^{-/-}$) have a significantly higher number of proliferating cells, as assessed by the incorporation of the nucleotide analogue bromodeoxyuridine in the lateral ventricle wall, compared to wild-type littermates [25].

As mentioned above, the anticancer roles of p53 may come at the cost of proliferative reserve and thereby compromise tissue repair and promote the aging phenotype [23,26–28]. Tyner et al [26] created transgenic mice with a p53-mutation that confers phenotypes consistent with an activated form of p53. The animals had very few cancers, but developed several features of aging and showed reduced longevity. Further support for the role of p53 in accelerating aging comes from a report showing that transgenic mice that overexpress p44 (a protein that enhances p53 activity) have a shortened lifespan and accelerated aging, and an extraordinary low incidence of cancer compared to wild-type mice [29]. Additional support for the concept that hyperactivation of the tumor suppressor p53 may be related to accelerated aging comes from a study showing that mice deficient in Zmpste24, a metalloproteinase involved in the maturation of lamin A, show a senescence phenotype at the cellular level and accelerated aging at the organism level, together with a marked upregulation of p53 target genes [28]. If p53 enhancement leads to aging and reduced longevity, the opposite should be expected in p53 knockout mice. Until recently, no effect of p53 on longevity had been detected, because the predisposition to tumors precluded an analysis of the role of p53 in longevity. However, genetically manipulated mice showing increased activity of the Arf/p53 pathway but conserving the normal regulation of p53, show both cancer resistance and decreased aging [30], which is what would be expected if cancer, a major cause of death in mice, is prevented. Also, transgenic mouse models with elevated p53 activity, but under normal regulatory control, show reduced tumor formation without accelerated aging [31,32]. Therefore, the regulation of p53 activity is crucial to determine the role that p53 will assume. For example, depending on the tissue, the same acetylation of the Lys amino acid at position 320 of p53 can promote neurite outgrowth in neuronal cells [33] or cell cycle arrest in other tissues [34].

Taken together these results show that the regulation of p53's actions in cells is extremely important to determine the fate of the cells or tissues. p53 is activated and integrates the different incoming signals that sense different forms of cellular stress. Therefore, it is conceivable that small deregulations towards one or the other side, could favor survival/regeneration or death/senescence of the cells. The inactivation of p53 is implicated in the development of cancer, and p53 activation might play a role in promoting aging. Elevated p53 levels have been detected in the central nervous system of patients diagnosed with neurodegenerative diseases, such as Huntington's disease and Amyotrophic Lateral Sclerosis [35,36] and in mouse models [37] and in the brains of Parkinson's disease patients [38]. The intracellular expression of the Aβ protein under a neuron-specific promoter led progressively to degeneration and death of neurons in the brains of transgenic mice and Aβ accumulation was correlated with activation of p53 [39]. Also, elevated levels of p73, a member of the p53 family, have been described in mice injected with fibrils of Aβ and in mice models of AD [40]. In neuroblastoma cell lines, intracellular Aβ42 directly activated the p53 promoter, resulting in p53-dependent apoptosis [41]. Intracellular Aβ40 had a similar but smaller effect in the same study [41]. Several reports have described upregulation of p53 in the brains of patients with AD [41,42,43]. The presenilins (PS1 and PS2) form part of the gamma secretase complex that cleaves the amyloid precursor protein (APP) to generate Aβ. Mutations in the presenilins cause familial forms of AD and have also been shown to trigger p53-dependent cell death [44,45]. The intracellular C-terminal fragments of the gamma secretase cleavage of APP trigger the activation of caspase-3 and an increase in p53activity and mRNA [45].

Another important tumor suppressor pathway is the pRB/p16 pathway. The p16 gene functions as a negative regulator of cell cycle and is therefore considered to represent a tumor suppressor. As with p53, deletion of p16 is frequently observed in cancer cell lines and some malignant tumors including acute lymphoblastic leukemia of childhood, melanomas, gliomas, as well as carcinoma of the pancreas, esophagus, lung, bladder, head, and neck [46,47]. On the other hand, increased levels of p16 expression and of the incidence of p16-positive cells are associated with age in many mouse and rat tissues [48,49]. Until recently however, there was no evidence that enhanced pRB function accelerated aging. Three reports show that increased levels of p16 contribute to aging by limiting self-renewal of regenerative cells in different tissues such as brain, endocrine pancreas and bone marrow [50–53].

Alterations in p53, or other tumor suppressors, could play a role in explaining the opposing results we found with regard to the development of cancer and DAT (Figure 1). Patients with slight increases in the activity of tumor suppressor proteins would have lower risks of developing cancers, but instead would be at higher risk of developing AD because of an increased susceptibility to cell death or senescence against stressors such as Aβ, tau hyperphosphorylation, and/or oxidative stress. These slight alterations could be due to polymorphisms or differences in DNA methylation in tumor suppressors that confer an increased risk across the lifespan. Augmented levels of tumor suppressors could also limit the renewal capacity of stem cells, and in this way induce AD by preventing, in the long run, the replenishment of apoptotic neurons, or the reparation of dendrites and spines in damaged neurons, processes which are compatible with the slow course of the disease. Similarly, the low incidence of AD in the cancer group could be explained by the presence of an inactivated form of a tumor suppressor, which in addition to favoring previous cancer development, could also favor a decreased susceptibility to neuronal death, conferring protection against AD. Additional support for a role of tumor suppressors in aging and AD comes from a microarray study, in which an up-regulation of a disproportionately high number of tumor suppressors or tumor suppressor co-factors, including several of the retinoblastoma (Rb) family, were found in the CA1 region of the hippocampus of AD patients [54].

Propyl isomerase (Pin1)

Variations in factors upstream of p53 that ultimately result in its altered activity could also contribute to the observed opposing presentation of cancer and AD phenotypes. One such mechanism could involve the action of Pin1. Pin1 (protein interacting with NIMA 1) is a ubiquitous enzyme that catalyses *cis*/*trans* isomerization of phosphorylated serine or threonine residues that immediately precede a proline [55–58]. Pin1 is conserved from yeast to humans and has been shown to regulate a diverse array of cellular processes of cell proliferation and differentiation, such as cell-cycle control, transcription and splicing regulation, DNA replication checkpoint control, DNA damage response, neuronal survival, and germ cell development [55]. Aberrant Pin1 function has been implicated in both cancer and AD [57, 58]. Investigations show that Pin1 binds to and isomerizes hyperphosphorylated tau, specifically at the Thr231-Pro site, to restore the ability of tau to bind microtubules and promote their assembly and facilitate tau dephosphorylation [59–61]. Furthermore, in addition to this role on tau, Pin1 is also involved in regulating APP processing and Aβ production. Pastorino et al [62] have shown that Pin1 binds to APP and accelerates its *cis*/*trans* isomerization. Overexpression of Pin1 reduces Aβ secretion from cell cultures, whereas Pin1 KO increases its secretion. In addition, Pin1 KO alone, or in combination with overexpression of mutant APP in mice selectively elevates insoluble brain Aβ 42 in an age-dependent manner. Therefore, deletion of the *Pin1* gene alone in mice causes progressive deposition of tau and Aβ, and neuronal degeneration [56,60]. Pin1 expression is induced during neuronal differentiation and is highly expressed in most neurons in the brain [61–63]. In accordance with these results down-regulation of Pin1 has been reported in the hippocampus of AD patients [64]. However, a compensatory activation or up-regulation of Pin1 may also be induced in AD brains [65]. The complex regulation of Pin1 is strengthened by recent studies showing opposite effects of Pin1 on tau protein stability and tauopathy phenotype depending on whether the tau is wild-type

(WT) or has the P301L mutation [65]. Pin1 knockdown or KO increased stability of WT tau protein stability and Pin1 overexpression suppressed the tauopathy phenotype in WT tau transgenic mice. In contrast, the opposite was found with mutant P301L tau; Pin1 knockdown or KO decreased P301L tau protein stability and abolished its robust tauopathy phenotype in the mutant mice, whereas its overexpression exacerbated the tauopathy phenotype in P301L tau mice [65]. Pin1 promoter polymorphisms appear to associate with reduced Pin1 levels and increased risk for late-onset Alzheimer's disease [66–69], but not all case-control studies agree (70,71]. Evidence for a participation of Pin1 in ALS has also been reported [72].

A prevalent overexpression of Pin1 has been shown in most human cancers including prostate, breast, lung, colon and liver [73–76], but not in others such as renal cancer [77]. Pin1 is important for the activation of multiple oncogenic pathways involved in tumorigenesis, such as cyclin D1, Wnt/β-catenin, NF-κB, p53, and p73 [73,76,78–83]. Accumulating evidence suggests that Pin1 regulates the timing of p53 activation, modulating its interaction with DNA and cofactors [84]. In response to toxic stimuli, the interaction between p53 and Pin1 markedly increases with phosphorylation of a subset of Ser/Thr-Pro motifs of p53 and its subsequent isomerization. Cells lacking Pin1 fail to efficiently stabilize p53 and are then able to escape cell cycle arrest and apoptotic responses [83,85], thus promoting the 'prone to cancer' direction in figure 1. Also, a role of Pin1 in promoting the mitochondrial apoptotic machinery has been described in neurons [86,87]. Taken together, these data suggest that alterations in Pin1 activity could explain an inverse association between cancer and AD. Patients with less active Pin1 would be at a greater risk of developing AD and not cancer and, conversely, those with an active Pin1 would be more prone to develop cancer and not AD.

Wnt signaling pathway

The Wnt (wingless-type murine-mammary tumour virus integration site) signaling pathway is important for many developmental and adult processes, such as gastrulation, axis formation, cell polarity, organ development and maintenance of stem cell pluripotency and is remarkably conserved in a wide range of organisms, from Caenorhabditis elegans to humans [88]. In the canonical pathway, wnt proteins bind to cell-surface receptors composed of members of the Frizzled family and a low density lipoprotein receptor 5/6 (LRP 5/6). The receptor complex in turn is associated with a large cytoplasmic protein complex comprised of axin, (axis inhibition protein), APC (adenomatosis polyposis coli), CK1α (casein kinase 1 alpha), GSK-3β (glycogen synthase kinase 3 beta) and GβP/frat [88]. The activation of the pathway by the binding of Wnt proteins ultimately stabilizes cytoplasmic β-catenin that translocates to the nucleus and is involved in gene expression regulation that promotes several physiological functions, among them cell survival and proliferation, through the binding to TCF/LEF transcription factors and the expression of wnt-target genes. In the absence of Wnt binding GSK-3β phosphorylates β-catenin molecules which are then directed to the ubiquitin-mediated degradation pathway, thus preventing their survival-promoting action.

The Wnt signaling pathway has been related to cancer and neurodegeneration [88–91]. Several components of the Wnt pathway have been implicated in carcinogenesis. Perturbations of the Wnt signaling pathway are best known to be involved in colorectal cancer [92,93] and are associated with several other cancers including lung, prostate, breast [92–96]. Recent evidence also shows that an upregulation of the Wnt signalling pathway is a key step in skin cancers, both for melanomas and for basal and squamous cell carcinomas [97–102].

A role of the Wnt signaling pathway has also been implicated in AD [91,103–108]. The initial work of Inestrosa and collaborators found a relationship between Aβ-induced neurotoxicity and a loss of the wnt signaling pathway activity, with decreased cytoplasmic levels of β-catenin. They demonstrated that inhibition by lithium of GSK-3β, a central modulator of the Wnt pathway, protected rat hippocampal neurons from Abeta-induced damage [109]. Also, pre-treatment of neurons with wnt-3a conditioned media preserved neurons from the neurotoxic effect of Aβ [110]. In primary cultures of cortical and hippocampal neurons Aβ neurotoxicity increases the activation of GSK-3β, the hyperphospholylation of tau proteins, and loss of microtubule network [111,112]. Wnt ligands are able to prevent the Aβ-induced decrease in the number of neurites on hippocampal primary cultures [113]. Therefore, defects in wnt signaling have been proposed in the pathogenesis of AD [90,114,115]. The role of β-catenin as a survival element in AD is reinforced by results showing that phosphorylation of tau stabilizes beta catenin, antagonizing apoptosis, and the knock down of β-catenin produces an increase in the number of apoptotic cells [116].

In accordance with a role of Wnt signaling in AD, a recent study among bipolar patients Nunes et al [117] reported a lower incidence of AD in those patients who had been taking lithium than in those without lithium therapy, suggesting that the inhibition of GSK3 might also have effects in clinical grounds. In a recent report they show a dose dependent reduction of GSK3β expression in hippocampal cells in culture and in the brain and leucocytes of rats treated with lithium [118]. β-catenin levels are markedly reduced in AD patients carrying presenilin-1 (PS-1) inherited mutations [119]. Furthermore, recent studies have shown that Apolipoprotein E4, known to be a risk factor for AD, inhibits the Wnt signaling pathway in PC12 cells [120], and an association between a highly conserved LRP6 polymorphism and the risk of developing late-onset Alzheimer's disease in ApoE 4 allele carriers was found in a case-control and a large family-based study of AD patients [121]. LRP5/6 is a component of the receptor complex on Wnt, and interestingly, functional analyses revealed that the associated polymorphism of LRP6 has decreased β-catenin signaling in HEK293T cells [121].

In all, these results suggest that a deregulation of the Wnt signaling pathway could possibly explain our inverse association between cancer and AD. A subtle deregulation favoring Wnt activation could explain a greater tendency to develop tumors, and at the same time protect against degeneration, favoring neuronal survival. On the other hand, a small change towards suppression of Wnt signaling could explain a greater susceptibility to neuronal death or loss of dendritic spines, while at the same time protect against the development of cancer (Fig 2). Polymorphisms or perturbations of the epigenome [20] in key molecules in the pathway that might favor or unfavor the activity of the pathway could determine the chances of developing a cancer, thus avoiding neurodegeneration, or development of AD, and avoiding hyperproliferation.

Since the inverse association between cancer and AD that was found in our study was present in cancers of different organs, a speculative biological mechanism should be applicable to all cells in the organism. That is, the alteration in the survival mechanisms that theoretically could protect from AD should be present in neurons as well as in other cells in the body, that would be then be more predisposed to develop cancer. And vice versa, defects in survival mechanisms that would favor AD development would protect against cancer development in all the cells in the organism. In favor of a systemic deregulation of cell survival mechanisms, it has been reported that lymphocytes from AD patients are more susceptible to cell death caused by apoptosis-inducing factors, compared to a similarly-aged control group [122]. Also, lymphocytes and fibroblasts from AD patients show increased levels of p53 compared to healthy controls of comparable age [123]. Furthermore, fibroblasts derived from the p53-mutated mice with enhanced p53 activity were more resistant to transformation by activated ras plus myc oncogene [26].

A hypothetical common biological mechanism explaining an inverse association between the development of cancer and AD could be extended to other neurodegenerative diseases characterized by increased cell death. A "prone to die" status of cells could favor all those diseases characterized by progressive neurodegeneration, such as Parkinson's disease (PD), frontotemporal dementia and other tauopathies. In support of this, two longitudinal studies and a case control study suggest that overall cancer mortality risk and tumor frequency are reduced in individuals with PD, for both smoking-related and non-smoking related cancers [124–126]. Interestingly, several of the genes that are now known to be associated with PD were studied in cancer research before their involvement in PD was recognized [127,128]. In frontotemporal lobar degeneration loss-of-function mutations have been recently identified in progranulin in chromosome 17 [129/132]. Progranulin is a multifunctional protein expressed in peripheral tissues and in the central nervous system, both in neurons and glia, involved in wound healing and inflammation. Interestingly, it contributes to tumorigenesis in diverse cancers when overexpressed, including breast cancer, clear cell renal carcinoma, invasive ovarian carcinoma and glioblastoma, [133]. Not just neuronal cells would be in the prone-to-die state, but also cells in other tissues could be more susceptible to degeneration. Following this idea, it is conceivable to speculate that other degenerative systemic disorders, such as osteoarthritis or osteoporosis, could also be associated with a reduced risk of cancer, and vice versa, patients with a history of cancer could have a reduced risk of systemic degenerative disorders.

Concluding remarks

The finding of an inverse association between cancer and AD opens up several avenues of investigation that may lead to clues about the nature of both AD and cancer. A putative common biological mechanism that inversely operates in the two disorders, one leading to increased cell growth or survival, and the other to a higher risk of cell death, could explain these results. Understanding the basis of the association between cancer and AD is made more imperative considering that treatments currently under investigation to prevent and treat Alzheimer's disease might lead to a greater risk of cancer development, and inversely, treatments to prevent cancer could predispose to the development of AD. Although much work remains to be done to determine whether cancer and AD are in fact linked via a common biological mechanism, the eventual identification of such a mechanism may provide insight into therapeutic strategies that could aid in preventing both disorders.

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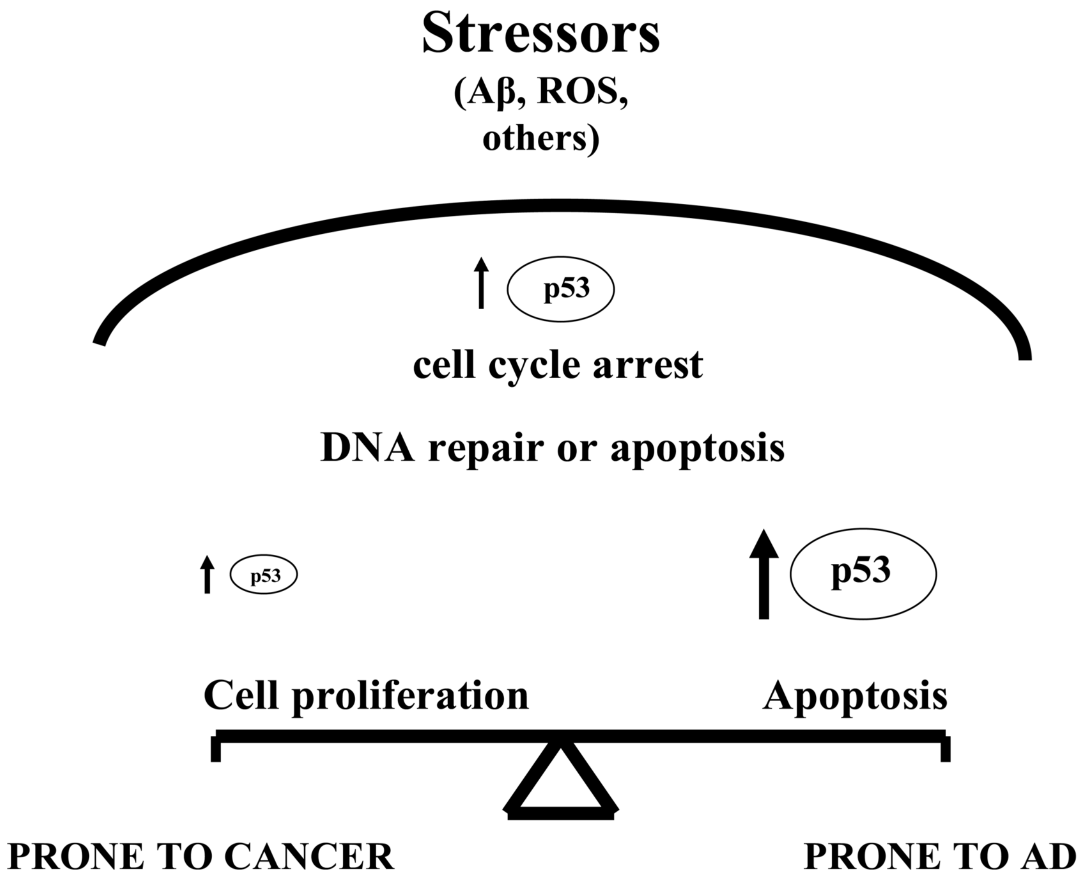

Figure 1.
Role of p53 in cancer and AD. In response to toxic or stress signals, p53 is activated through a number of post-translational modifications and induces cell cycle arrest among other functions. The decision is made whether to induce DNA repair or apoptosis of damaged cells to maintain genomic stability. If the cell machinery in the whole organism were shifted to high p53 in response to stressors, the cells would be more prone to cell death and AD could develop. If, on the contrary, the cell machinery were shifted to low or no p53, the cells would be more prone to develop a cancer. ROS, reactive oxygen species.

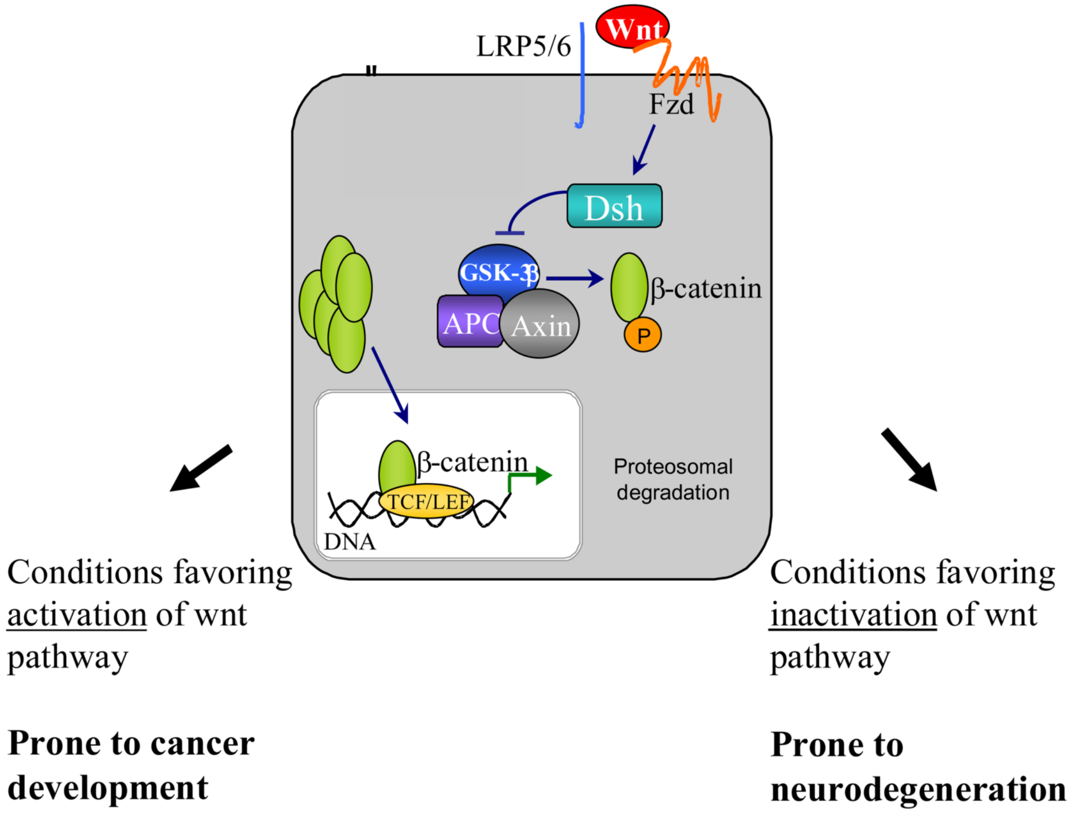

Figure 2.
The wnt signaling pathway involvement in cancer and neurodegeneration. When wnt binds to the LRP-frizzled receptor in the surface of the cell,β-catenin is stabilized promoting expression of wnt target genes and proliferation. Subtle disequilibrium in any step of the pathway in a manner that determines activation of the pathway, such as increased expression or polimorphisms that induce activation of wnt or β-catenin would favor cancer development, preventing neurodegeneration. On the contrary, conditions that induce inactivation of the pathway would favor the development of Alzheimer's disease or other degenerative disorder, and as a consequence protect from cancer development.