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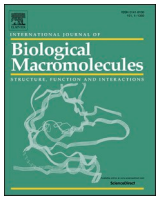

Review

Developing theragnostics for Alzheimer's disease: Insights from cancer treatment

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ABSTRACT

The prevalence of Alzheimer's disease (AD) and its associated economic and societal burdens are on the rise, but there are no curative treatments for AD. Interestingly, this neurodegenerative disease shares several biological and pathophysiological features with cancer, including cell-cycle dysregulation, angiogenesis, mitochondrial dysfunction, protein misfolding, and DNA damage. However, the genetic factors contributing to the overlap in biological processes between cancer and AD have not been actively studied. In this review, we discuss the shared biological features of cancer and AD, the molecular targets of anticancer drugs, and therapeutic approaches. First, we outline the common biological features of cancer and AD. Second, we describe several anticancer drugs, their molecular targets, and their effects on AD pathology. Finally, we discuss how protein–protein interactions (PPIs), receptor inhibition, immunotherapy, and gene therapy can be exploited for the cure and management of both cancer and AD. Collectively, this review provides insights for the development of AD theragnostics based on cancer drugs and molecular targets.

1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative ailment, yet current interventions are not curative and merely slow disease progression [1]. Despite declines in mortality rates for other leading causes of death (e.g., cardiovascular disease and stroke), AD mortality has increased over the past decade [2]. Therefore, transformative therapeutics are needed to cure/treat AD. Interestingly, patients with cancer are at lower risk of developing AD, suggesting that susceptibility to cancer is associated with resilience to AD pathoprogression [3,4]. Moreover, cancer patients who have undergone chemotherapy have lower AD mortality, implying therapeutic effects of anticancer therapies on AD [5].

AD and cancer are important causes of death in the elderly globally. Although the pathologies of these diseases differ markedly neuronal deterioration/death in AD and sustained cell proliferation in cancer [6,7] AD and cancer share risk factor genes and have similar underlying molecular mechanisms of pathoprogression [8,9]. For example, protein kinase-encoding genes (e.g., *PRKD3* and *TOP3A*) and cell growth/survival-related genes (e.g., *RHOH*) are shared risk factors in AD and cancer [10]. In addition, AD and cancer progression lead to oxidative stress, which hinders the destruction of cytotoxic Aβ and host defense peptides in tumor or neuronal cells [11,12]. Furthermore, there is evidence that mammalian target of rapamycin (mTOR) plays important roles in cancer and neurodegenerative diseases, including AD. Specifically, AKT/mTOR signaling is activated by c-reactive protein in inflammation-mediated neurodegenerative disease and in the development of oral squamous cell carcinoma [13,14]. Additionally, Ras/PI3K/AKT/mTOR signaling-mediated cell cycle dysregulation promotes AD and prostate cancer development [15]. Dysregulated Pin1/p53/Wnt signaling and autophagy-related Sirt/mTOR signaling are also closely associated with both AD and cancer physiopathology [16,17].

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Interestingly, upregulation of mTOR levels/activity in the brain in patients with AD is associated with various AD pathologies, including Aβ/tau accumulation, suppression of autophagy induction, defects in long-term potentiation, neuronal degeneration, and memory impairment [18].

Although previous epidemiological studies have investigated the inverse association between AD and cancer and identified several risk factors that affect both AD and cancer, the etiological associations of the shared risk genes for AD and cancer have not been systematically addressed. Resolving these etiopathological associations and the underlying mechanisms will provide feasible strategies for the development of AD theragnostics. Therefore, in this review, we first discuss the common pathogenic pathways of cancer and AD, including cell-cycle regulation, angiogenesis-associated genes, cell type-specific mitochondrial dysfunction, and protein misfolding and aggregation. Second, we discuss potential molecular targets for AD and cancer therapeutics and the possibility of repurposing clinical anticancer drugs as AD therapeutics. Finally, we highlight potential therapeutic approaches, including immunotherapy and gene therapy, for AD and cancer.

2. Biological features of cancer and Alzheimer's disease

Unraveling the shared pathological mechanisms of cancer and AD will lead to feasible strategies for diagnosing, managing, and treating these diseases. The close association between cancer and AD pathogenesis is related to six biological functions: angiogenesis, mitochondrial function, proteostasis, proteases and cell–cell junctions, transcription, and cell-cycle regulation.

2.1. Angiogenesis

Angiogenesis is the formation of new blood vessels from existing vessels and is vital for delivering oxygen and nutrients to tissues [19,20]. Under normal conditions, angiogenesis is regulated by maintaining a balance between angiogenic stimulators (i.e., VEGF/VEGFR1, angiopoietin 1, TGF-α, and PDGF) and antiangiogenic mediators (i.e., PEDF, prolactin, IFN-α, and IL-12) [21]. Imbalanced angiogenesis is crucial for cancer development, invasion, and metastasis [22]. Interestingly, genes associated with angiogenesis in cancer are also implicated in neurodegenerative diseases, including AD [23] Specifically, angiopoietin 1, an angiogenic factor, exacerbates Aβ pathology and memory impairments in APP/PS1 mice, a model of AD [24]. Conversely, angiogenic PDGF-BB, which maintains blood–brain barrier (BBB) integrity, is downregulated in the brains of patients with AD and mouse models of AD [25]. AD-related proteins such as amyloid precursor protein (APP) and members of the disintegrin and metalloprotease (ADAM) family are also associated with angiogenesis due to their interactions with the angiogenic factor EGFR and its ligand EGF [26,27]. These observations indicate that homeostasis of angiogenesis is a therapeutic target for cancer and AD. In this section, we discuss the functions of angiogenesis-associated genes in cancer and AD.

2.1.1. Amyloid precursor protein (APP)

APP is highly expressed in neurons and is involved in neuronal development, signaling, and intracellular transport under normal conditions [28,29]. However, amyloidogenic proteolytic processing of APP by β- and γ-secretases leads to the release of amyloid-β (Aβ), which, upon misfolding, contributes to the formation of neurotoxic amyloid plaques, a major hallmark of AD [30]. In TgCRND8 mice, a model of AD, β-secretase (BACE1)-mediated APP processing exacerbates angiogenesis through NOTCH3 signaling [31].

Because APP interacts with angiogenic factors (i.e., EGF and TGF-α), it also promotes cancer development. For example, APP triggers cancer cell growth and proliferation in prostate and lung cancer [32,33]. In addition, APP plays a critical role in cancer pathoprogression. For example, APP levels are elevated in breast cancer cell lines, and knockdown of APP slows breast cancer progression by inducing $p27^{kip1}$ and caspase-3-mediated apoptosis in vitro and in vivo [34]. In addition, APP triggers cancer cell growth and proliferation in prostate and lung cancer [32,33]. This evidence suggests that APP is a promising target and biomarker for both cancer and AD.

2.1.2. A disintegrin and metalloprotease (ADAM) family

ADAM proteins are transmembrane cell-surface proteins that are involved in cell fusion and spermatogenesis [35]. ADAM10 reduces tau pathology and promotes the maintenance of synaptic function, suggesting that enhancing ADAM10 activity could have beneficial effects on AD. Interestingly, synaptic levels of ADAM10 are significantly lower in AD patients than in age-matched healthy controls [36,37]. By contrast, ADAM family members have pro-tumorigenic effects by interacting with angiogenic factors (e.g., EGFR). ADAM10 and ADAM17 promote cancer cell invasion via MMP signaling [38], and ADAM17 promotes tumor cell proliferation in head and neck squamous cell carcinomas by upregulating EGFR-GPCR-mediated ERK/AKT signaling [39]. In addition, inhibition of ADAM10/ADAM17 has anticancer effects on breast and pediatric cancer [40,41]. These observations suggest that ADAM blockade is a therapeutic strategy for cancer. Thus, the ADAM family comprises angiogenesis-associated genes that affect both cancer and AD.

2.1.3. Epidermal growth factor receptor (EGFR)

EGFR belongs to a family of receptor tyrosine kinases (RTKs) that regulate cell proliferation and differentiation via Ras-MAPK and PI3K-AKT-mTOR signaling [42]. However, mutational activation transforms EGFR into an angiogenic factor that mediates tumor cell proliferation and further metastasis either directly or by upregulating vascular endothelial growth factor (VEGF) [43]. Tumor-promoting mutations in EGFR occur in different types of cancers. For example, overexpression of EGFR and truncation of EGFR mediated by large deletions (e.g., EGFRvIII, EGFR-KDD, and EGFR-SEPT14) are frequently observed in brain cancer, whereas point mutations and small deletions are common in lung cancer [44]. Therefore, targeting EGFR has emerged as a promising strategy for cancer therapy, although overcoming EGFR inhibitor resistance remains a formidable challenge in drug development. Fourth-generation EGFR inhibitors have been developed to overcome drug resistance, and 14 EGFR tyrosine kinase inhibitors have received FDA approval for cancer therapy [45].

EGFR is also involved in the pathophysiology of AD via interactions with Aβ, a predominant hallmark of AD. EGFR co-localizes with Aβ plaques in the brain in AD patients, and EGFR activation is mediated by Aβ oligomers [46,47]. In addition, EGFR inhibitors rescue Aβ-induced memory deficits in a mouse model of AD and reduce neuroinflammation in astrocytic cultures [47,48]. Furthermore, we demonstrated that inhibiting EGFR ameliorates tau pathology and tau-mediated neuroinflammation in PS19 mice, a tau-overexpressing model of AD [49]. Taken together, these findings suggest that EGFR is a strategic target for modulating the pathoprogression of both cancer and AD.

2.1.4. Vascular endothelial growth factor (VEGF)

VEGF is a potent angiogenic factor that promotes tumor cell growth the metastasis microenvironment via activation of PI3K/MAPK/Src/PLCγ signaling [50]. The expression of VEGF and its receptors, Fms-like tyrosine kinase 1 and fetal liver kinase 1, is increased in colorectal carcinoma (CRC) [51]. Therefore, anti-angiogenic therapies that inhibit VEGF/VEGFR have therapeutic efficacy against cancer. For example, genetic ablation of VEGF suppresses carcinogenesis in the colorectal cancer cell line HCT116 and in a mouse model of pancreatic cancer [51,52].

VEGF is also involved in AD pathophysiology via differential interactions with VEGFR1 and VEGFR2. Under AD pathological conditions, pro-angiogenic VEGFR2 expression increases, whereas anti-angiogenic VEGFR1 expression decreases. As a result, "VEGF is more likely to bind VEGFR2 than VEGFR1" [53]. In addition, VEGF

colocalizes with Aβ plaques, and VEGF levels in the brain are elevated in AD patients with cognitive deficits and AD mouse models [54,55]. Furthermore, we demonstrated that the VEGF inhibitor vatalanib attenuates Aβ plaque deposition and tau hyperphosphorylation in a mouse model of AD [56]. These observations suggest that the angiogenic factor VEGF is a promising therapeutic target for cancer and AD.

2.1.5. Semaphorin (SEMA)

Unlike the angiogenic factors described previously, SEMA, an axonal guidance molecule, plays diverse roles in regulating axonal growth and angiogenesis. Depending on the subclass or status of vascular development, SEMA can exhibit angiogenic (SEMA4D, SEMA6D, SEMA7A), antiangiogenic (SEMA3A, SEMA3B, SEMA3D, SEMA3E), or dual (SEMA3C, SEMA4A) properties [57]. Among the eight subclasses of SEMA proteins, SEMA4 and SEMA7 are associated with cancer progression, and SEMA3 and SEMA4 are involved in AD pathology. Specifically, the transcription and translation of SEMA4C are upregulated in lymphatic and endothelial cells derived from breast cancer tissues [58]. In lung cancer, upregulation of SEMA7 expression via mTOR signaling is involved in EGFR-tyrosine kinase inhibitor (TKI) resistance [59]. In AD patients, SEMA3A/SEMA4D levels are elevated in the brain [60,61]. SEMA3 colocalizes with neurofibrillary tangles (NFT) in the hippocampus, and SEMA3 upregulation is associated with neuronal degeneration [60]. Importantly, inhibition of SEMA4D restores cognitive function and alleviates neuroinflammation in an AD mouse model [61]. Thus, regulating SEMA expression may attenuate the pathologies of cancer and AD.

2.1.6. Neuropilins (NRPs)

NRPs promote vasculogenesis and neurite outgrowth by binding to the angiogenic factors SEMA and VEGF [62,63]. NRP1-positive lung cancer cells exhibit a tumor-initiating cell phenotype, indicating that NRP1 is a potential biomarker of lung cancer [64]. In melanoma cells, NRP1 cooperates with VEGFR-2 to promote cell migration and ECM invasion [65]. Furthermore, upregulation of NRP1 and VEGFA is correlated with cognitive function impairment in APOEε4 carriers [66]. More research is needed to determine whether NRPs can be used as biomarkers for AD detection or therapeutic targets for AD treatment.

2.2. Mitochondrial dysfunction

Mitochondria are double-membrane–bound organelles in eukaryotic cells that produce cellular energy in the form of adenosine triphosphate (ATP) [67]. Mitochondria also store calcium to activate downstream signaling pathways and regulates cell growth and death [68,69]. Therefore, mitochondrial dysfunction is a pivotal factor contributing to the aging process and is closely associated with the development of diseases related to excessive cell proliferation, such as cancer, and neurodegenerative diseases, including AD.

2.2.1. Mitochondrial dysfunction in cancer

Various types of mitochondrial defects are associated with cancer development/invasion. First, mitochondrial respiratory dysfunction in cancer cells causes a phenomenon called the ‘Warburg effect’ in which reduced mitochondrial oxidative phosphorylation and increased anaerobic glycolysis are followed by increased lactate production and subsequent tumor proliferation [70]. Second, alterations in mitochondrial DNA (mtDNA), including changes in mitochondrial copy number, point mutations, frame-shifting insertions, and large-scale deletions, cause mitochondrial dysfunction, which contributes to tumorigenesis [71]. Third, mutation hotspots in mitochondria have been identified in several types of cancers. For example, the 12418insA mutation, in which an additional adenosine nucleotide is inserted in the mtDNA polyadenosine sequence at nucleotide positions 12,418–12,425, is found in breast, gastric, and hepatocellular cancers [72–75]. This frameshift mutation results in premature termination of the *ND5* gene and a truncated polypeptide [76]. Mutations in the MT-ND4, MT-ND5, D-loop, and CO1 genes are associated with the development of gastric and breast cancers [77,78]. These associations emphasize the importance of mitochondrial mutations in tumor development, although the specific mechanisms are unknown. Fourth, increased mitochondrial fission and decreased mitochondrial fusion are commonly observed in many tumors. Drp1 dysregulation is thought to cause excessive fission [79], and inhibiting or knocking down Drp1 restores mitochondrial network formation in lung cancer, significantly reduces cancer cell proliferation, and increases spontaneous apoptosis [80]. Kashatus et al. [79] found that ERK2-mediated phosphorylation of Drp1 at serine 616 increases mitochondrial fission. Ultimately, mitochondrial mutations provoke reactive oxygen species (ROS) production and oxidative stress, resulting in a critical cycle for tumorigenesis.

In addition, various pathogenic bacterial proteins target the mitochondria and nuclei of host cells, disrupting normal cell growth and leading to diverse types of cancers, including lung cancer, prostate cancer, and colon cancer. Specifically, the DNA binding proteins, nuclease, and methyltransferase of *Mycoplasma hominis* dysregulate the DNA repair system in host cell mitochondria, thereby promoting prostate carcinogenesis [81]. Consistent with this observation, the *Mycoplasma hominis* infection rate is significantly higher in patients with prostate cancer than in healthy controls and patients with benign prostatic hyperplasia [82]. The glyceraldehyde-3-phosphate dehydrogenase and endonuclease of *Chlamydia pneumoniae* target host mitochondria and dysregulate glycolysis and DNA repair, thereby contributing to the development of lung cancer [83]. Furthermore, DNA binding/repair/damage proteins from *Salmonella typhimurium* promote colon cancer cell growth by targeting host cell nuclei [84]. Collectively, these observations imply that mitochondrial dysfunction caused by pathogenic bacterial proteins plays a critical role in carcinogenesis. Further characterizing the role of mitochondrial dysfunction in cancer might provide reliable therapeutic strategies for managing/treating cancer.

2.2.2. Mitochondrial dysfunction in AD

The hallmarks of AD, including Aβ, tau, neuroinflammation, and cognitive impairment, are associated with the induction of mitochondrial dysfunction, which exacerbates AD pathologies. First, Aβ-induced neuronal toxicity causes mitochondrial metabolic dysfunction [85]. Aβ (25–35) blocks the entry of nuclear-encoded proteins into the mitochondria, decreases mitochondrial membrane potential, and increases ROS production in PC12 cells [86]. In APP/PS1 mice, Aβ plaque accumulation induces changes in mitochondrial fusion and fission [87].

Second, tauopathy affects mitochondrial function, including mitochondrial transport, mitochondrial dynamics (morphology), bioenergetics, mitochondrial permeability transition pore formation, mitophagy, and neurosteroidogenesis [88,89]. Hyperphosphorylation of tau at residues S199, S202, and T205 suppresses mitochondrial transport by increasing the inter-microtubule distance [90]. In addition, tau-overexpressing SY5Y cells exhibit changes in mitochondrial morphology and reduced rates of mitochondrial fusion and fission [91].

Third, Drp1, which plays a role in mitochondrial fission, activates the NLRP3 inflammasome. NLRP3 activation promotes the inflammatory cascade, exacerbating Aβ deposition and tau-induced neurodegeneration. The induction of this proinflammatory pathway is an early event in AD [92]. Conversely, mitochondrial dysfunction in AD drives cognitive impairment by reducing mitochondrial membrane potential and ATP levels [93]. Collectively, the relationships between mitochondrial dysfunction and AD pathologies suggest that mitochondrial dysfunction is a leading factor in AD development and a promising target for novel therapeutic interventions.

2.2.2.1. Neuronal mitochondrial dysfunction in AD. Differentiating the effects of mitochondrial dysfunction according to brain cell types

(neurons, microglia, and astrocytes) can provide further insights into the pathological features of AD. Neuronal cells need a large number of mitochondria to supply the high synaptic energy required to release neurotransmitters and respond to signals in the postsynaptic region [94]. Compared with non-synaptic mitochondria, synaptic mitochondria are overloaded with Ca^{2+} [95]. Furthermore, in Tg mAPP mice, a model of AD, Aβ levels are higher in synaptic mitochondria than in non-synaptic mitochondria, exacerbating oxidative stress and impairing mitochondrial respiration at synapses [96]. Synaptic mitochondrial impairment can also be inferred from the negative effect of tau pathology on mitochondrial complex I and the effect of Aβ at synaptic terminals [91,97]. Among the genes involved in mitochondrial fusion and fission, the expression of Drp1, OPA1, Mfn1, and Mfn2 in the brain is reduced in AD patients, whereas Fis1 expression is increased [98,99]. In addition, presynaptic mitochondria in the brains of AD patients exhibit abnormal morphology and structure, including decreases in the number and length of mitochondria compared with those in healthy controls. By contrast, postsynaptic mitochondria do not differ between AD patients and healthy controls [100]. A recent study demonstrated that petunidin may protect HT22 neuronal cells from $A\beta_{42}$-induced reductions in mitochondrial membrane potential and ATP levels, potentially reversing $A\beta_{42}$-induced mitochondrial dysfunction [101]. Thus, neuronal mitochondrial dysfunction appears to be critical for AD pathology.

2.2.2.2. Microglial mitochondrial dysfunction in AD. Microglia function as immune cells in the central nervous system (CNS), and mitochondrial oxidative stress in microglia has also been linked to AD progression. Specifically, Aβ-mediated mitochondrial metabolic reprogramming induces microgliosis and the subsequent release of proinflammatory cytokines (e.g., IL-1β, TNF-α, and IFN) and neurotoxic molecules, resulting in excessive neuroinflammation and neuronal deterioration/death [102]. Mitochondrial damage and Drp1–Fis1-mediated mitochondrial fission cause microglial activation in 5xFAD mice, a model of AD [103]. This mitochondrial-mediated microglial activation is ameliorated by increased SIRT1 expression or treatment with P110 (a selective inhibitor of mitochondrial fission) [103,104]. In addition, microglial mitochondrial dysfunction induces neuroinflammation, leading to neuronal loss and neural circuit disorder and ultimately resulting in AD development [105]. The level of microglial mitochondrial dysfunction varies among pathological conditions and depends on the specific changes in microglial mtDNA. For example, Scheffler et al. demonstrated that microglial mtDNA polymorphisms directly impact microglial activation and phagocytosis of cerebral Aβ in congenic mtDNA mice [106]. Therefore, targeting microglial mitochondria may provide therapeutic interventions for AD.

2.2.2.3. Astrocytic mitochondrial dysfunction in AD. Astrocytes play important roles in maintaining CNS homeostasis, including in BBB formation, mitochondrial transfer to neurons, and ion and neurotransmitter transport [107]. Glycolytic metabolism is elevated in astrocytes compared to neurons, and inhibition of glycolytic enzymes in astrocytes leads to Aβ accumulation [108]. In AD, astrocytes are exposed to oxidative stress, resulting in DNA damage and loss of cognitive ability [109]. Treatment of astrocytes with Aβ induces mitochondrial fragmentation and depolarization and ultimately metabolic impairment [110]. Lampinen et al. [111] recently found that the internalization of neuronal mitochondria in astrocytes is significantly increased in AD mice. In addition, astrocytes from 6-month-old AD model mice exhibit increased degradation of neuronal mitochondria [111]. Aβ accumulation within astrocytes induces changes in the mitochondrial network by altering mitochondrial number and mitochondrial motility, including mitochondrial displacement, distance, speed, and velocity, indicating a significant impact of Aβ accumulation on mitochondria in human astrocytes [112]. A recent study showed that glucagon-like peptide-1 (GLP-1) has neuroprotective effects in AD by attenuating astrocytic mitochondrial abnormalities through the cAMP/PKA pathway [113]. Further characterizing cell type-specific mitochondrial dysfunctions (i.e., neurons, microglia, and astrocytes) in AD-related pathologies will contribute to the development of AD therapeutics.

2.3. Protein misfolding and aggregation

Correct folding of translated proteins is critical for normal protein function. Protein misfolding causes conformational changes that can promote the formation of protein aggregates, which have been implicated in the development of pathological conditions [114]. The formation of neurotoxic aggregates of misfolded proteins increases with age [115]. To counteract misfolding and aggregation, cellular quality-control mechanisms and recovery mechanisms, such as the proteasome [ubiquitin–proteasome system (UPS)] or autophagy-induced degradation, tag misfolded proteins in the cytoplasm [116]. Chaperones prevent misfolding by blocking interactions between proteins [117]. However, the body produces countless protein molecules, and chaperones cannot regulate all protein misfolding events [118]. Protein aggregation can be caused by protein hyperphosphorylation, autocatalysis of prion structure conversion, or destabilization due to protein mutations. In addition, intracellular aggregation may occur if the concentrations of the components of the aggregate are imbalanced. Such imbalances include the duplication of amyloid-generating genes or mutations that cause changes in amino acid sequences. Concentration imbalances can also occur as a result of proteasome deficiency or autophagy inhibition, which can lead to neurodegenerative diseases and cancer [119].

The role of protein aggregation caused by reduced autophagy in AD has recently attracted attention [120]. Autophagy decreases with age, and this reduction contributes significantly to the correlation between aging and neurodegenerative diseases [121]. There are four types of selective autophagy: mitophagy, lipophagy, aggrephagy, and lysophagy. Dysfunctions of mitophagy and aggrephagy have been implicated in AD. Mitophagic dysfunction in AD increases ROS production and proapoptotic signaling and decreases respiratory function [122–124]. Aggrephagy targets toxic protein aggregates. Suppressing autophagy reduces aggrephagy, which prevents cargo removal and accelerates neurodegenerative diseases [124,125].

Many functional proteins are characterized by alpha-helix abundance [126], including amyloidogenic proteins, which tend to misfold into β-sheet-rich intermediates that can become toxic. In particular, β-sheet formation exposes hydrophobic amino acid residues, promoting self-assembly into water-soluble oligomers that ultimately become toxic mature fibrils [127]. The aggregation of amyloidogenic proteins follows a two-step mechanism comprising a slow step, i.e., amyloid nucleus formation, and a quick step, i.e., large aggregate formation. The most widely studied amyloidogenic proteins are Aβ plaques in AD, α-synuclein in Parkinson's disease, and islet amyloid polypeptide in type 2 diabetes mellitus [128]. Misfolding and aggregation of the microtubule protein tau results in the sequential formation of insoluble β-sheet fibrils, neurotoxic paired helical filaments (PHFs), and neurofibrillary tangles (NFTs) [129]. In AD, specific gene expression patterns that are related to protein folding and degradation have been identified [130]. Specifically, weakening of the BAG2-HSC70-STUB1-MAPT molecular network is significantly correlated with AD progression via increased NFT formation and abnormal tau aggregation [130]. These results imply that this network is a potential biomarker for the early diagnosis of AD.

P53, a tumor suppressor protein implicated in carcinogenesis, can also form amyloid-like aggregates [131,132]. P53 aggregation is observed in breast cancer, colon cancer, and AD [133]. In breast tumors, aggregation of p53 results in loss of tumor suppressor function and oncogenicity [134]. Oligomerization of p53 and inhibition of its function prevent apoptosis and promote AD by impairing the DNA damage response [133]. Both α-helices and β-sheets are abundant in p53 aggregates. The conversion of α-helices to β-sheets induces protein

aggregation and the accumulation of fibril aggregates [135,136]. Mutant proteins are prone to misfolding, and changes in protein structure can expose hidden hydrophobic or aromatic residues, enabling hydrophobic or domain–domain interactions that drive self-aggregation [137,138]. Mutations in p53, particularly missense mutations of the nine hydrophobic residues in the tetramerization domain, induce aggregation-evoked loss of anticancer activity and accelerate further aggregation [139,140]. The Y220C mutant of p53 undergoes the normal amyloid aggregation process of slow and quick steps [141]. The cell-penetrating peptide ReACp53, which suppresses mutant p53 function by inhibiting its aggregation, is being developed for cancer treatment [134].

2.4. Proteases and cell–cell junctions

2.4.1. Matrix metalloproteinases (MMPs)

MMPs are zinc-dependent endopeptidases that are involved in extracellular matrix (ECM) remodeling [142]. MMP-2, MMM-9, and MMP-14 contribute to carcinogenesis by promoting angiogenesis in a CD44-dependent manner [143,144]. In AD, elevated MMP-1 and MMP-2 levels are involved in Aβ-mediated pathophysiology [145–147]. Thus, modulating MMP activity may be a novel therapeutic strategy for cancer and AD.

2.4.2. Zonula occludens-1 (ZO-1)

The peripheral membrane protein ZO-1 is related to tight junction (TJ) formation and is responsible for BBB integrity [148,149]. Downregulation of ZO-1 results in BBB disruption and subsequent blood–brain tumor barrier formation during brain cancer progression [150]. $A\beta_{1-42}$ treatment reduces ZO-1 expression in vitro [149], indicating that reducing ZO-1-mediated BBB disruption might exacerbate Aβ pathology [151] The role of ZO-1 in BBB function suggests that ZO-1 may be a target for treating cancer and AD.

2.4.3. Claudins

Claudins are transmembrane proteins found in TJs [152]. Claudins act as tumor promoters and/or suppressors via Wnt/PI3K/AKT/mTOR, EGFR/PKC, or cAbl/Ras/ERK signaling [153,154]. Claudins have opposing roles in cancer depending on their expression pattern (up- vs downregulation), localization of the cell (subcellular vs perijunction), subtype (27 family members), and tissue [153,154]. For example, claudin-1 expression is increased in thyroid, colorectal, stomach, and ER- breast cancers and promotes metastasis, whereas claudin-1 expression is decreased in pancreatic, prostate, ER+ breast, and brain cancers and acts as a tumor suppressor [153–155]. Claudins are crucial but complex therapeutic targets for cancer.

Claudins are also expressed in brain endothelial cells. Claudin-5 regulates BBB permeability, and increased expression of claudin-5 is critical for AD pathologies [156]. Claudin-5 modulates GABAergic transmission/synaptic plasticity and improves learning and memory in APP/PS1 mice, a model of AD [157]. The expression of claudin-2, claudin-5, and claudin-11 in the brain is increased in patients with AD or vascular dementia (VaD) compared to aged controls [158]. Although the mechanisms underlying the increase in claudin family expression in the brain in AD are unknown, this preliminary evidence suggests that the claudin family of proteins contributes to cancer and AD progression.

2.4.4. Occludin

Occludin is a core component of TJs and regulates TJ stabilization and optimal BBB function [159]. Reduced occludin expression suppresses cell proliferation and apoptosis in lung cancer [160], whereas increased occludin expression promotes angiogenesis in the bladder by activating the IL-8/STAT3 pathway [161]. Occludin expression is reduced in a mouse model of AD, and reduced occludin expression increases BBB permeability in cultured brain endothelial cells [162]. Notably, occludin levels are slightly but significantly higher in brain endothelial cells (iBECs) derived from human induced pluripotent stem cells (hiPSCs) from AD patients than in iBECs derived from healthy controls [163]. Thus, modulating occludin expression may be a novel therapeutic target for cancer and AD.

2.5. Transcriptional regulation

2.5.1. Nuclear factor erythroid 2-related factor 2 (NRF2)

NRF2 is involved in cellular redox homeostasis and antioxidant pathways [164]. NRF2 inhibits carcinogenesis in the early stages of cancer [165]. NRF2 activates the proangiogenic role of the VEGF/NRF2-dependent pathway in rat gastric epithelial cells, glioma cells, and pancreatic cancer cells [166–168]. Inhibition of NRF2 suppresses angiogenesis by blocking hypoxia-induced HIF-1α/VEGF signaling to suppress angiogenesis [169]. Moreover, NRF2 is a crucial transcription factor in neurodegenerative diseases, including AD. Specifically, NRF2 downregulation in AD increases ROS generation, which is also linked to the hallmarks of AD [170]. Aβ and tau accumulation, which are the main molecular characteristics of AD, reduce NRF2 levels, suppressing the antioxidant response and further accelerating Aβ and tau accumulation [170]. NRF2 expression in the hippocampal CA1 region is lower in AD patients than in controls [171]. In APP/PS1 mice, the prevalent AD mouse model, the expression levels of NRF2 and its target genes are significantly reduced [172]. Conversely, activation of NRF2 expression alleviates tauopathy/oxidative stress and improves memory function in Tau Tg P301S mice, a model of AD, indicating that NRF2 is a potential marker of AD [173].

2.5.2. Hypoxia-inducible factor (HIF)-1α

The transcription factor HIF participates in oxygen homeostasis, glycolysis, erythropoiesis, angiogenesis, cancer cell invasion, and metastasis [174–176]. HIF-1α mediates stress-induced pancreatic tumor growth and angiogenesis by regulating VEGF, MMP-2, and MMP-9 expression [177]. HIF-1α and VEGF levels are elevated in human glioma cells, suggesting that inhibition of HIF-1a may inhibit VEGF secretion [178]. Genetic ablation of HIF-1 reduces Aβ-induced apoptosis and β-secretase 1 (BACE1)-mediated Aβ metabolism in vitro and in vivo [179,180]. In addition, chronic hypoxia, a risk factor for AD, upregulates HIF-1α expression, which results in tau hyperphosphorylation and cognitive deficit through decreased PP2A activation, implying a relationship between HIF-1α and AD [181]. Thus, investigating HIF-1a may provide new perspectives on cancer and AD therapies.

2.5.3. Nuclear factor kappa B (NFκB)

NFκB is a dimeric transcription factor that mediates innate/adaptive immune responses, inflammation, and cell survival. Degradation of the NFκB inhibitor IκB is followed by NFκB p50/p65 activation (canonical pathway) or p100 phosphorylation and sequential translocation of NFκB p52/RelB (non-canonical pathway) [182]. Activation of the canonical NFκB pathway exacerbates tumor cell proliferation by suppressing apoptosis in a mouse model of colon cancer [183]. In addition, NFκB-dependent cancer-accelerating cytokines (e.g., tumor necrosis factor α (TNF-α), IL-1β, and IL-6) play pivotal roles in the tumor microenvironment [184]. NFκB is also involved in various pathogenic pathways of AD. For example, NFκB promotes the expression of BACE-1, an essential enzyme in amyloidogenic APP proteolysis, and apolipoprotein E (APOE), which activates Aβ fibril formation [185]. In addition, NFκB regulates the expression of microRNAs (miRNAs) in the hippocampal CA1 and temporal lobe neocortical regions of the brain in patients with AD and in LPS-stressed human neuronal glial cells [186]. Dysregulation of these miRNAs is related to the onset of various AD pathologies, including failure to clear Aβ, amyloidogenesis, and astrogliosis [186]. Furthermore, NFκB-mediated inflammatory signaling in reactive microglia/astrocytes results in neuronal degeneration during AD pathoprogression [185]. Taken together, these observations suggest that NFκB signaling is a promising therapeutic target for cancer and AD.

2.5.4. Peroxisome proliferator-activated receptor gamma (PPARγ)

The transcription factor PPARγ is involved in lipid metabolism, glucose homeostasis, cellular differentiation, and inflammatory responses [187]. In addition, PPARγ exhibits proangiogenic properties in embryonic endothelial cells (ECs) and diabetic endothelial progenitor cells but antiangiogenic potential in mature ECs [188]. Due to the diverse biological roles of PPARγ, agonists of PPARγ predominantly act as anticancer therapeutics, including for brain cancer, lung carcinoma, pancreatic cancer, intestinal adenoma, and liver cancer [189]. PPARγ is also associated with bladder carcinogenesis and prostate cancer progression [189,190]. Furthermore, the anti-inflammatory effects of PPARγ have therapeutic efficacy against inflammation-related diseases, including AD. PPARγ agonists such as thiazolidinediones or nonsteroidal anti-inflammatory drugs suppress Aβ accumulation/toxicity by inhibiting the amyloidogenic enzyme BACE1 and promoting the degradation of Aβ by insulin-degrading enzyme (IDE) [191]. In addition, PPARγ agonists ameliorate AD pathologies by suppressing the NFκB-mediated inflammatory signaling pathway [191]. For instance, treating APP/PS1 mice, a model of AD, with the PPARγ receptor agonist pioglitazone attenuates memory deficits and Aβ deposition in the cerebral cortex [192]. Collectively, these findings indicate a crucial role of PPARγ in the pathophysiologies of cancer and AD.

2.5.5. Activator protein 1 (AP-1)

The transcription factor AP-1 is a heterodimer comprising DNA-binding proteins belonging to the Fos, JUN, activating transcription factor (ATF), and musculoaponeurotic fibrosarcoma (Maf) families of proteins. Upon stimulation by cytokines, growth factors, or neurotransmitters, AP-1 is activated by the mitogen-activated protein kinase (MAPK) signaling pathway [193]. The members of the Fos and Jun families have both pro-oncogenic and anti-oncogenic properties; thus, the effect of AP-1 on carcinogenesis depends on dimer composition. For example, the AP-1 containing c-Jun and c-Fos contributes to tumorigenesis, progression, and invasion in cooperation with RAS signaling [194]. By contrast, the AP-1 composed of JUNB and JUND suppresses angiogenesis and DNA methylation, inhibiting cancer development and progression [194]. Pro-oncogenic c-JUN is activated by c-Jun N-terminal kinase (JNK) and is also involved in Aβ-mediated inflammation in the brain in patients with AD [195]. Activation of c-Jun/AP-1 promotes neuronal apoptosis and subsequent neurodegeneration in AD [196]. Thus, AP-1 is closely associated with the pathoprogression of both cancer and AD.

2.6. Cell-cycle dysregulation

2.6.1. Cyclin-dependent kinases (CDKs)

The cell-cycle phase is strictly controlled by subcellular pathways, and each checkpoint is promoted by the activation of CDKs and cyclin complexes [197] Cell-cycle regulation ensures maintenance of cellular homeostasis, and disruption of cell-cycle regulation results in sustained cell proliferation and carcinogenesis [198]. Therefore, the cell-cycle exit step (e.g., CycB/CDK1), cell-cycle entry (e.g., INK4, CDK4/6), and other cell-cycle checkpoints (Cip/Kip, CDK2) are major targets for anticancer drugs [199]. Although the cell-cycle control mechanism in cancer is well understood, the role of this process in AD has received little attention.

Under normal conditions, mature neurons remain in the inactive G0 phase, and cell-cycle entry does not occur. However, under pathological conditions, including AD, abnormal release of CDK4/cyclin D stimulates mature neurons to enter G1 phase (cell-cycle re-entry) [200]. Due to a lack of appropriate CDKs/cyclins, further cell-cycle progression is not possible [200]. Consequently, cell-cycle re-entry contributes to neuronal deterioration/death and subsequent cognitive impairment in AD pathoprogression. The literature suggests that cell-cycle regulation is critical for cancer and AD pathoprogression and that CDK4/6 may be a therapeutic target for both diseases. With the development of new approaches for studying abnormal cell-cycle regulation by CDKs in AD, additional regulatory mechanisms of the CDK/cyclin complex in AD pathogenesis will likely be uncovered.

2.6.2. Breast cancer type 1 (BRCA1)

CDK and cyclin complexes are the predominant regulators of the cell cycle, but other mediators are involved in cell-cycle checkpoints. For example, transcription of the *Brca1* gene and hyperphosphorylation of the BRCA1 protein are enhanced in the G1/S phase of the cell cycle [201]. Under normal conditions, activated BRCA1 phosphorylates retinoblastoma (RB), which interacts with E2F to inhibit entry into S phase [201]. When DNA is damaged by γ-irradiation, the BRCA1-BARD1 heterodimer phosphorylates p53, which activates p21 and arrests the cell cycle in G1/S phase [201]. Therefore, BRCA1 acts as a tumor suppressor by regulating cell-cycle G1/S phase entry. Mutations in *Brca1* are closely associated with tumorigenesis in breast and ovarian cancer. Although the function of BRCA1 in breast cancer has been established, its roles in other diseases have not been fully investigated.

Interestingly, imbalanced BRCA1 expression has been linked to AD pathogenesis. In patients with AD, BRCA1 and pBRCA1^{Ser1524} levels in the brain are enhanced, and in neuronal cultures, Aβ oligomer treatment decreases BRCA1 expression [202,203]. In addition, genetic ablation of neuronal *Brca1* results in neuronal deterioration and impaired cognition and synaptic plasticity [202]. Notably, aberrant expression of BRCA1 in NFTs in the brains of AD patients might be associated with cell-cycle reentry [204]. The specific neurological mechanisms by which BRCA1 is associated with cell-cycle reentry in AD neurons require further study.

2.6.3. Transcription factor EB (TFEB)

TFEB has pivotal roles in autophagosome formation, lysosome biogenesis, and autophagic lysosome fusion [205]. Recent studies indicate that TFEB also plays an essential role in cell-cycle regulation. DNA damage increases the translocation of TFEB into the nucleus, where it stabilizes/activates p53, leading to p21 activation and cell-cycle arrest [206]. Despite its inhibitory effects on cell-cycle progression, TFEB is regarded as an oncogenic factor in cancer etiology. TFEB promotes the transcription of genes involved in cell proliferation, metastasis, and angiogenesis and is associated with the development and progression of pancreatic cancer, melanoma, non-small cell lung cancer (NSCLC), and breast cancer [207].

Compared with healthy controls, TFEB levels in the brain are reduced in patients with AD and in mouse models of AD [208]. Conversely, preclinical and clinical studies have shown that TFEB overexpression restores autophagic function, reduces amyloid plaque accumulation, and rescues cognitive function [10,209]. Taken together, these observations indicate that disruption of the balance among the multiple functions of TFEB is crucial in the etiopathologies of cancer and AD.

2.6.4. Mammalian target of rapamycin (mTOR) signaling

mTOR is a receptor serine/threonine kinase that forms two complexes, mTORC1 (mTOR, raptor, and mLST8) and mTORC2 (mTOR, RICTOR, mSLT8, and mSin1), which regulate cell growth/metabolism or cell proliferation/survival, respectively [210]. mTOR modulates cell growth by promoting G1 phase progression via S6K1/4E-BP1/eLF4E-dependent pathways [211]. In addition, activation of PI3K/AKT/mTOR1 and insulin receptor substrate 1 (IRS1)/mTORC2 signaling is required for cell-cycle progression in prostate cancer [15]. Consistent with the contribution of sustained activation of mTOR signaling to carcinogenesis, inhibition of mTOR has antitumor efficacy in pancreatic cancer, breast cancer, endometrial cancer, and thyroid cancer [212].

Aberrant activation of mTOR signaling is also observed in AD pathoprogression, including tau pathology, neuroinflammation, and memory impairment [213]. Aβ oligomers stimulate cell-cycle re-entry by enhancing mTOR1 signaling at the plasma membrane (not lysosomal), and activation of lysosomal mTOR via insulin treatment suppresses Aβ-mediated cell-cycle re-entry in primary cortical neurons [214].

Moreover, Aβ oligomers activate AKT/mTOR signaling, which promotes tau hyperphosphorylation and subsequent memory impairment [18]. These observations indicate that mTOR activity is crucial for cell-cycle progression in cancer/AD pathologies.

In summary, six key pathophysiological mechanisms are linked to both cancer and AD: angiogenesis, mitochondriopathy, proteostasis, cell to cell junction, transcriptional dysfunction, and cell-cycle dysregulation. Targeting mediators of these shared biological features of cancer and AD may be a feasible strategy for developing AD theragnostics (Table 1).

3. Potent druggable targets and therapeutic strategies for AD

On the basis of the shared pathological mechanisms and related biomarkers of AD and cancer described above, we propose two predominant druggable targets for the management/treatment of AD pathologies: protein–protein interactions and receptor inhibition.

3.1. Cancer biomarkers as therapeutic targets for AD

3.1.1. Protein–protein interactions (PPIs)

PPIs form biological networks with roles in signaling pathways, metabolism, and transcription networks [221]. There are approximately 650,000 PPIs in human cells, and new network interactions are continually identified [222]. The PPI context affects protein function, as the PPI network enables connections between an enzyme, its protein substrate, and protein activity [223]. PPI dysfunction contributes to various disorders. Oncogenic PPI networks modulate cell survival, proliferation, tumor-promoting inflammation, invasion, and metastasis, spurring interest in the development of specific inhibitors of PPIs as anticancer drugs. For example, Yoon et al. [224] found that inhibiting the direct binding of ribosomal S6 kinase A2 (RSK3) to IκBα impairs RSK3-induced IκBα phosphorylation and reduces breast tumorigenesis. The construction of a PPI network for colon cancer stem cells (CSCs) identified TMEM17 as a novel CSC-related gene [224], and depleting TMEM17 inhibits CRC cell proliferation and increases chemotherapy drug sensitivity [224]. Additionally, Hozhabri et al. identified four candidate genes—SPARC, THY1, IL-1B, and CXCL8—as pivotal regulators affecting co-regulation within PPI networks of brain metastasis tumors derived from breast cancers [225].

Research on the prevention, diagnosis, and treatment of AD has also explored PPI networks. Specifically, Karbalaei et al. [226] conducted a PPI network analysis of nonalcoholic fatty liver disease and AD and identified 190 common genes between the two diseases, highlighting the potential utility of PPI networks for analyzing complicated related disorders. In a mouse model of AD, NXPZ-2, a small-molecule inhibitor of the Keap1–Nrf2 PPI, enhances cognitive function and restores damaged brain structure, implying that Keap1–Nrf2 PPI inhibition is a potential therapeutic strategy for AD [227]. A recent PPI network analysis revealed that Keap1-Nrf2 PPI inhibition by POZL enhances cognitive function and recovers Aβ-induced synaptic damage by activating Nrf2 in both neurons and AD mouse model [228]. Although the body of research on PPIs in AD is small compared with that on PPIs related to cancer, understanding the specific PPIs associated with AD may facilitate the discovery of novel therapeutic agents.

3.1.2. Receptor inhibition

Receptor tyrosine kinases (RTKs) are enzyme-linked receptors that regulate a wide range of cellular processes, including proliferation, differentiation, metabolism, and migration [229]. Alteration or dysregulation of RTK signaling causes various cancers, and the potential effectiveness of TKIs as therapeutics for neurodegenerative diseases, including AD, has been explored. Representative RTKs are described below.

Toll-like receptors (TLRs) located on the surface of immune cells activate innate immunity upon stimulation by conserved pathogen-expressed molecules [230]. TLRs are classified according to whether they recognize ligands on the cell membrane (TLR1, 2, 4, 5, 6) or within the cell on the endosomal membrane (TLR3, 7, 8, 9) [230]. TLR4, one of the best-known TLRs, is overexpressed in esophageal squamous cell carcinoma (ESCC) and lung cancer [231]. An evaluation of the anticancer effects of TLR4 inhibitors in the breast cancer cell lines MCF7, SKBR3, MDA-MB-231, and BT-474 revealed that the expression levels of TLR4 and its downstream genes (e.g., MyD88 and RELB) vary depending on the cancer cell line [232]. TAK-242, a small-molecule inhibitor of TLR4, reduces the viability of breast cancer cells, suggesting that TAK-242-mediated TLR4 inhibition might be a promising strategy for treating breast cancer [232].

Table 1
Shared biological features of cancer and Alzheimer's disease (AD).

Feature	Mediator	Role in cancer	Role in AD pathology	References
Angiogenesis	APP	Cancer cell growth/proliferation	Aβ plaque deposition	[30,32,33]
	ADAM	Tumor invasion	Non-amyloidogenesis	[36,38,215]
	EGFR	Tumor proliferation/metastasis	Aβ/tauopathy, neuroinflammation, cognitive function	[43,47–49,216,217]
	VEGF	Cancer cell growth/proliferation	Aβ/tauopathy, cognitive function	[51,52,54–56]
	SEMA	EGFR-mediated carcinogenesis	Neuronal degeneration, neuroinflammation, cognitive function	[58–61]
	NRP	VEGF-induced tumor progression	Cognitive function	[62,65,218,219]
Mitochondriopathy		Aberrant anaerobic glycolysis-mediated tumor cell proliferation, mtDNA mutation-induced cancer progression	Abnormal mitochondrial dynamic-caused neurodegeneration, Glial activation, Aβ/tauopathy	[70,71,77,78,85,87–89,220]
Proteostasis		Aggregated p53-mediated tumor progression	Neurotoxic Aβ plaque and neurofibrillary tangle	[128–130,134]
Protease and cell–cell junction	MMP	CD44-dependent carcinogenesis	Aβ pathology	[143–147]
	ZO-1	Blood–brain tumor barrier	BBB integrity, neurodegeneration	[149–151]
	Claudin	Tumor promotor or suppressor	BBB permeability, cognitive function	[153–157]
	Occludin	Cancer cell proliferation	BBB permeability	[160,162]
Transcriptional dysfunction	NRF2	Anti-carcinogenic or proangiogenic	Aβ pathology Tauopathy, cognitive function	[166–168,170,173]
	HIF-1a	VEGF-mediated tumor growth	Aβ pathology, Tauopathy, cognitive function	[177,179–181]
	NFκB	Cancer cell proliferation, tumor microenvironment	Amyloidogenesis, neuroinflammation	[183–186]
	PPARγ	Tumor promoter or suppressor	Aβ pathology, neuroinflammation, cognitive function	[188–192]
	AP-1	Tumor promoter or suppressor	Neurodegeneration, neuroinflammation	[194–196]
Cell cycle dysregulation	CDKs	Tumor proliferation	Neurodegeneration	[198,200]
	BRCA1	Carcinogenesis	Cognitive function, synaptic plasticity	[201,202]
	TFEB	Cancer progression	Autophagy-mediated Aβ pathology and cognition	[10,207,209]
	mTOR	Tumorigenesis, carcinogenesis	Dual role in Aβ pathology	[211,212,213]

TLR4 was also recently implicated in AD. TLR4 expression is significantly higher in APP/PS1 transgenic mice than in WT mice, and TAK-242 attenuates cognitive impairment and Aβ deposition and inhibits neuronal apoptosis in APP/PS1 transgenic mice [233]. According to a recent study, the TLR4/NF-κB signaling pathway is activated in AD mice, and this activation is significantly inhibited by the overexpression of miR-107-5p, which is induced by TLR4 [234]. In human iPSC-derived microglia, the cytokines produced upon TLR9 activation trigger phagocytosis of $A\beta_{42}$ oligomers and inhibit inflammation [235]. Taken together, these findings indicate that blocking TLR4 may be a promising strategy for treating AD and cancer.

Endothelial mitogens promote angiogenesis and vascular permeability, and most of the endothelial mitogens identified and isolated thus far are derived from vascular endothelial growth factors (VEGFs) [236]. VEGF/VEGFR signaling plays roles in immunity and cancer by promoting angiogenesis [237]. Overexpression of VEGF regulates glioblastoma multiforme (GBM), a brain tumor, and VEGFR2 overexpression accelerates the growth and metastasis of gastric cancer cells [238]. Thus, inhibitors of VEGF and VEGFR are potential anticancer treatments. For example, the VEGFR2 inhibitor YLL545 inhibits angiogenesis and cell growth and has antitumor effects on breast cancer cells [237]. VEGF blockade by bevacizumab decreases the number and alters the morphology of dendritic spines in the hippocampus and reduces long-term potentiation (LTP), suggesting therapeutic potential for GBM [239]. Drugs targeting VEGF, including sunitinib, sorafenib, axitinib, tanibirumab, and ramucirumab, have received approval for treating advanced and metastatic cancers [240]. In 5xFAD mice, a model of AD, VEGF inhibition by bevacizumab significantly improves BBB integrity, the cerebrovascular response, and long-term memory, implying therapeutic potential of VEGF blockade for AD [241]. Vascular dysregulation is also involved in AD pathogenesis. We recently determined that the VEGF inhibitor vatalanib reduces Aβ plaque number and tau phosphorylation in 5xFAD mice [56]. Therefore, VEGF may be a novel molecular target/biomarker for both cancer and AD.

Platelet-derived growth factor receptor (PDGFR) regulates cell proliferation, migration, and angiogenesis [242]. The roles of PDGFs and PDGFRs in oncogenesis and drug resistance have been studied extensively, and PDGF signaling is an important target for inhibiting tumorigenesis [243]. Several recent studies have examined the ability of regorafenib, imatinib, and sunitinib to act as PDGFR inhibitors to inhibit breast cancer progression [244]. Regorafenib significantly decreases the migration and proliferation of breast cancer cells [244]. Combining radiotherapy with biological or pharmaceutical drugs (e.g., PDGFR-β inhibitors) is a potential therapeutic strategy for cancer to minimize the side effects and enhance the efficacy of RT [245]. However, inhibiting PDGFR-β (a marker of pericytes) delays tumor growth but enhances metastasis when combined with RT and Endostar therapy [245]. Moreover, a recent study demonstrated that PDGFRs act in BBB formation in cerebral vessels by preventing pericyte degeneration [25]. Interestingly, another study suggested that cerebrospinal fluid (CSF) PDGFRβ levels reflect tau pathology rather than BBB integrity [246]. However, further study of the effects of PDGFR inhibitors on AD is needed.

4. Repurposing of anticancer drugs as AD medications

Given that cancer biomarkers may be potential druggable targets for AD treatment, FDA-approved anti-cancer drugs might be repurposed as AD therapeutics. In this section, we describe the current status and trends in the development of AD drugs and summarize the therapeutic efficacy of promising anti-cancer drugs against AD pathologies based on our latest translational research. Then, we propose immunotherapy and gene therapy as potential therapeutic approaches for AD.

4.1. Current status of AD drug development

Many drugs developed for the treatment of AD target the primary pathology. To decrease amyloid levels, clearance-based approaches appear to have a greater chance of success than amyloid production-based approaches (e.g., Aβ and β-secretase inhibitors); the pursuit of the latter has primarily been halted due to toxicity issues and safety concerns [247,248]. AD initially progresses via Aβ accumulation in the brain. Over the last 15 years, numerous studies have focused on drugs that inhibit Aβ production/aggregation/degradation or increase Aβ clearance in the brain in patients with mild to moderate AD [249]. Aducanumab was recently conditionally approved by the FDA as an anti-amyloid drug and is the first treatment for AD to be introduced in two decades [250]. Aducanumab is a human immunoglobulin gamma 1 (IgG_1) monoclonal antibody against soluble and insoluble forms of amyloid-β [251]. However, aducanumab does not completely rescue memory loss in AD patients and only slows the rate of decline in cognitive function [252]. Gantenerumab and solanezumab, which were designed to target fibrillar or soluble Aβ in patients with dominantly inherited AD, produce adverse outcomes, suggesting that Aβ is not the sole trigger of AD development [253].

In addition to anti-Aβ therapies, drug development for AD must target CNS inflammation, brain insulin resistance, and tau aggregation. Consequently, multitarget strategies may be necessary to achieve clinical success in treating AD. In fact, according to the 2023 Alzheimer's Drug Development Pipeline, numerous disease-modifying therapies are based on a multitarget strategy [254]. The potential relationship between cancer and AD may also influence therapeutic development, but evidence on the nature of this relationship is conflicting. Specifically, Shafi [255] suggested an inverse relationship between AD and cancer, whereas Nudelman et al. [256] proposed overlapping hallmarks of AD and cancer. This section discusses the repurposing of FDA-approved anticancer drugs as AD treatments and potential druggable targets for AD.

4.2. Translational approaches for treating AD with anticancer drugs

4.2.1. Ibrutinib

Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor that is approved by the FDA for the treatment of chronic lymphocytic leukemia and mantle cell lymphoma [257]. In addition to B cell lymphoma, ibrutinib suppresses the pathoprogression of other cancers, including skin cancer cell proliferation, breast tumorigenesis, and lung cancer metastasis [258–260]. We have demonstrated therapeutic effects of ibrutinib on AD pathology. Specifically, we found that ibrutinib attenuates LPS-induced neuroinflammation in WT mice by reducing the expression of Iba-1 and GFAP, which are microglial and astrocyte markers, respectively [261]. Moreover, we were the first to demonstrate that ibrutinib alleviates AD-related pathologies, such as neuroinflammation, tau phosphorylation, and Aβ accumulation, in 5xFAD and PS19 mice (models of AD) [262]. In 5xFAD mice, ibrutinib increases long-term memory and dendritic spine number, indicating that ibrutinib can improve cognitive function [262]. This evidence suggests that ibrutinib may be a therapeutic small molecule for cancer and AD.

4.2.2. Abemaciclib

Abemaciclib is an inhibitor of CDK4/6 that is approved by the FDA for hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer [200]. We were the first to report that abemaciclib attenuates Aβ/tauopathy, memory impairments, and neuroinflammation in AD mouse models and/or LPS-treated WT mice [200]. We also demonstrated that abemaciclib has therapeutic efficacy in AD mouse models and WT mice by modulating DYRK1A/STAT3 signaling [200]. Furthermore, abemaciclib has protective effects on neurons in a p97-mediated motor neuronal degeneration model [263]. Taken together, these results indicate that the anticancer drug

abemaciclib may have therapeutic effects on neurodegenerative diseases, including AD.

4.2.3. Nilotinib

Nilotinib is a Bcr-abl TKI that is used to treat chronic myeloid leukemia (CML) [264]. Nilotinib also inhibits long-term estrogen deprivation in MCF-7 breast cancer cells. Silveira et al. [265] used spheroids cultured from patient tumor-derived ACC-T36 cells to investigate the effect of nilotinib on adrenocortical carcinoma (ACC). They found that nilotinib decreases cell viability more than mitotane, which is already used as an ACC therapy, via effects on the ERK1/2 pathway [265]. In addition, nilotinib inhibits tamoxifen-resistant breast cancer cell growth by reducing estrogen receptor (ER)α expression [266]. Interestingly, nilotinib also downregulates AD and PD pathology [267]. Specifically, Adli Moghaddam et al. found that nilotinib modulates brain mitochondrial bioenergetics and biogenesis in 3xTg astroglia. In Tg2576 mice, nilotinib reduces the loss of dopaminergic (DA) neurons and rescues cognitive function [268]. In addition, Stevenson et al. discovered that treating AD patients with nilotinib for 12 months significantly reduced collagen levels, discoidin domain receptor (DDR)-1 gene expression, proinflammatory cytokine levels, and caspase-3 gene expression [269]. These studies suggest that nilotinib is a promising drug for cancer and AD.

4.2.4. Regorafenib

Regorafenib is an oral multifunctional TKI that targets VEGFR, PDGFR, Kit, RET, and Raf-1 and is FDA approved for the treatment of CRC, gastrointestinal stromal tumors (GISTs), and hepatocellular carcinoma (HCC) [270]. Regorafenib inhibits tumorigenesis and cell proliferation by downregulating MAPK signaling in vivo [271]. Cai et al. [272] generated 5-FU-resistant colon cancer cell lines to evaluate the effects of regorafenib on CRC and found that regorafenib inhibits CSC-like phenotypes by increasing miR-34a levels. Regorafenib also significantly increases autophagy in liver cancer cells and has synergistic effects with cisplatin, a common treatment for HCC, suggesting that regorafenib inhibits HCC progression by promoting autophagy [273]. Notably, we recently found that regorafenib downregulates LPS-induced proinflammatory cytokines in WT mice; in 5xFAD mice, regorafenib decreases Aβ accumulation/tau phosphorylation and increases dendritic spine formation [274]. Furthermore, Eby et al. applied AutoDock Vina, a type of computational modeling methodology, to model the peptide–receptor binding between regorafenib and Aβ and elucidate regorafenib's effects on Aβ aggregation [275]. They found that regorafenib binds strongly to $A\beta_{42,}$ implying that regorafenib is a potential inhibitor of Aβ aggregation [275]. However, validation of regorafenib as a potential therapy for AD awaits in-depth studies of its effects on AD pathology.

4.2.5. Axitinib

Axitinib is a TKI targeting VEGFR1/2/3 and is approved by the FDA for the treatment of advanced renal cell carcinoma (RCC) [276]. Axitinib has anticancer effects on melanoma by suppressing the expression of proinflammatory cytokines (IL-6, TNF-α, and IFN-γ) and on HCC by inhibiting CaMKIIα/ERK or AKT/mTOR signaling [277,278]. Furthermore, axitinib inhibits epithelial ovarian cancer cell survival by decreasing VEGFR2-mediated AKT and ERK signaling [274]. Interestingly, axitinib rescues cognitive function, decreases angiogenesis, and disrupts TJs and the BBB in Tg2576 mice, a model of AD [279]. Further investigations are required to determine the specific indications and mechanisms of action of axitinib as a therapy for AD.

4.2.6. Sunitinib

Sunitinib inhibits RTKs, including VEGFR2 and PDGFRβ, and is FDA approved for the treatment of GISTs, pancreatic neuroendocrine tumors (PNETs), and RCC [280]. Sunitinib facilitates apoptosis by inhibiting NFκB signaling, suppressing breast cancer cell proliferation and growth [281]. However, sunitinib has also been reported to exacerbate breast cancer cell metastasis by inducing endothelial cell senescence and changes in the tumor microenvironment [282]. Notably, sunitinib is proposed to interact with the catalytic site of acetylcholinesterase (AChE), and inhibition of AChE activity by sunitinib attenuates scopolamine-induced amnesia in mice [283]. Furthermore, sunitinib exhibits neuroprotective efficacy in HIV-1 tat mice, a model of neurodegeneration, by facilitating autophagic function [284], indicating that repurposing the anticancer drug sunitinib as a novel therapeutic agent for neurodegenerative diseases, including AD, may be an effective strategy.

4.2.7. Neratinib

Neratinib is a TKI targeting HER2 and EGFR and is approved by the FDA for the treatment of HER2-positive breast cancer [285]. Neratinib has synergistic anticancer effects with everolimus, trametinib, and palbociclib, which target HER2-downstream mTOR, MEK, and CDK4/6 signaling, respectively [286]. Neratinib promotes autophagic function [287] and inhibits APP, Tau, and TDP-43 expression in colon cancer cell lines transfected with APP, Tau, or TDP-43, respectively [288]. This evidence suggests that neratinib may have potential therapeutic efficacy for neurodegenerative diseases, but further validation of the effects of neratinib in AD mouse models and the underlying mechanism of action is required.

4.2.8. Binimetinib

Binimetinib is a TKI targeting MEK1/2 and is approved by the FDA for the treatment of melanoma [289]. Binimetinib has synergistic antitumor efficacy with other anticancer drugs. For example, the addition of binimetinib enhances the anticancer efficacy of encorafenib against metastatic NSCLC and capecitabine against biliary tract cancer [289,290].

Importantly, binimetinib treatment suppresses Aβ-mediated decreases in autophagosome and lysosome fusion and has neuroprotective effects in SH-SY5Y cells [291]. The therapeutic effects of MEK1/2 inhibitors on AD pathologies in a mouse model of AD are closely related to the promotion of autophagic function [291], but further investigation of the specific efficacy and mode of action of binimetinib is required for repurposing binimetinib as a drug for AD. The molecular structures, mechanisms of action, and therapeutic indications of anticancer drugs that could be repurposed as AD medications are summarized in Fig. 1.

4.3. Potential therapeutic approaches

4.3.1. Immunotherapy

Immunotherapies ameliorate immunologically mediated diseases by upregulating or downregulating the immune system [292]. Immunotherapies generate long-term endogenous antibodies by relying on cellular and humoral immune responses. Immunotherapies can be active or passive. Active immunotherapies elicit the development of specific immune effectors, such as antibodies and T cells, by inducing the immune response in patients [293]. By contrast, passive immunotherapies administer ex vivo-generated immune elements (e.g., antibodies and immune cells) to patients and do not provoke the host immune response [293].

The immune system plays an important role in regulating cancer development and in cancer treatment, and immunotherapies have been developed for the treatment of cancer. Bevacizumab, a monoclonal antibody targeting VEGF, blocks regulatory T cell (Treg) accumulation in the peripheral blood in patients with metastatic colorectal cancer (mCRC) [294]. To explore anti-VEGF therapy resistance, Dalton et al. [295] investigated the resistance of macrophages to VEGF inhibition and found that VEGFR-1 and VEGFR-3 expression are downregulated and angiogenic pathways are upregulated in macrophages treated with VEGF inhibitors. Interest in macrophage-based immunotherapies for cancer is gradually increasing [296]. For instance, anti-PD-1 and anti-

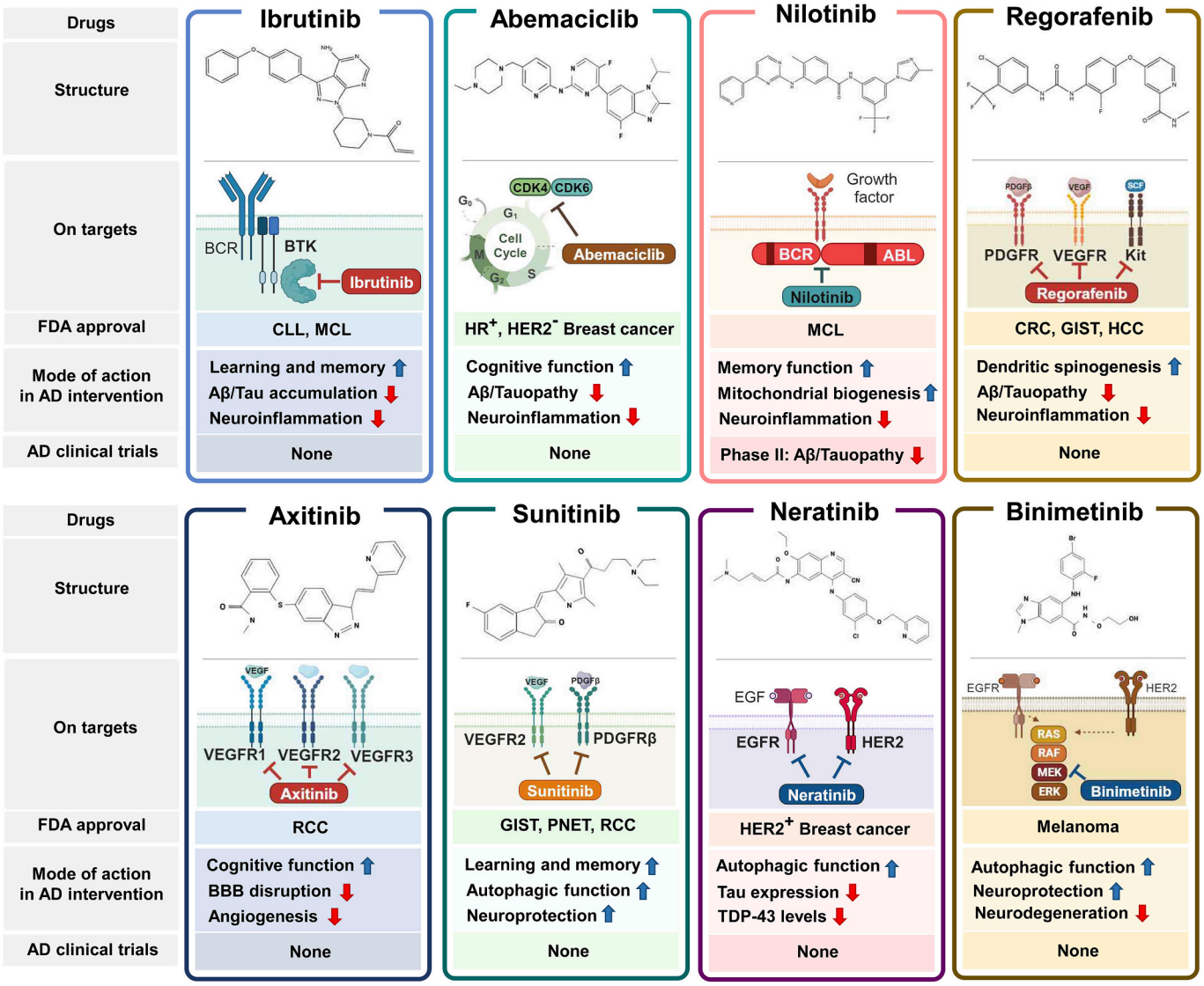

Fig. 1. Structures and biological functions of anticancer drugs in cancer and AD. Ibrutinib, abemaciclib, nilotinib, regorafenib, axitinib, sunitinib, neratinib, and binimetinib are FDA-approved anticancer drugs with potential for repurposing to ameliorate AD pathology.

PD-L1 therapies inhibit the immune checkpoints CTLA-4 and PD-1 to promote immune responses and relieve immune suppression [296]. Efforts to develop small-molecule inhibitors targeting immune checkpoints are also underway. One target for small-molecule immunotherapy is indoleamine 2,3-dioxygenase 1 (IDO1), which catalyzes the initial step of the urinary ammonia pathway. IDO1 plays a crucial role in carcinogenesis by promoting immune evasion [297]. Weiskopf et al. discovered that immunotherapies based on CD47 blockade can promote macrophage-mediated destruction of small-cell lung cancer (SCLC) [298]. Immunotherapies based on antibodies and macrophages may lead to effective cancer therapies.

Immunotherapies could also potentially target AD pathologies such as Aβ deposition and tau hyperphosphorylation. Anti-Aβ immunotherapy can reduce extracellular or intracellular Aβ accumulation and promote early clearance of tau pathology [299]. Spencer and Msaliah were the first to report the effects of immunotherapy with bapineuzumab (an Aβ antibody) on AD in clinical trials [300]. The clinical development of Aβ and tau immunotherapies is actively proceeding. A short Aβ peptide was used to design CAD106 (Novartis), which induces Aβ-specific antibodies and Aβ-specific T-cell inactivation [301]. ACI-24 comprises short $Aβ_{1–15}$ peptides immobilized on liposomes and adjuvants and is designed to induce potent antibody responses without Aβ-specific T-cell activation [299]. Aβ immunotherapy induces microhemorrhages in AD mice; these microhemorrhages are correlated with the activation of perivascular macrophages and the recruitment of peripheral monocytes [302].

Studies of tau immunotherapies may provide insights into the effects of tau on AD progression. Strikingly, AADvaac1, an anti-tau antibody, reduced brain atrophy and cognitive decline in patients with mild-to-moderate AD in a phase I trial [303]. Furthermore, AADvac1 significantly decreases the levels of p-tau181 and p-tau217, CSF biomarkers of AD [304]. Intrahippocampal administration of PHF1, an adeno-associated virus (AAV)-vectored anti-phospho-tau antibody, in a mouse model of tauopathy (expressing the human tau P301S mutation) induces high antibody levels and reduces the levels of pathological tau species and NFTs [305]. In Tg AβPPswe/PS1dE9 mice, brain delivery of an rAAV overexpressing an anti-Aβ single-chain antibody (scFv59) decreases Aβ load [306]. In conclusion, immunotherapy may be a promising approach for treating and curing cancer and AD.

4.3.2. Gene therapy

In gene therapy, defective genes are replaced with normal genes to add new functions [307]. Transgene delivery is mediated by a vector, most commonly a virus, that infects the host cell. Subsequent gene

expression in the host cell results in enhanced enzymatic activities and levels of bioactive molecules [307]. More than 1340 clinical trials targeting over 100 genes have been approved for various diseases, primarily cancer [308]. Cancer/tumor-specific promoters targeting therapeutic nucleic acids (TNAs) have been used as novel gene therapies [309]. Wang et al. [310] used a luciferase reporter gene to show that the COX-2 gene promoter is activated in CRC cells but not in normal intestinal epithelial cells. The AFP promoter, which is commonly used in HCC gene therapy, has been utilized in RNAi strategies (AFP-Cre/LoxP-shRNA) to inhibit HCC growth [311]. Another vector for gene therapy targeting prostate cancer, JC polyomavirus virus-like particles (PSAtk-VLPs), selectively triggers apoptosis in AR-positive CRPC 22Rv1 cells in vitro and suppresses the proliferation of tumor nodules in a xenograft mouse model [312]. Gene therapy may be an efficient strategy for treating cancers.

Gene therapy has also been successfully applied to several neurodegenerative and neurological diseases, including AD. For example, AAV-mediated gene transfer to directly overexpress sAPPα in the brain in APP/PS1ΔE9 mice restores dendritic spine density and working memory [313]. In an APP transgenic mouse model, targeting BACE1 with siRNA-mediated knockdown using lentiviral vectors reduces Aβ pathology and improves behavioral deficits [314]. Recently, Ng et al. constructed AAV2/8 carrying a mutated mouse APN gene (APN^{C39S}) and transduced this virus into the liver in 5xFAD mice, resulting in the production of low-molecular-weight trimeric adiponectin (APN^{Tri}) [315]. Treatment with AAV2/8-APN^{Tri} reduced the secretion of IL-1β and IL-18 induced by Aβ, and these effects were attributed to inhibition of microglial NLRP3-inflammasome activation [315]. In addition, 5xFAD mice treated with AAV-APN^{Tri} exhibited significant improvements in memory functions and decreases in dystrophic neurites [315].

miRNA-based therapeutic strategies for cancer and AD have also been explored. AAV-miR-26a leads to cell-cycle arrest, apoptosis of cancer cells, and inhibition of tumor growth in human HCC [316]. Abd-Aziz et al. suggested that miRNA restoration therapy with AAVs is a safe and effective cancer treatment [317]. However, there are few studies of the relationship between changes in miRNAs and AD pathology. In WT mice, miR-34c overexpression causes dendritic spine loss and memory impairment [318]. In addition, miR-124 expression is elevated in Tg2576 mice, a model of AD, leading to deficiencies in synaptic plasticity and memory [318]. Moreover, lentiviral vector-mediated treatment of APP/PS1 mice with miR-195 improves learning and memory by inhibiting Aβ plaque deposition [319]. Therefore, gene therapy may eventually become an effective means of treating cancer and AD.

5. Clinical practice: from cancer to AD

Due to the long duration, high cost, and high failure rate of new drug development, research on repurposing existing drugs to treat various diseases has become a new trend. Drugs used to treat cancer have diverse mechanisms of action, reflecting the complex and heterogeneous nature of cancer [320]. The mechanisms of these drugs are often effective not only in cancer but also in other diseases [321–323]. Thus, anticancer drugs are good candidates for drug repurposing research. Given the mechanistic overlap between AD and cancer, research on repurposing anticancer drugs for AD treatment is actively underway. The diversity of shared molecular targets/signaling molecules between cancer and AD increases the possibility that a variety of anticancer drugs may have applications in AD treatment.

5.1. Anticancer drugs in clinical trials for repositioning as AD treatments

The therapeutic effects of several anticancer drugs on AD are currently being evaluated in phase 2 clinical trials [324,325]. First, the effectiveness of combining dasatinib (NCT04685590), a TKI widely used to treat Philadelphia chromosome-positive (Ph+) CML, and quercetin for treating AD is being assessed in a multicenter phase 2 trial [326]. Intermittent senolytic therapy (dasatinib+quercetin) has a good safety profile and promising therapeutic outcomes based on mechanisms such as reduction of tau accumulation and neuroinflammation. Second, lenalidomide (NCT04032626), which is approved for treating multiple myeloma, is in a phase 2 trial for AD treatment based on its ability to inhibit the expression of proinflammatory cytokines, including TNFα, IL-1, IL-6, and IL-12, and enhance the production of the anti-inflammatory cytokine IL-10 [327]. CD38+ CD8+ T-cells are notably elevated in the bloodstream in patients in the early stage of AD. These cells can migrate to the CNS and induce toxic effects [328,329]. Third, daratumumab (NCT04070378), an IgG1 monoclonal antibody against cluster of differentiation 38 (CD38), can penetrate the BBB and is in a phase 2 trial for the treatment of AD [330]. CD38, which is found in neurons, astrocytes, and microglia, is involved in inflammatory processes and neurodegeneration, and knocking out the CD38 receptor decreases soluble Aβ and Aβ plaque load in vivo [331,332].

Other anticancer drugs are in phase 3 clinical trials. Nilotinib, a TKI also approved for Ph + CML treatment, significantly reduces protein misfolding and aggregation in animal models of neurodegeneration [333]. In a phase 2 trial, nilotinib treatment reduced Aβ levels in the frontal lobe and phosphorylated tau levels [334]. Nilotinib inhibits discoidin domain receptor (DDR)-1, revealing multifaceted effects of nilotinib on the clearance of amyloid and tau and inflammation. Thus, nilotinib could potentially alleviate cerebrovascular fibrosis [269]. Phase 3 clinical trials of nilotinib (NCT05143528) have been underway since February 2022. Masitinib, a TKI targeting the c-kit pathway that is currently approved for the treatment of mast cell tumors in dogs, significantly improved cognitive performance in a phase 2b/3 clinical trial (NCT01872598), making it a potential treatment for AD [335]. An upcoming phase 3 trial of masitinib (NCT05564169) seeks to confirm these findings. In summary, clinical trials to repurpose anticancer drugs as therapeutic options for AD are actively underway. If these trials are successful, many anticancer drugs may ultimately play critical roles in the treatment of AD.

5.2. Potential mechanisms of AD treatment and related anticancer drugs

A potential target for AD treatment is EGFR, which is upregulated in AD and is involved in AD pathology, including the induction of Aβ neurotoxicity and neuroinflammation [48,336,337]. We previously discussed the potential of EGFR inhibitors as AD treatments [46]. Several EGFR inhibitors have shown potential as AD treatments in AD mouse models [47,49,338,339], but lapatinib and varlitinib may be preferential candidates for AD treatment because they can cross the BBB.

VEGFR and PDGFR are also relevant for the potential repurposing of anticancer drugs for AD treatment. The TKI axitinib targets VEGFR1, 2, and 3. In aged Tg2576 AD mice, axitinib improves memory and cognitive function by reducing amyloid plaques and cerebrovascular neoangiogenesis and restoring BBB integrity [279]. The TKI regorafenib targets multiple kinases, including PDGFR. We found that regorafenib downregulates proinflammatory cytokine expression and reduces tau phosphorylation, making it a potential candidate for treating AD [274]. According to a recent study, regorafenib also restores $A\beta_{1-42}$-induced cognitive dysfunction and attenuates microglial activation and neuronal damage [340]. As the shared mechanisms of cancer and AD are gradually revealed, repositioning anticancer drugs will be an effective way to identify novel therapeutic candidates for AD.

6. Conclusion

In the past decade, epidemiological research on cancer survivors has suggested new clinical approaches for treating AD. Specifically, cancer patients have a markedly reduced risk of AD and vice versa, indicating an inverse relationship between AD and cancer [341,342]. Consequently, identifying specific biomarkers shared by AD and cancer and elucidating the common pathological pathways of AD and cancer have

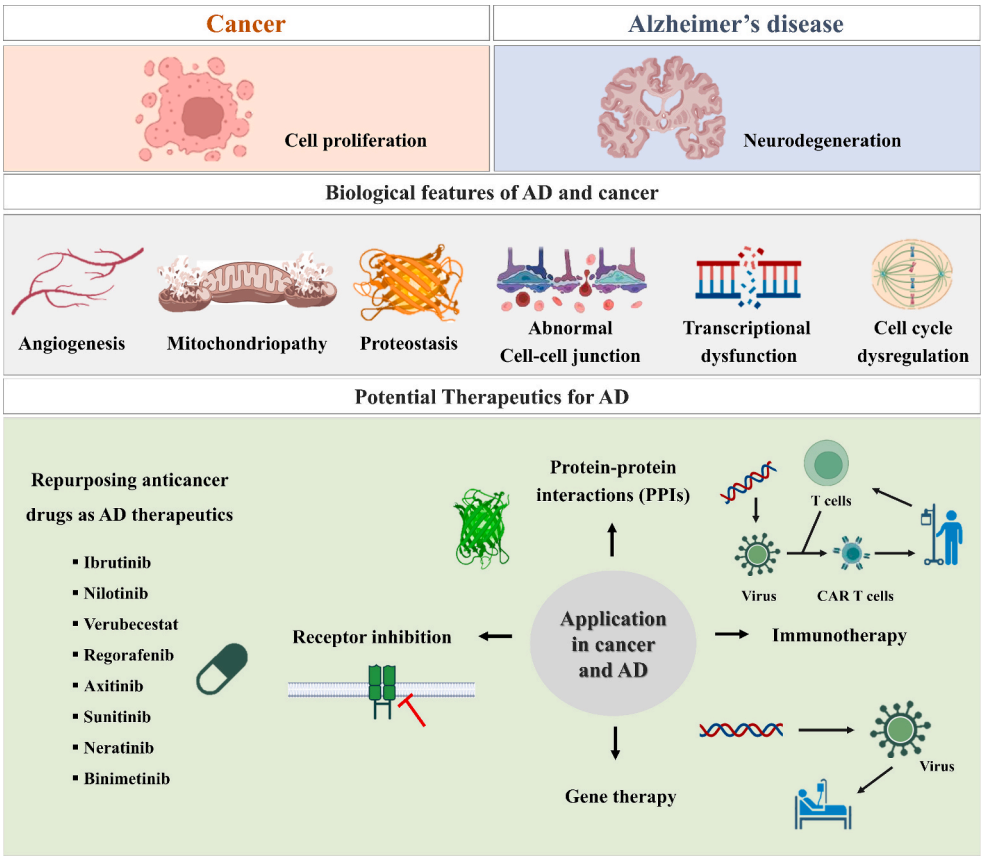

Fig. 2. Summary of insights from cancer treatment for developing theragnostics for AD. AD and cancer share several common biological features, including angiogenesis, mitochondrial dysfunction, protein misfolding, and protein aggregation. Several recent studies have found that the anticancer drugs ibrutinib, nilotinib, verubecestat, and regorafenib ameliorate AD pathology in mouse models of AD. Immunotherapies and gene therapies that target protein–protein interactions and receptor inhibition may find applications in the treatment of both AD and cancer.

become attractive strategies for developing AD therapeutics [343]. Nevertheless, the pathophysiological associations of the shared risk genes for AD and cancer have not been systematically unraveled.

Interestingly, recent genome-wide association studies (GWASs) aimed at identifying cancer susceptibility genes have revealed networks of cancer-related pathways and suggested various targets for anticancer drugs [344]. However, there have been few studies of AD patients with somatic mutations in cancer susceptibility genes. In addition, cancer recurrence and genetic mutations are correlated with age at diagnosis [345]. To overcome this limitation, large-scale genomic studies are required. Comparing the genetic profiles of cancer patients and AD patients matched for sex, age, and other complications may be a more practical clinical approach to AD treatment. In the current review, we delineate six shared pathological mechanisms of cancer and AD: angiogenesis, mitochondriopathy, proteostasis, protease and cell–cell junctions, transcriptional dysfunction, and dysregulation of the cell cycle. For each mechanism, we identify major mediating genes (Fig. 2). Building on this understanding, we propose that protein–protein interactions and receptor inhibition are strategic therapeutic targets for AD treatment. Furthermore, we provide an overview of the current landscape of AD drug development based on repurposing anticancer drugs, from translational approaches to clinical trials.

Although we suggest that RTKs (i.e., EGFR, PDGFR and VEGFR) are potential targets of anticancer drugs for AD treatment, further studies are required to demonstrate the mechanisms by which novel classes of anticancer agents reduce AD risk. In addition, critical questions remain to be answered before repurposing anticancer drugs for AD treatment. Do nucleic acid-based agents remain stable in the brain? Do anticancer agents cross the BBB? Is the efficacy of anticancer agents targeting specific tissues the same in the brain environment? Moreover, dosages and administration periods should be optimized to minimize adverse effects or toxicity of anticancer drugs in AD treatment. Further preclinical studies addressing the ability of anticancer agents to rescue or prevent AD progression are needed to dissect drug delivery and effector mechanisms and determine cell component- or tissue-specific drug kinetics. In summary, cancer development may be associated with AD progression, and anticancer therapeutics could be strategic theragnostics for AD. Continued investigation of the shared pathways of cancer and AD could lead to the development of clinically approved therapeutics.

Abbreviations

ACC	Adrenocortical carcinoma
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADAM	A disintegrin and metalloprotease
AP-1	Activator protein 1
APOE	Apolipoprotein E
APP	Amyloid precursor protein
BBB	Blood–brain barrier
BRCA1	Breast cancer type 1
CDK	Cyclin-dependent kinase
CML	Chronic myeloid leukemia
CSC	Colon cancer stem cell
CSF	Cerebrospinal fluid
EC	Endothelial cell
ECM	Extracellular matrix

EGFR	Epidermal growth factor receptor
GBM	Glioblastoma multiforme
GIST	Gastrointestinal stromal tumor
HCC	Hepatocellular carcinoma
HER2	Human epidermal growth factor receptor 2
HIF-1a	Hypoxia-inducible factor-1a
MAPK	Mitogen-activated protein kinase
MMP	Matrix metalloproteinase
mTOR	Mammalian target of rapamycin
NFT	Neurofibrillary tangle
NRF2	Nuclear factor erythroid 2-related factor 2
NRP	Neuropilin
NSCLC	Non-small cell lung cancer
PDGFR	Platelet-derived growth factor receptor
PHF	Paired helical filament
PNET	Pancreatic neuroendocrine tumor
PPARγ	Peroxisome proliferator-activated receptor gamma
PPI	Protein–protein interaction
ROS	Reactive oxygen species
SEMA	Semaphorin
TFEB	Transcription factor EB
TJ	Tight junction
TKI	Tyrosine kinase inhibitor
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor α
VEGF	Vascular endothelial growth factor
ZO-1	Zonula occludens-1

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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