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# RESEARCH PROGRESS ON KEY MECHANISMS AND TARGETS FOR THE NEGATIVE CORRELATION BETWEEN ALZHEIMER'S DISEASE AND CANCER

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**Abstract:** Alzheimer's disease (AD) and cancer are both age-related diseases whose incidence and prevalence increase exponentially as the population ages, and which are the leading causes of disability and death, respectively, as well as the most significant threat to human health. It has been observed in more than 10 epidemiological studies that patients with a past history of cancer have a lower risk of developing AD, and that patients with AD have a lower risk of developing cancer in the future. The risk of developing cancer in the future is even lower in patients with AD. AD is mainly caused by irreversible degeneration and death of neurons, whereas cancer is characterised by excessive cell proliferation. The two diseases may share common gene and protein signalling pathways, but they are regulated in different and sometimes opposite directions. In this paper, we provide a review of the possible key mechanisms and targets of AD negatively associated with cancer.
**Keywords:** Alzheimer's disease; Cancer; P53; Pinl: Wnt signalling pathway; MiRNA

## 1 INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease with progressive cognitive decline, which is mainly manifested by the gradual loss of memory, judgement, and social skills [1]. β-amyloidpeptide deposition and hyperphosphorylation of Tau proteins are the main pathological features [2]. AD tends to occur after the age of 65 years, and increasing age also increases the risk of developing the disease. Cancer is also age-related and is currently one of the leading causes of death in humans before the age of 70 [3-4]. Cancer represents a series of events characterized by irrepressible mutation, proliferation, differentiation, invasion, and metastasis of cells, accompanied by an increase in energy expenditure, whereas AD pathology, on the contrary, is characterized by the presence of cellular proliferation, regression of differentiation, degenerative cellular deletion, and a decrease in the energy metabolism of parts of the organism and of different brain regions. Despite the emergence of new treatments every year, AD and cancer are still the leading causes of disability and death, respectively, and the most significant threat to human health [5]. With the advent of the aging era, AD and cancer may become the diseases with the greatest healthcare burden for families and society. The reason for this is that the unclear mechanism of AD and cancer is the main reason. Recently, more than 10 epidemiological studies have shown that AD is negatively associated with the incidence of cancers, including colorectal, prostate, and lung cancers [6-15]. This suggests that there may be common mechanisms and targets for the negative correlation between AD and cancer. Clarifying the key mechanisms and targets will help to elucidate the mechanisms and therapeutic drugs.

It is well known that AD is mainly caused by neuronal degeneration and death, whereas cancer is characterized by excessive cell proliferation, which implies that there may be a mechanism to regulate cell survival in an inverse way: favoring survival (cancer) or favoring death (AD) [16-17]. Researchers have shown that these two diseases may share common gene and protein signaling pathways, but they are regulated in different and sometimes opposite directions [18-19]. There have been successive studies reporting the possible common genetic mechanisms negatively correlated between AD and cancers, and this paper provides a review of the possible key mechanisms and targets for the negative correlation between AD and cancers.

## 2 THE ROLE OF P53 IN THE NEGATIVE ASSOCIATION BETWEEN AD AND CANCER

P53 is a classical oncogene, and P53 mutations are prevalent in all cancer types [20]. It has been reported that the tumor suppressor gene P53 with transcriptional roles is significantly down-regulated in cancer and up-regulated in AD [5, 21]. It acts as a transcription factor, regulating many genes that are involved in important cellular pathways such as cell cycle control, DNA repair, cellular metabolism, senescence, apoptosis, or stress response [20]. In tumors, P53 can promote various pathways and metabolic changes in cell cycle arrest, DNA damage repair, and cell death. Numerous studies have demonstrated that a substantial increase in P53 levels and activity appears to be a common feature of all Alzheimer's diseases, including AD [22]. P53 has now been shown to induce neuronal and glial cell apoptosis, which in turn exacerbates the pathological process of AD [22]. Therefore, P53 may be a key protein for the negative correlation between AD and tumors, which protects against possible neuronal and glial cell apoptosis in P53 and mitigates the risk

of AD, and upregulates the p53 protein in large amounts after the onset of AD, which then exerts its inhibitory effect in tumors and reduces the risk of tumor development.

## 3 ROLE OF PIN1 IN THE NEGATIVE CORRELATION BETWEEN AD AND CANCER

Pin1 is a unique enzyme mainly involved in protein folding and cell cycle regulation [23]. It distorts proteins themselves into different conformations by acting on specific phosphorylation sites (serine/threonine residues before proline) [19].Pin1 has the ability to catalyze cis-trans isomeric conversion of proline, which results in a change in shape that affects protein activity, localization, and interactions, leading to a range of functional changes [19, 24].Pin1 is overexpressed in many human cancers, including colorectal, prostate, breast, mammary, and acute myeloid leukemia, where increased expression of PIN1 is observed, and its up-regulation is usually associated with poor prognosis, and it serves as a key catalyst for a variety of oncogenic pathways [23, 25, 26]. Inhibition or deletion of Pin1 leads to cell cycle abnormalities and mitotic catastrophes [24]. Pin1 promotes CyclinD1 transcription through various signaling pathways, including β-catenin and c-JUN, and promotes its nuclear localization upon stimulation of the growth factor pathway, resulting in a positive feedback loop that promotes tumor proliferation [27-29]. Pin1 promotes tumor proliferation through the up-regulation of oncogenes and proliferation-promoting factors or the down-regulation of tumor suppressors and proliferation inhibitors to promote tumorigenesis, progression, and resistance to cell death and to enable replicative immortalization [30].

Khoei et al. transfected PIN1siRNA into human colon adenocarcinoma cells (SW-48 cells), which inhibited cancer cell proliferation, migration, and increased apoptosis and autophagy [26]. Zhu and Fan et al. demonstrated that Pin1 promotes the proliferation and migration of prostate cancer cells through activation of the Wnt/β-catenin signaling pathway, and Pin1 knockdown can effectively inhibit prostate cancer cell proliferation and migration via β catenin effectively inhibits the growth of prostate cancer cells [31, 32]. Furthermore, in addition to its effects on the tumor itself, PIN1 can also act as an amplifier of oncogenic signals, inducing migratory and invasive phenotypes in breast cancer cells, as well as mediating drug resistance in breast cancer cells [29]. Therefore, Pinl inhibitors have strong anticancer effects, which has led to the use of several PIN1 inhibitors, such as huperzine, in tumor therapy. Among them, Wei and Kozono et al. found that both arsenic trioxide and all-trans retinoic acid, the classical drugs for acute promyelocytic leukemia (APL), could promote the down-regulation of several of their oncogenic substrates by inhibiting PIN1, which provided an additional mechanistic explanation for the efficacy of arsenic trioxide and all-trans retinoic acid in APL [29, 33, 34].

Moreover, Pin1 plays a key role in AD. On the one hand, it can affect the conformational changes of Tau proteins by acting on different phosphorylation sites of tau proteins to maintain normal Tau protein function; on the other hand, it can also avoid AD by affecting APP production. Pin1-catalyzed proline isomerization is involved in regulating APP processing and antibody production. Cellular experiments have demonstrated that overexpression of Pin1 decreases Aβ secretion and knockdown of Pin1 increases it [35]. Increased oxidative damage is an early event in AD [36]. And oxidative stress induces loss of Pin1 activity, resulting in loss of synaptic plasticity aggravating AD memory damage. Targeting upregulation and/or activation of Pin1 may be a key target for AD therapy.

In conclusion, Pin1 may play an important role in the negative correlation between AD and cancer, and targeted drugs against Pin1 are promising, but it should be noted that Pin1 inhibitors used in cancer therapy have the potential to exacerbate the risk of AD, and choosing drugs that avoid penetrating the blood-brain barrier may provide more benefit to patients. Precise targeting of Pin1 in neuronal cells, glial cells, associated with AD pathology may reduce the risk of cancer in AD patients.

## 4 THE ROLE OF WNT SIGNALLING PATHWAY IN THE NEGATIVE ASSOCIATION BETWEEN AD AND CANCER

Wnt Ligands (Wnts) are a large family of secreted glycoproteins that were initially identified in Drosophila and mouse breast cancer, and have now been found to be widely expressed in human tissues [37-39].Wnts arise in the endoplasmic reticulum and consist of 350-400 amino acid residues, with a size of approximately 40 kDa.The amino-terminal signalling sequences are predominantly hydrophobic of varying lengths of amino acids, which are used for secretion and can undergo cleavage for maturation [37, 40].Wnts are also enriched in cysteine residues, which are hypothesised to form intramolecular S-S bonds and maintain secondary structure [37, 40, 41].Wnts transmit signals from the extracellular environment to the intracellular via cell surface receptors, which play an important role in embryonic development and homeostatic processes in adult tissues, regulating cell proliferation, differentiation, polarity, adhesion, motility, death and stem cell self-renewal [38, 41, 42]. Nineteen Wnt family members have been identified in humans, including Wnt1, Wnt2, Wnt2b, Wnt3, Wnt3a, Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a, Wnt7b, Wnt8a, Wnt8b, Wnt9a, Wnt9b, Wnt10a, Wnt10b, Wnt11, and Wnt16 [37]. There are two hypotheses as to how the Wnt signaling pathway is activated: one suggests that the amino terminus can determine which Wnt signals will be activated [43], while the other hypothesis suggests that the activation of Wnt signals might be conferred by a specific cellular context, such as some non-classical ligands, Wnt5a and Wnt11, which can activate the classical Wnt/β-catenin signaling pathway [37].

As extracellular ligands, Wnts receptors include the Frizzled family of G-protein-coupled receptors (FZD), low-density lipoprotein receptor-associated proteins (LRP), and orphan tyrosine kinase-like receptors 1 and 2 (ROR1/2), as well as the related receptor tyrosine kinase (Ryk) [41]. Binding of Wnt to its receptors leads to intracellular signaling protein

(Dvl) phosphorylation and activation [44]. Downstream of Dvl, three different Wnt pathways exist: (1) the Wnt/β-catenin pathway, also known as the classical Wnt pathway, which is mainly regulated by Wnt1, Wnt3a, Wnt8a, and Wnt8b. In this pathway, the binding of Wnt to FZD-type receptors inhibits the activity of glycogen synthase kinase-3β (GSK3-β), which in turn inhibits the degradation of β-catenin, leading to the aggregation of β-catenin in the cytoplasm [40, 45, 46]. Then, β-catenin enters the nucleus, binds to T-cell factors/lymphoid enhancers, and activates the transcription of downstream target genes such as matrix metalloproteinase 7 (MMP7), proto-oncogene (c-myc), and cytokinin D1 [47]. Abnormal activation and up-regulation of this pathway is closely associated with the development of many tumors, such as colon, breast, lung, nephroblastoma, ovarian, and cholangiocarcinoma [37, 47-49]. In addition, the Wnt/β-catenin pathway is involved in multiple stages of adult hippocampal neurogenesis, where it regulates proliferation by altering the expression of Cyclin D1 and promotes neuronal differentiation through the expression of neuronal transcription factors such as Ngn2, NeuroD1, and Prox1 [50]. And it protects against neurotoxicity caused by Aβ and Tau proteins, thus improving cognitive function [46, 51]. (2) The second pathway is the Wnt/Ca2+ pathway, which belongs to the non-classical Wnt pathway. It is mainly activated by Wnt4, Wnt5a, Wnt11, etc. [52]. Wnt ligands can bind to FZD receptors and increase intracellular Ca2+ concentration, which activates calmodulin-dependent kinase II (CaMKII) and protein kinase C (PKC). PKC and CaMKII then activate nuclear factor of T-cell transcription (NFAT) to regulate cell adhesion, migration, and differentiation [52]. Wnt ligands also promote axonal and dendritic development and synapse formation in newborn neurons on the one hand and regulate the biological functions of tumor-associated macrophages on the other hand, through activation of Wnt/JNK and Wnt/CaMKII signaling, remodel the tumor microenvironment to promote tumor growth and metastasis [38, 53]. (3) The third pathway is the Wnt/PCP pathway, which is also a non-classical Wnt pathway, in which Wnt ligands bind to the FZD receptor to activate Dvl, which then binds to the small GTPases RhoA and Rac to activate Rho-associated kinase (ROCK), leading to cytoskeletal reorganization as well as alterations in cell polarity and migration [52].

Thus, the Wnt signaling pathway plays an important role in cell proliferation, differentiation, migration, and repair of tissue damage. Abnormal activation of the classical Wnt pathway inhibits apoptosis and promotes tumor cell proliferation; conversely, Wnt is down-regulated in patients with AD, and activation of Wnt signaling improves cognitive function and protects against neurotoxicity caused by Aβ and Tau proteins. The role of the Wnt signaling pathway in the AD and tumor negative correlation may play an important role. However, although Wnt genes are structurally similar, different Wnt genes play different roles during cell growth, and there are multiple signal transduction pathways and interactions between different pathways in the cell, which ultimately form a complex Wnt signaling network.

## 5 THE ROLE OF MIRNAS IN THE NEGATIVE ASSOCIATION BETWEEN AD AND CANCER

MicroRNA (miRNA) is a non-coding ribonucleic acid (RNA) with a total length of about 18-25nt, which plays an important role in post-transcriptional regulation of gene expression [54]. MiRNAs play their roles mainly by binding to the 3‘UTR, and a small portion of them can play their roles either by binding to the 5’UTR or by facilitating the transcription, translation, or enhancing mRNA stability [54-56]. Numerous studies have shown that several miRNAs are differentially expressed in AD and cancer, suggesting that miRNAs are associated with the pathogenesis of AD and cancer and that they may play an important role in the mechanism of negative correlation between AD and cancer [57]. miR-34 is up-regulated in different brain regions and blood individual nuclei in AD patients [58]. miR-34a and miR-34c both target the 3'-UTR region of Tau, which in turn inhibits Tau protein expression, which may contribute to ameliorating AD pathology and act as a barrier to AD pathogenesis and disease progression [59, 60]. In cancer, the classical oncogene P53 has been found to inhibit cancer through activation of miR-34a expression, which in turn can directly target P53 to inhibit P53 expression and thereby promote cancer development and growth [61]. In addition, miR-34a and miR-34c have been shown to increase drug resistance in cancer [59, 62]. Thus, miR-34 may be a key target for the negative association between AD and cancer.

Plasma and serum samples of AD patients have decreased levels of miR-125b, whereas in the CNS miR-125b expression is mostly upregulated [58]. HuiTang et al. demonstrated that miR-125b and its target GluN2A are involved in melatonin receptor 2 (MT2) activation, which reduces AD-like dendritic damage (including complexity and dendritic spine loss), which could be a novel therapeutic target for early memory impairment in AD [63]. miR-125b has also been found to be involved in several signaling pathways involved in cancer development and progression, such as the Wnt, PI3K/Akt, STAT-3, MAPK, NF-κB, and P53 pathways [64]. miR-125b expression is enhanced in pancreatic cancer cells and tissues and is mediated via the TXNIP and hif1α pathways to promote metastasis and progression of pancreatic cancer [65]. miR-125b is overexpressed in cervical cancer, which is significantly correlated with progression-free survival, overall survival, and prognosis of cervical cancer. miR-125b is capable of exerting an oncogenic effect by targeting the 3′UTR of the tumor suppressor High Mobility Group Protein a (HMGA1) in the PI3K/Akt signaling pathway [66]. However, it cannot be ignored that miR-125b can also play a tumor-suppressive role in certain tumors. For example, in bladder cancer, miR-125b-5p can inhibit bladder cancer cell viability and migration and induce apoptosis by targeting HK2 regulation through inhibiting the PI3K/AKT pathway [67]. Therefore, as a miRNA that can broadly regulate cancer-related signaling pathways, miR-125b-5p may only be involved in the negative correlation between certain cancers and AD.

## 6 CONCLUSION

In summary, the negative correlation between AD and cancer is not a simple biological phenomenon, which involves the action of multiple key targets such as p53, pin1, Wnt signaling pathway, miRNAs, and so on. Further studies on the mechanism will help to elucidate the pathophysiological mechanisms of AD and cancer and to develop new therapeutic approaches based on its key targets. Currently, studies on AD and tumors are mostly limited to the level of pan-cancer studies, while studies on specific cancer types are lacking. With the advent of the era of precision medicine, there is a need to focus more on research on the negative correlation between specific cancer types and AD.

## COMPETING INTERESTS

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