Ageing and Cancer Research & Treatment

Science Exploration

Open Access Review

Targeting YWHAG protein: A unified therapeutic strategy against tumors or neurodegenerative diseases

Rui Jing[1], Tongxin Jia[1], Xiang Pan[2], Zhenying Lu[1], Runzi Zheng[1], Jiahua Liu[1], Shuting Jia[1], Jing Liu[1,*]

[1]Laboratory of Molecular Genetics of Aging and Tumor, Medical School, Kunming University of Science and Technology, Kunming 650500, Yunnan, China.
[2]Department of Radiation Oncology Yunnan Cancer Hospital, The Third Affiliated Hospital of Kunming Medical University, Peking University Cancer Hospital Yunnan, Kunming 650118, Yunnan, China.

***Correspondence to:** Jing Liu, Laboratory of Molecular Genetics of Aging and Tumor, Medical School，Kunming University of Science and Technology, Kunming 650500, Yunnan, China. E-mail: jingliu@kust.edu.cn

Received: March 05, 2026 **Accepted:** June 26, 2026 **Published:** June 29, 2026

Cite this article: Jing R, Jia T, Pan X, Lu Z, Zheng R, Liu J, et al. Targeting YWHAG protein: A unified therapeutic strategy against tumors or neurodegenerative diseases. Ageing Cancer Res Treat. 2026;3:202607. https://doi.org/10.70401/acrt.2026.0028

Abstract

YWHAG is a subtype of the 14-3-3 protein family that regulates the transduction of multiple signaling pathways in cells, such as the phosphoinositide 3-kinase–protein kinase B (PI3K-AKT) and mitogen-activated protein kinase (MAPK) pathways, by recognizing and binding to specific phosphorylated target protein motifs. These signaling pathways are widely found to be abnormally activated or shut down in human diseases, such as cancer and neurodegenerative diseases. Different evidence has shown that the expression levels and functions of YWHAG in different tumors are not the same. Meanwhile, the potential functions of YWHAG in these diseases and its role in regulating abnormal signaling pathways are still unknown. Therefore, further exploration and research are needed to determine YWHAG's core role in regulating signaling pathways and whether YWHAG can be a therapeutic target for diseases to develop corresponding drugs. This review will revisit the structure and function of YWHAG, elaborate on the newly identified YWHAG-interacting proteins in recent years, summarize the functions of YWHAG in cancer while comparing it with the homologous family member YWHAZ, explore the functions of YWHAG in neurodegenerative diseases, and present our perspectives on drug-screening strategies targeting YWHAG.

Keywords: 14-3-3 protein, YWHAG, tumors, neurodegenerative, duality, targeted strategies

1. Introduction

The 14-3-3 protein family is a small and highly conserved family that is widely present in eukaryotic cells[1]. Humans have seven genes (YWHAB, YWAHE, YWHAH, YWHAG, YWHAQ, YWHAZ, and SFN) that express seven subtypes (β, ε, η, γ, θ, ζ, and σ)[2,3]. They possess a protein-binding domain that can interact with a large number of proteins and mainly regulate the interactions between target proteins by recognizing and binding to the specific phosphorylated serine/phosphorylated threonine motifs of target proteins, thereby controlling a variety of biological processes[4-6].

YWHAG, also known as 14-3-3γ, is a protein subtype of the 14-3-3 family. Compared with other members of the 14-3-3 family, although YWHAG does not have the highest protein abundance, it has the largest binding spectrum and a higher capacity to bind target proteins, which is why we have chosen to focus on it[3].

YWHAG is widely distributed in multiple tissues and organs, especially in the brain[7]. Accumulating evidence indicates that YWHAG plays an extremely important role in aging-related neurodegenerative diseases. The YWHAG protein has been detected in the cerebrospinal fluid and blood samples of patients with Parkinson's syndrome and Alzheimer's disease; YWHAG is also involved in the pathological aggregates of Tau protein and amyloid protein, which suggests an inseparable relationship between YWHAG and neurodegenerative diseases[8,9]. The review by Sanders *et al.* also mentions that loss or dysfunction of 14-3-3 proteins may accelerate amyloid aggregation and deposition in Parkinson's disease (PD), and that specific isoforms of 14-3-3 proteins have different effects on disease progression versus protection in Alzheimer's disease (AD). This suggests that developing compounds targeting interactions with different 14-3-3 isoforms may have potential therapeutic significance for neurodegenerative diseases[10]. However, the review concludes that relatively few compounds targeting YWHAG interactions have been identified. Here, we aim to summarize recent

compounds targeting YWHAG specifically.

In addition to the above, it has been found that YWHAG is expressed abnormally in a variety of malignant tumors, and it plays completely different roles in different tumor contexts. In most tumors, such as gastric cancer, cervical cancer, and hepatocellular carcinoma, YWHAG is highly expressed and significantly promotes the occurrence and development of tumors[11,12]. In contrast, in uterine fibroid tissues, the expression level of YWHAG is significantly lower than that of the surrounding normal tissues, and overexpression of YWHAG can induce apoptosis of uterine fibroid cells[13]. The above shows that the role of YWHAG in tumors seems to be dual.

This review will focus on YWHAG of the 14-3-3 protein family, discuss its roles and mechanisms in tumors and aging-related neurodegenerative diseases, and analyze the drug-screening strategies targeting YWHAG, laying the foundation for potential therapeutic interventions targeting this key structural protein.

2. The Structure and Function of 14-3-3 Protein

YWHAG has a highly similar protein structure to other members of the 14-3-3 protein family, which is due to the highly conserved nature of the amino acid sequences in the 14-3-3 family. Each 14-3-3 protein is composed of nine antiparallel α-helices, forming a shape like a "crab claw (Figure 1a)". The core of the crab claw is filled with highly conserved amino acid residues, while the relatively less conserved amino acid residues are distributed on the periphery of the protein[14]. 14-3-3 protein can recognize and bind to the phosphorylated serine or threonine residues of target proteins through its conserved core sequence. This recognition pattern is specific and highly regular. 14-3-3 protein mainly recognizes two binding motifs: RSXpSXP and RXY/FXpSXP, and binds to target proteins in a 1:1 manner (Figure 1b)[15-17]. Additionally, the peripheral amino acids confer upon 14-3-3 protein the ability to form homodimers, creating a larger channel to accommodate the target protein (Figure 1c)[14].

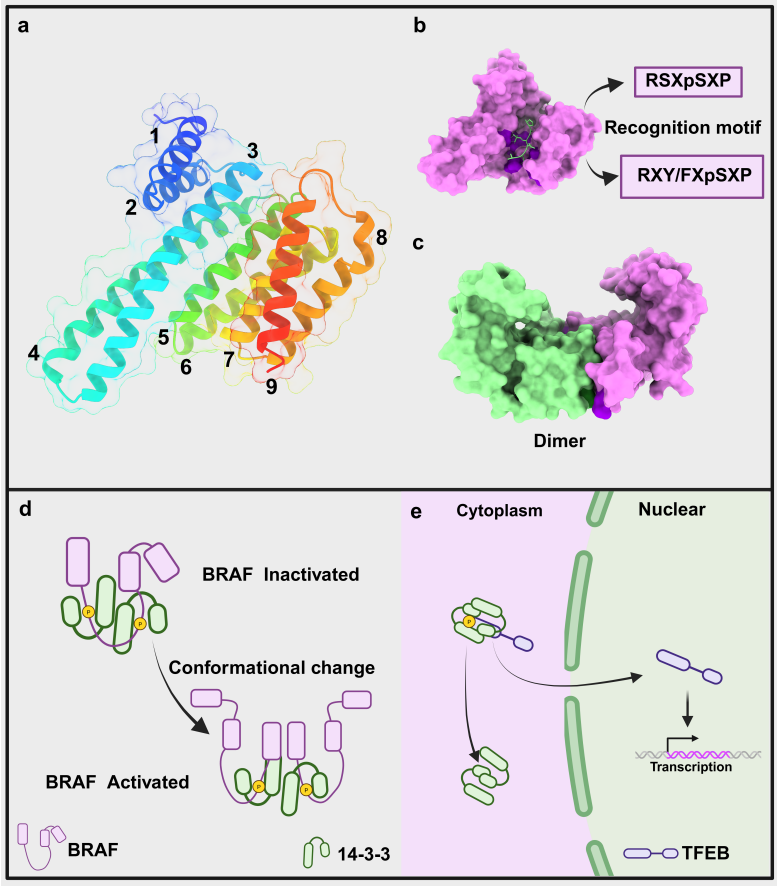

Figure 1. . The structure and function of 14-3-3 protein. (a) 14-3-3 protein possesses nine parallel α-helices; (b) The two primary recognition motifs of 14-3-3 protein; (c) 14-3-3 protein generally presents as a dimer; (d) 14-3-3 protein can bind to target proteins to alter their conformation, thereby affecting target protein activity; (e) 14-3-3 protein can also sequester target proteins to specific cellular locations through binding. (The structure is derived from the article by Xu[20], and the structure was created using ChimeraX[92].) Created in BioRender. Liu, J. (2026) https://app.biorender.com/illustrations/686728f44fbd4d1171df3cdd. TFEB: transcription factor EB.

A deep understanding of the structure of 14-3-3 protein has greatly enhanced our comprehension of its functions. At present, two main functions of 14-3-3 protein have been discovered. The first function is to bind to target proteins and alter their conformations,

thereby exposing or masking sites that can be activated or inhibited. For example, 14-3-3 protein can interact with the B-Raf proto-oncogene, serine/threonine kinase (BRAF) kinase of the mitogen-activated protein kinase (MAPK) family. By binding to the phosphorylated serine at positions 729 and 365 of BRAF, it maintains the auto-inhibited state of BRAF. Alternatively, by releasing the phosphorylated serine at position 365 and only binding to the phosphorylated serine at position 729, it stabilizes the activated conformation of BRAF (Figure 1d)[18].

The second function is to regulate the subcellular localization of target proteins within the cell by binding to them[19]. Recently, Xu *et al.* discovered that 14-3-3 protein interacts with the transcription factor transcription factor EB (TFEB). By sequestering TFEB in the cytoplasm, 14-3-3 protein prevents its entry into the nucleus, thereby inhibiting its transcriptional functions and affecting the occurrence of autophagy (Figure 1e)[20].

In summary, the structure and function of 14-3-3 protein are closely linked. Its unique recognition mode determines that 14-3-3 protein can interact with a considerable number of proteins in the cell. As a "scaffold" structural protein, 14-3-3 protein plays an important role in regulating multiple biological processes within the cell[16].

3. YWHAG Regulates Multiple Biological Processes Through Protein Interactions.

We already know that YWHAG, as a junction protein, can interact with a considerable number of proteins to regulate multiple signaling pathways and a variety of biochemical reactions. For example, earlier studies have shown that YWHAG binds to BRAF kinase and RAF-1 proto-oncogene, serine/threonine kinase (CRAF) kinase in the survival signaling pathway and that this binding not only fully catalyzes the activity of these two kinases but is also critical for their dimerization[21]. In addition, YWHAG interacts with four regulators of the mammalian target of rapamycin (mTOR) complex1 to regulate the level of energy uptake and metabolism of the cell[21]. Recent studies have identified YWHAG as a versatile hub protein that integrates various cellular signals, including cytoskeletal dynamics, the cell cycle, oxidative stress response, and autophagy, through precise spatiotemporal control of protein localization and protein-protein interaction networks.

3.1 Cytoskeleton

YWHAG also interacts with cortactin (CTTN) protein, a cytoplasmic protein that promotes rearrangement of the cytoskeleton involving actin[22]. In addition, CTTN is also associated with vesicle endocytosis and transport[23]. It has been shown that it can co-localize with YWHAG in the cytoplasm and interact with it to perform its biological functions[24]. This also suggests that YWHAG can be involved in the regulation of cytoskeleton and vesicle trafficking (Figure 2a).

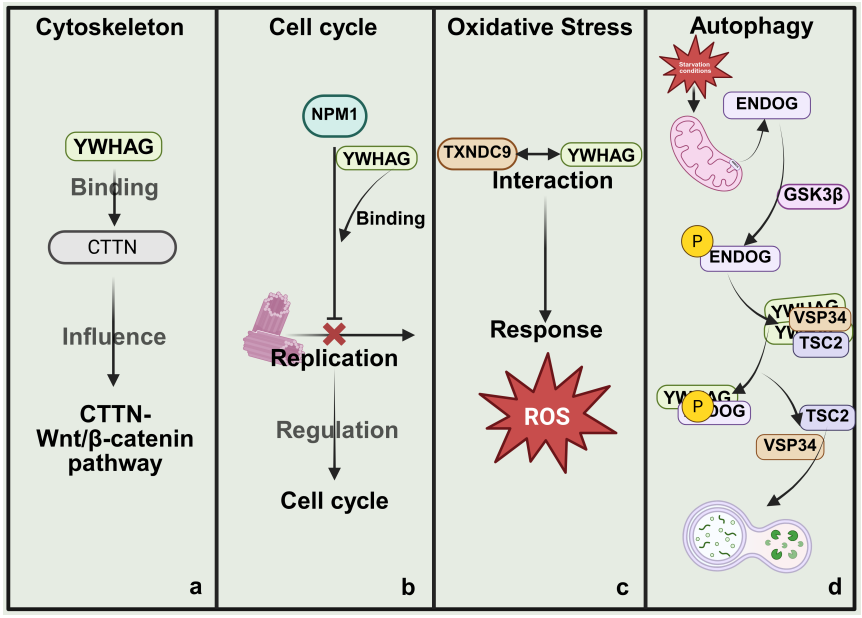

Figure 2. YWHAG regulates multiple biological processes through protein interactions. YWHAG can regulate a considerable number of biological processes, and Figure 2 mainly demonstrates four of them. (a) Autophagy; (b) Oxidative stress response; (c) Cytoskeleton; (d) Cell cycle. Created in BioRender. Liu, J. (2026) https://app.biorender.com/illustrations/686a6afa48147f5f82b3c34f. CTTN: cortactin; NPM1: nucleophosmin 1; TXNDC9: thioredoxin domain containing 9; ENDOG: endonuclease G; GSK3β: glycogen synthase kinase 3 beta; TSC2: tuberous sclerosis complex 2; VSP34: vacuolar protein sorting 34; ROS: reactive oxygen species.

3.2 Cell cycle

Nucleophosmin 1 (NPM1) is a multifunctional nucleolar protein that functions to maintain genome stability and regulate ribosome

biogenesis[25]. It has been demonstrated that the binding of YWHAG and NPM1 inhibits centrosome replication, which may be a new way for YWHAG to regulate centrosome replication and thus the cell cycle (Figure 2b)[26].

3.3 Oxidative stress response

Thioredoxin-containing structural domain 9 (V), also known as phosphorylated protein-like protein 3 (PHLP3), belongs to the small but highly conserved thioredoxin (TRX) family, like YWHAG[27]. The TRX family plays a key role in cellular defense against oxidative stress[28]. Previous studies have shown that thioredoxin domain containing 9 (TXNDC9) can interact directly with Myc proteins and affect the Myc transcriptional network[27]. Now some studies have demonstrated that it can bind to YWHAG, linking between YWHAG and oxidative stress is revealed; but the mechanism of binding is not clear(Figure 2c)[29].

3.4 Autophagy

YWHAG can affect the autophagy pathway by regulating the activity and subcellular localization of autophagy-related proteins. When cells are starved, YWHAG binds to the endonuclease G (ENDOG) released from the mitochondria into the cytosolic matrix. ENDOG, a nuclease mainly located in the mitochondrial intermembrane space, is phosphorylated by GSK3β and interacts with YWHAG in the cytosolic matrix. YWHAG bound to ENDOG dissociates from the originally bound TSC2 and PIK3C3/VPS34, promoting autophagy[30]. Also, YWHAG can keep the phosphorylated transcription factor TFEB in the cytosol, preventing it from entering the nucleus. When TFEB is dephosphorylated, it quickly separates from YWHAG and translocates to the nucleus to promote transcription of autophagy-related genes, thus initiating autophagy[20]. This reflects YWHAG's role in regulating autophagy (Figure 2d).

4. Comparison of the Differential Roles of YWHAZ and YWHAG in Tumors

The 14-3-3 protein family comprises seven members. Although they have different names and tissue distributions, their functions and modes of action appear to exhibit considerable overlap, as evidenced by their relatively conserved binding domains (recognizing similar phosphorylation motifs). Nevertheless, the binding spectra of these seven members are not entirely identical, especially in tumors, where different members play vastly different roles in tumorigenesis[3]. Here, we will discuss how two proteins with the most abundant binding spectra, YWHAZ and YWHAG, influence tumor progression through distinct mechanisms within the same protein family.

YWHAZ is significantly upregulated in various high-incidence malignant tumor tissues, and YWHAZ promotes tumor progression in most cancers. Specifically, high YWHAZ expression promotes tumor progression, correlates with poor prognosis, and is associated with drug resistance.

In digestive system tumors, YWHAZ plays an important role in promoting tumor progression. For example, YWHAZ expression is significantly increased in colorectal cancer (CRC) tissues. YWHAZ can regulate the epithelial-mesenchymal transition (EMT) process in CRC by interacting with thyroid hormone receptor interactor 13 (TRIP13)[31,32]. Additionally, YWHAZ overexpression can induce upregulation of N-cadherin and β-catenin, restoring the invasive ability of tumor cells[32]. Furthermore, in hepatocellular carcinoma (HCC), YWHAZ promotes HCC cell metastasis through the hypoxia-inducible factor 1α (HIF-1α)/EMT signaling pathway by enhancing HIF-1α protein stability[33].

YWHAZ is induced and upregulated in non-small cell lung cancer (NSCLC) tissues and cell lines. YWHAZ can interact with Hsp27 to promote cell proliferation, migration, and invasion[34,35]. Meanwhile, it was found that paclitaxel can stimulate YWHAZ expression, which may be the cause of acquired drug resistance in NSCLC[35]. In breast cancer, tamoxifen increases YWHAZ expression by downregulating miR-451, thereby promoting endocrine resistance in breast cancer cells. Additionally, others found that YWHAZ and LAPTM4B gene amplification jointly promote chemotherapy resistance and recurrence in breast cancer[36].

Compared with YWHAZ, YWHAG exhibits "tissue context-dependent functional inconsistency" in various cancers, meaning that its expression levels do not have a linear relationship with tumor progression. Instead, it shows a dual role in promoting or inhibiting tumors depending on the tumor mutation spectrum and cellular origin.

In osteosarcoma and gastric cancer tissues, YWHAG expression levels are significantly higher than in normal tissues and are associated with poor prognosis[11,37]. Downregulation of YWHAG can inhibit tumor invasion and proliferation. However, in gliomas and uterine leiomyoma, high expression of YWHAG is associated with longer progression-free survival. The differential expression of YWHAG in various tumors indicates its diverse functions according to cancer type[38,39].

Generally, YWHAG exhibits tissue-specific functions and plays either oncogenic or tumor-suppressive roles, depending on the context. For example, YWHAG can enhance the proliferation and migration of pancreatic cancer cells by upregulating the expression of pentose phosphate pathway-related proteins and by regulating the RAF1-ERK signaling pathway to enhance RAF1 phosphorylation[40]. Similarly, YWHAG can also promote bladder cancer cell metastasis by regulating TMOD3 to activate the MAPK pathway[41]. Furthermore, YWHAG upregulation can affect the Wnt/β-catenin signaling pathway by interacting with the CTTN protein, thereby promoting the proliferation and migration of colorectal cancer cells[24]. YWHAG also enhances cell motility by promoting the formation and elongation of pseudopodia, which in turn promotes the migration and invasion of breast cancer cells[42]. Additionally,

high YWHAG expression in lung adenocarcinoma and squamous cell carcinoma interacts with leucine-rich repeat kinase 2 (LRRK2) to activate the PI3K/AKT pathway, promoting EMT and driving NSCLC progression[43,44].

However, in some other tumors, high YWHAG expression inhibits tumor progression. For example, in gliomas, YWHAG is expressed at low levels, possibly due to regulation by certain microRNAs (miRNAs) or molecular sponges. Overexpression of YWHAG in gliomas can suppress glioma metastasis[38,45]. Furthermore, YWHAG protein levels are significantly reduced in human uterine leiomyoma. Knockdown of YWHAG in uterine leiomyoma cells significantly affects the phosphorylation levels of signaling molecules such as AKT, GSK-3β, and Foxo1, and induces cell apoptosis, demonstrating a negative regulatory role of YWHAG in cell survival in uterine leiomyoma[39].

The expression and function of YWHAG in tumors exhibit significant inconsistencies. This variability raises questions about the role of YWHAG in tumor biology and necessitates further investigation to elucidate its potential implications in cancer progression and treatment. Therefore, we used GEPIA2 to analyze YWHAG expression levels in different cancer types from the TCGA database[46]. As shown in Figure 3, compared to adjacent normal tissues, high expression of YWHAG was observed in in lung squamous cell carcinoma (LUSC), pancreatic adenocarcinoma (PAAD), colon adenocarcinoma (COAD), and stomach adenocarcinoma (STAD). Conversely, low expression was detected in glioblastoma multiforme (GBM), Thyroid cancer (THCA), and acute myeloid leukemia (LAML). These findings highlight the variability of YWHAG expression, which is dependent on cancer type. This underscores the necessity for further research to elucidate its role in cancer progression and therapeutic applications.

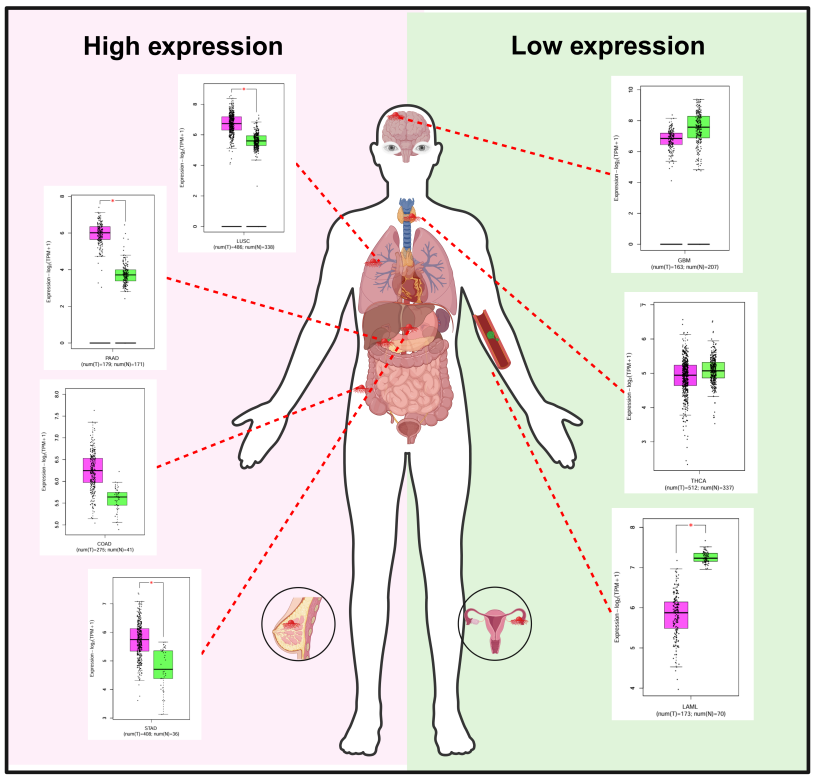

Figure 3. Inconsistency of YWHAG Expression and Function in Tumors. GEPIA2[46] was used to analyze YWHAG expression levels in different cancer types from the TCGA database. The results showed significant tissue specificity. The left side indicates high expression (compared to adjacent normal tissue), including lung squamous cell carcinoma, pancreatic cancer, colon cancer, and gastric cancer; the right side indicates low expression (compared to adjacent normal tissue), including glioma, esophageal cancer, and acute myeloid leukemia. including glioma, Thyroid Carcinoma, and acute myeloid leukemia. In the box plots, magenta indicates tumor tissue, and bright green indicates adjacent normal tissue. Created in BioRender. Liu, J. (2026) https://app.biorender.com/illustrations/686a92258f1a0ff034251a37.

5. YWHAG in Neurodegenerative Diseases

The 14-3-3 protein family was originally named in 1967 during the classification of brain protein systems[47], and it accounts for a large proportion of the soluble proteins in brain tissue[48]. YWHAG can bind to a variety of proteins, such as activity-dependent neuroprotective protein (ADNP), to regulate the formation, maturation, and functional cortical connections of neurites[49]. It also binds to proteins that are closely related to neurodegenerative diseases, including Alzheimer's disease and Parkinson's syndrome.

Alzheimer's disease is one of the most common forms of dementia, characterized by cognitive decline. Its typical pathological features include hippocampal and cerebral cortex atrophy due to neuronal loss[50,51]. Researchers conducted proteomic sequencing of

cerebrospinal fluid obtained from patients with AD. The protein YWHAG exhibited significant differences in expression levels between AD patients and control subjects, with the most pronounced upregulation observed in the former group[8,52]. YWHAG may serve as a hub for protein-protein interactions in Alzheimer's disease and demonstrated strong accuracy in combined predictive diagnostic tests for Alzheimer's disease, indicating that YWHAG could serve as a novel diagnostic biomarker for Alzheimer's disease[52,53]. The possible mechanism is that high YWHAG expression increases tau protein phosphorylation (p-tau), leading to tau protein neurofibrillary tangles and ultimately inducing cognitive impairment[54].

Parkinson's syndrome is characterized by memory decline and impaired mobility[55]. In the brains of Parkinson's patients, dopaminergic neurons contain a large number of Lewy bodies and Lewy neurites, whose fibrillar aggregates, primarily composed of α-synuclein (aSyn), are considered one of the pathological hallmarks of the disease. As early as 1999, Ostrerova *et al.* first reported the co-immunoprecipitation of α-synuclein and 14-3-3 protein in mammalian brain, suggesting a direct physical interaction between the two[56]. Subsequent studies by Kawamoto *et al.* and Berg *et al.* confirmed that 14-3-3 protein coexists with α-synuclein in Lewy bodies in the substantia nigra and brainstem regions of PD patients, suggesting that 14-3-3 protein may be involved in the pathological process of PD[47,57]. Studies have shown that soluble 14-3-3 protein levels are decreased in the brain tissue of PD patients, while phosphorylation levels of 14-3-3 proteins in the insoluble fraction are increased[58]. This alteration in post-translational modification may affect the normal function of 14-3-3 proteins, possibly because α-synuclein binds to 14-3-3, preventing 14-3-3 from interacting with its normal substrates, thereby weakening the neuroprotective function of 14-3-3 proteins and contributing to neurodegenerative processes.

As the isoform of 14-3-3 protein with the largest binding spectrum, the binding of YWHAG to key proteins in PD has also attracted much attention[3]. For example, LRRK2 is the most common autosomal dominant causative gene for PD, and various PD-associated LRRK2 mutations (such as G2019S, R1441G/C/H, Y1699C, etc.) can disrupt the binding between YWHAG proteins and LRRK2. This disruption of interaction leads to abnormal accumulation of LRRK2 in the cytoplasm, dysregulation of kinase activity, and consequently promotes neurodegeneration[59,60].

Additionally, a study measured plasma YWHAG levels in both healthy individuals and Parkinson's disease patients. The results showed that plasma YWHAG was significantly elevated in Parkinson's patients. Furthermore, diagnostic prediction of Parkinson's disease was performed based on cognitive impairment scores and YWHAG levels, with prediction results demonstrating the powerful efficacy of YWHAG in distinguishing Parkinson's patients. These findings suggest that YWHAG may serve as a promising biomarker for cognitive impairment in PD[9,61].

6. Strategies of Pharmacological Targeting of YWHAG

In the preceding discussion, we examined the roles of YWHAG in tumors and neurodegenerative diseases, highlighting its potential as a therapeutic target for these conditions. This section will summarize the current strategies aimed at targeting YWHAG, which encompass natural products, miRNA, molecular glue, and various other approaches.

6.1 Natural products

Natural products and their derivatives play an important role in the treatment of diseases such as cancer. However, research on natural products targeting YWHAG is relatively limited[62].

Curcumol, a sesquiterpene natural product from the family of ginger plants[63], has been shown to reduce YWHAG expression in human cervical cancer cells, thereby inhibiting their proliferation. Moreover, curcumol can significantly enhance the sensitivity of human cervical cancer cells to apoptosis induced by cisplatin chemotherapy[64]. This combined treatment may address the problem of chemotherapy resistance in clinical practice. However, so far, curcumol has only been tested for drug activity in cells and animal models. There is still a gap in its systematic pharmacokinetics and clinical validation, and further research is needed.

Existing literature shows that corn silk has a significant effect in the treatment of gout caused by hyperuricemia[65]. Ethyl linoleate is an active product identified from corn silk. Studies using molecular docking have shown that ethyl linoleate can bind significantly with YWHAG[66], suggesting that YWHAG may be a target for the treatment of gout by ethyl linoleate.

6.2 miRNA

As small non-coding RNAs, miRNAs can regulate protein-coding genes post-transcriptionally, thereby increasing or decreasing the expression levels of proteins[67].

The abnormal expression of miRNAs in various diseases also makes it possible to treat related diseases by supplementing or removing the crucial miRNAs for the diseases[68]. Currently, the number of miRNAs or miRNA mimics that have been included in clinical trials is still very limited, which may be due to the difficulty in resolving off-target effects[67]. Similarly, miRNAs targeting YWHAG have been even less studied, but there are still some miRNAs targeting YWHAG that may become strong candidates for treating YWHAG - related diseases (Table 1).

Table 1. Some miRNAs targeting YWHAG other 14-3-3 subtypes in different diseases.

miRNA	Bckground disease	Supplement /Remove	Affect the expression of YWHAG	Therapeutic effect	Refs
miR-222	Osteosarcoma	supplement	Down-regulation	Inhibit cell proliferation and invasion	[37]
miR-182	Esophageal squamous cell carcinoma	remove	Up-regulation	Suppressive cell growth and metastasis.	[93]
miR-199a-3p	Hepatocellular carcinoma	Supplement	Down-regulation	Suppressed HCC progression	[94]
miR-509-5p	non-small lung cancer	supplement	Down-regulation	Inhibited the proliferation, migration, invasion	[95]
miR-181b-3p	Breast cancer	remove	Up-regulation	Promotes EMT	[96]
miR-217	Glioma	remove	Up-regulation	Suppressed the viability and mitosis	[38]
miR-200c	Alzheimer	supplement	Down-regulation	Inhibit cognitive impairment.	[54]
miR-30-5p	Cerebral ischemia/reperfusion injury	remove	Up-regulation	Protective neural injury	[97]
miR-217-5p	Pancreatic cancer	Supplement	Down-regulation	Inhibited proliferation and metastasis	[40]
Some miRNAs targeting other 14-3-3 subtypes in different diseases					
miR-217-5p14-3-3ζ	Pancreatic cancer	Supplement	Down-regulation	Inhibited proliferation and metastasis	[40]
miR-200cYWHAZ	Pan-cancer	supplement	Down-regulation	promotes epithelial gene expression and suppresses cell invasion	[98]

miRNAs: microRNAs; HCC: hepatocellular carcinoma; EMT: epithelial-mesenchymal transition.

6.3 Molecular glue

Molecular glues, initially considered as small molecules that can induce new binding interactions between proteins[69]. Nowadays, molecular glues can also be regarded as small molecule compounds that bind at the protein-protein interface to stabilize or enhance binding, and may become a powerful approach to addressing the issue of "undruggable" targets[70]. The 14-3-3 protein does not have the traditional enzyme activity and relies solely on its interaction with target proteins to regulate their localization and activity. When the binding of 14-3-3 protein to target proteins is conducive to the treatment of certain diseases, molecular glues may represent a novel approach to targeting proteins that interact with the 14-3-3 protein.

For example, the treatment of estrogen receptor alpha (ERα)-positive breast cancer primarily utilizes tamoxifen to inhibit tumor progression by suppressing the transcriptional activity of ERα. Studies have shown that the 14-3-3 protein can interact with the phosphorylated threonine (p-Thr594) at the C-terminus of the dimerized ERα receptor, leading to the sequestration of the ERα receptor and the inhibition of its transcriptional function[71]. Markella *et al.* exploited this unique regulatory mechanism and developed a scaffold-hopping approach for optimizing small-molecule compounds based on the Groebke-Blackburn-Bienaymé multi-component reaction. They optimized the known compound 127, which binds at the interface of the two proteins, and the optimized compound significantly stabilized the binding of the 14-3-3 protein and the ERα receptor at lower concentrations[70]. Such molecular glues can provide a new therapeutic approach for breast cancer. However, further validation of the compound is still needed at the cellular level and even *in vivo*.

In addition, Liora *et al.* based their work on the carbohydrate response element binding protein alpha (ChREBPα), a glucose-responsive transcription factor that, when bound to 14-3-3 protein, is sequestered in the cytoplasm and unable to enter the nucleus to perform its transcriptional function, namely, inducing the expression of another splice variant, ChREBPβ, which leads to the death of insulin-secreting β-cells. They carried out structural optimization of compound "1", which stabilizes the 14-3-3/ChREBPα complex, resulting in a potent stabilizer of the ChREBPα/14-3-3 protein interaction. This compound was validated in cells and effectively protected pancreatic β-cells from the effects of glucolipotoxicity. This work provides a foundation for the treatment of type 2 diabetes[72].

As a scaffold protein, YWHAG features a flat and highly dynamic interface with its client proteins, making it difficult to optimize through traditional structure-activity relationship approaches[73]. Additionally, the 14-3-3 family is highly homologous, making molecular glues prone to cross-reactivity with other isoforms and leading to off-target effects[70]. YWHAG has hundreds of client proteins, and non-selective stabilization may simultaneously activate multiple pathways, causing toxicity. Pathogenic mutations in YWHAG alter protein surface charge and conformation, rendering wild-type molecular glues potentially ineffective against mutant variants, necessitating the development of "personalized" molecular glues targeting specific mutations[74]. Diseases associated with YWHAG require drugs to effectively penetrate the blood-brain barrier; although molecular glues have relatively small molecular weights, their polarity is often high, and central nervous system (CNS) permeability still needs optimization[75]. Long-term inhibition of YWHAG function may lead to compensatory pathway activation, and differences in E3 ligase expression levels across tissues may affect degradation efficiency[53]. Molecular glues may become a powerful regulatory tool for the unique target of 14-3-3 protein, but it is still necessary to comprehensively evaluate the feasibility and biosafety of molecular glues *in vivo*.

7. Discussion

The role of YWHAG in tumors exhibits significant tissue-specific duality, and this dual role provides important clues for understanding tumor heterogeneity and developing precision treatment strategies. In most solid tumors, YWHAG expression is upregulated and positively correlated with tumor malignancy, metastasis, and poor prognosis[76,77]. YWHAG promotes tumor cell progression by participating in the activation of multiple pro-oncogenic signaling pathways. However, in other tumors, YWHAG exhibits tumor suppressor functions. This diametrically opposite effect suggests that the function of YWHAG is highly dependent on tissue-specific contexts. Future research needs to deeply analyze the differences in YWHAG interactomes across different tumor types and truly understand the biological functions of YWHAG and other 14-3-3 proteins in different tissues, rather than focusing solely on this single but uncertain binding function.

The role of YWHAG in neurodegenerative diseases also exhibits complexity and diversity. In Parkinson's disease, insufficient YWHAG function can lead to dopaminergic system dysfunction and PD-like phenotypes, suggesting a neuroprotective role for YWHAG[78,79]. However, in the cerebrospinal fluid of Alzheimer's disease patients, YWHAG expression levels increase with cognitive decline, and the YWHAG:NPTX2 ratio may serve as a novel biomarker for predicting cognitive deterioration[80]. These differential expression patterns may reflect the unique pathological mechanisms of different neurodegenerative diseases, or may indicate distinct roles of YWHAG at different disease stages. Future research should systematically investigate the effects of altered YWHAG expression on neuronal development, synapse formation, and functional maintenance, and to precisely elucidate its physiological and pathological functions.

Cancer neuroscience is an emerging frontier interdisciplinary field in recent years, investigating the bidirectional interactions between the nervous system and tumors. Accumulating evidence indicates that neural signals can promote tumor growth, invasion, and metastasis, while tumors can also remodel neural circuits, forming a vicious cycle[81-84]. YWHAG plays important roles in both tumors and the nervous system, raising the question of whether YWHAG also plays a significant role in tumor-associated neurogenesis. For example, the LRRK2 protein plays a crucial role in exosome secretion[84-86]; whether YWHAG in tumors could influence exosome secretion by regulating LRRK2 to induce tumor neurogenesis remains to be explored[84]. However, the field faces significant research bottlenecks, including the extreme complexity of neural-tumor interactions where different nerve types may exert opposite effects depending on tumor type and disease stage, as well as technical limitations due to insufficient spatiotemporal resolution and loss of electrophysiological activity information during sample preparation, making it difficult to capture dynamic interactions. Additionally, challenges in translating findings from animal models to humans are hindered by species differences in neural subtype distribution and neurotransmitter receptor expression patterns[89-91]. Clinical translation is further impeded by lagging biomarker development, as parameters such as nerve invasion burden, innervation density, and tissue or serum norepinephrine concentrations lack standardized detection methods and prospective validation in large cohorts. The dynamic plasticity of neural and immune components during treatment further complicates biomarker development, and patient heterogeneity means that even within the same tumor type, individuals exhibit significant differences in innervation patterns and immune microenvironment characteristics[90].

Due to the lack of enzymatic active sites in YWHAG, traditional enzyme inhibitor design strategies are not applicable. RNA technologies such as microRNA provide effective means to directly reduce YWHAG expression. Key challenges for microRNA-based therapeutic strategies targeting YWHAG include developing efficient *in vivo* delivery systems to ensure effective accumulation of RNA molecules in target tissues, optimizing miRNA sequences, designing tissue-specific delivery strategies to achieve specific silencing of YWHAG, and avoiding off-target effects.

Molecular glues are also an effective means of intervention for proteins like 14-3-3 that primarily function through interactions. In some diseases, it is precisely because the binding of 14-3-3 proteins to disease-related proteins is unstable or lost that the structure, localization, and activity of disease-related proteins become unstable, ultimately leading to the onset of disease[60,70]. For example, the instability of cystic fibrosis transmembrane conductance regulator (CFTR) activity is the main cause of cystic fibrosis, and the binding of 14-3-3 proteins can stabilize its activity. Loes and colleagues reported that a macrocycle can stabilize the 14-3-3/CFTR complex, thereby improving cystic fibrosis[91,92]. Finding or synthesizing molecular glues that can enhance the binding strength between 14-3-3

proteins and client proteins is a direction for future research.

Declarations

Authors contribution

Liu J, Jia S: Conceptualization, methodology.
Jing R: Visualization, writing-original draft.
Jia T, Lu Z: Visualization, writing-review & editing.
Liu J, ZhengR: Formal analysis.
Pan X: Visualization.
All authors have confirmed that they have reviewed the manuscript.

Conflicts of interest

Jing Liu is a Youth Editorial Board member of *Ageing and Cancer Research & Treatment*. The other authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This study was supported by grants from the National Natural Science Foundation of China (Grant No. 82060660 to J.L). J.L are supported by the Yunnan Revitalization Talent Support Program Young Talent Project (XDYC-QNRC-2022-0285).

References

1. Sheikh AH, Zacharia I, Tabassum N, Hirt H, Ntoukakis V. 14-3-3 proteins as a major hub for plant immunity. Trends Plant Sci. 2024;29(11):1245-1253. [DOI]
2. Inamdar SM, Lankford CK, Laird JG, Novbatova G, Tatro N, Whitmore SS, et al. Analysis of 14-3-3 isoforms expressed in photoreceptors. Exp Eye Res. 2018;170:108-116. [DOI][PubMed][PMC]
3. Gogl G, Tugaeva KV, Eberling P, Kostmann C, Trave G, Sluchanko NN. Hierarchized phosphotarget binding by the seven human 14-3-3 isoforms. Nat Commun. 2021 Mar 15;12(1):1677. [DOI][PubMed][PMC]
4. Darling DL, Yingling J, Wynshaw-Boris A. Role of 14-3-3 proteins in eukaryotic signaling and development. Curr Top Dev Biol. 2005;68:281-315. [DOI]
5. Hwang Y, An HT, Kang M, Ko J. Roles of 14-3-3β and γ in regulation of the glucocorticoid receptor transcriptional activation and hepatic gluconeogenesis. Biochem Biophys Res Commun. 2018;501(3):800-806. [DOI]
6. Aitken A. 14-3-3 proteins: A historic overview. Semin Cancer Biol. 2006;16(3):162-172. [DOI]
7. Martin H, Rostas J, Patel Y, Aitken A. Subcellular localisation of 14-3-3 isoforms in rat brain using specific antibodies. J Neurochem. 1994;63(6):2259-2265. [DOI][PubMed]
8. Guo Y, Chen SD, You J, Huang SY, Chen YL, Zhang Y, et al. Multiplex cerebrospinal fluid proteomics identifies biomarkers for diagnosis and prediction of Alzheimer's disease. Nat Hum Behav. 2024;8(10):2047-2066. [DOI]
9. Peng Y, Zhu L, Bai Q, Wang L, Li Q. Serum level of YWHAG as a diagnostic marker of cognitive impairment in Parkinson's disease patients. Acta Neurol Belg. 2024;124(3):879-885. [DOI][PubMed][PMC]
10. Pair FS, Yacoubian TA. 14-3-3 proteins: Novel pharmacological targets in neurodegenerative diseases. Trends Pharmacol Sci. 2021;42(4):226-238. [DOI]
11. Ni J, Wang J, Fu Y, Yan C, Zhu M, Jiang Y, et al. Functional genetic variants in centrosome-related genes *CEP72* and YWHAG confer

susceptibility to gastric cancer. Arch Toxicol. 2020;94(8):2861-2872. [DOI][PubMed]
12. Jin T, Yin T, Xu R, Liu H, Yuan S, Xue Y, et al. Exploring the role of disulfidptosis-related signatures in immune microenvironment, prognosis and therapeutic strategies of cervical cancer. Transl Oncol. 2024;44:101938. [DOI][PubMed][PMC]
13. Jiang W, Luo H, Shen Z, Zhang W, Chen A, Zhu X. Down-regulation and gene hypermethylation of the 14-3-3 gamma in uterine leiomyoma. Front Biosci. 2016;21(6):1286-1295. [DOI][PubMed]
14. Xiao B, Smerdon SJ, Jones DH, Dodson GG, Soneji Y, Aitken A, et al. Structure of a 14-3-3 protein and implications for coordination of multiple signalling pathways. Nature. 1995;376(6536):188-191. [DOI][PubMed]
15. Yaffe MB, Rittinger K, Volinia S, Caron PR, Aitken A, Leffers H, et al. The structural basis for 14-3-3: Phosphopeptide binding specificity. Cell. 1997;91(7):961-971. [DOI]
16. Tzivion G, Shen YH, Zhu J. 14-3-3 proteins; bringing new definitions to scaffolding. Oncogene. 2001;20(44):6331-6338. [DOI]
17. Psenakova K, Petrvalska O, Kylarova S, Lentini Santo D, Kalabova D, Herman P, et al. 14-3-3 protein directly interacts with the kinase domain of calcium/calmodulin-dependent protein kinase kinase (CaMKK2). Biochim Biophys Acta Gen Subj. 2018;1862(7):1612-1625. [DOI][PubMed]
18. Park E, Rawson S, Li K, Kim BW, Ficarro SB, Pino GG, et al. Architecture of autoinhibited and active BRAF-MEK1-14-3-3 complexes. Nature. 2019;575(7783):545-550. [DOI][PubMed][PMC]
19. Muslin AJ, Xing H. 14-3-3 proteins: Regulation of subcellular localization by molecular interference. Cell Signal. 2000;12(11-12):703-709. [DOI][PubMed]
20. Xu Y, Ren J, He X, Chen H, Wei T, Feng W. YWHA/14-3-3 proteins recognize phosphorylated TFEB by a noncanonical mode for controlling TFEB cytoplasmic localization. Autophagy. 2019;15(6):1017-1030. [DOI][PubMed][PMC]
21. Morrison DK. The 14-3-3 proteins: Integrators of diverse signaling cues that impact cell fate and cancer development. Trends Cell Biol. 2009;19(1):16-23. [DOI][PubMed][PMC]
22. Dumitru CA, Bankfalvi A, Gu X, Eberhardt WE, Zeidler R, Lang S, et al. Neutrophils activate tumoral CORTACTIN to enhance progression of orohypopharynx carcinoma. Front Immunol. 2013;4:33. [DOI][PubMed][PMC]
23. Ammer AG, Weed SA. Cortactin branches out: Roles in regulating protrusive actin dynamics. Cell Motil Cytoskeleton. 2008;65(9):687-707. [DOI][PubMed][PMC]
24. Wang Y, Cao Y, Chen Y, Cheng H, Liu Z, Wang M, et al. YWHAG promotes colorectal cancer progression by regulating the CTTN-Wnt/β-catenin signaling axis. Med Oncol. 2024;41(5):100. [DOI][PubMed][PMC]
25. Grisendi S, Mecucci C, Falini B, Pandolfi PP. Nucleophosmin and cancer. Nat Rev Cancer. 2006;6(7):493-505. [DOI]
26. Bose A, Modi K, Dey S, Dalvi S, Nadkarni P, Sudarshan M, et al. 14–3-3γ prevents centrosome duplication by inhibiting NPM1 function. Genes Cells. 2021;26(6):426-446. [DOI]
27. Chen D, Zou J, Zhao Z, Tang X, Deng Z, Jia J, et al. TXNDC9 promotes hepatocellular carcinoma progression by positive regulation of MYC-mediated transcriptional network. Cell Death Dis. 2018;9(11):1110. [DOI][PubMed][PMC]
28. Lu J, Holmgren A. The thioredoxin antioxidant system. Free Radic Biol Med. 2014;66:75-87. [DOI]
29. Wang J, Pan X, Li J, Zhao J. TXNDC9 knockdown inhibits lung adenocarcinoma progression by targeting YWHAG. Mol Med Rep. 2022;25(6):203. [DOI][PubMed][PMC]
30. Wang W, Li J, Zhou Q. The biological function of cytoplasm-translocated ENDOG (endonuclease G). Autophagy. 2024;20(2):445-447. [DOI][PubMed][PMC]
31. Sheng N, Yan L, Wu K, You W, Gong J, Hu L, et al. TRIP13 promotes tumor growth and is associated with poor prognosis in colorectal cancer. Cell Death Dis. 2018;9(3):402. [DOI][PubMed][PMC]
32. Du G, Yu X, Chen Y, Cai W. miR-1-3p suppresses colorectal cancer cell proliferation and metastasis by inhibiting YWHAZ-mediated epithelial-mesenchymal transition. Front Oncol. 2021;11:634596. [DOI][PubMed][PMC]
33. Tang Y, Liu S, Li N, Guo W, Shi J, Yu H, et al. 14-3-3ζ promotes hepatocellular carcinoma venous metastasis by modulating hypoxia-inducible factor-1α. Oncotarget. 2016;7(13):15854-15867. [DOI][PubMed][PMC]
34. Dong N, Gu WW, Yang L, Lian WB, Jiang J, Zhu HJ, et al. miR-3074-5p suppresses non-small cell lung cancer progression by targeting the YWHAZ/Hsp27 axis. Int Immunopharmacol. 2024;138:112547. [DOI][PubMed]
35. Zhao GY, Ding JY, Lu CL, Lin ZW, Guo J. The overexpression of 14-3-3ζ and Hsp27 promotes non–small cell lung cancer progression. Cancer. 2014;120(5):652-663. [DOI][PubMed]
36. Li Y, Zou L, Li Q, Haibe-Kains B, Tian R, Li Y, et al. Amplification of LAPTM4B and YWHAZ contributes to chemotherapy resistance and recurrence of breast cancer. Nat Med. 2010;16(2):214-218. [DOI][PubMed][PMC]
37. Chu YW, Wang CR, Weng FB, Yan ZJ, Wang C. microRNA-222 contributed to cell proliferation, invasion and migration via regulating YWHAG in osteosarcoma. Eur Rev Med Pharmacol Sci. 2018;22(9):2588-2597. [DOI][PubMed]
38. Zheng Y, Miao Y, Xie J, Lin Y, Yao Q, Cai J, et al. Long noncoding RNA lysophospholipase-like 1-2 as ceRNA modulates glioma metastasis by regulating miR-217/YWHAG. Am J Transl Res. 2020;12(8):4204-4215. [PubMed][PMC]
39. Shen Q, Hu X, Zhou L, Zou S, Sun LZ, Zhu X. Overexpression of the 14-3-3γ protein in uterine leiomyoma cells results in growth retardation and increased apoptosis. Cell Signal. 2018;45:43-53. [DOI][PubMed]
40. Xu J, Wang J, He Z, Chen P, Jiang X, Chen Y, et al. LncRNA CERS6-AS1 promotes proliferation and metastasis through the upregulation of YWHAG and activation of ERK signaling in pancreatic cancer. Cell Death Dis. 2021;12(7):648. [DOI][PubMed][PMC]
41. Tian T, He S, Hao H, Guan B, Gong Y, Fan J, et al. YWHAG promotes bladder cancer metastasis by regulating TMOD3 to activate ERK1/2

and JNK phosphorylation in the MAPK pathway. J Transl Med. 2024;22(1):1159. [DOI][PubMed][PMC]
42. Hiraoka E, Mimae T, Ito M, Kadoya T, Miyata Y, Ito A, et al. Breast cancer cell motility is promoted by 14-3-3γ. Breast Cancer. 2019;26(5):581-593. [DOI]
43. Liu K, Han H, Huang S, Song L, Jiang J, Zheng D. YWHAG mediated epithelial-mesenchymal transition facilitates tumor progression and metastatic spread in non-small cell lung cancer. Cell Signal. 2025;136:112139. [DOI][PubMed]
44. Zheng H, Tang Y, Zang H, Luo J, Zhou H, Zou Y, et al. YWHAG promotes the progression of lung adenocarcinoma through the JAK2/STAT3 pathway. Cancer Cell Int. 2025;25(1):112. [DOI][PubMed][PMC]
45. Huang R, Kong Y, Luo Z, Li Q. LncRNA NDUFA6-DT: A comprehensive analysis of a potential LncRNA biomarker and its regulatory mechanisms in gliomas. Genes. 2024;15(4):483. [DOI][PubMed][PMC]
46. Tang Z, Kang B, Li C, Chen T, Zhang Z. GEPIA2: An enhanced web server for large-scale expression profiling and interactive analysis. Nucleic Acids Res. 2019;47(W1):W556-W560. [DOI][PubMed][PMC]
47. Berg D, Holzmann C, Riess O. 14-3-3 proteins in the nervous system. Nat Rev Neurosci. 2003;4(9):752-762. [DOI]
48. Boston PF, Jackson P, Thompson RJ. Human 14-3-3 protein: Radioimmunoassay, tissue distribution, and cerebrospinal fluid levels in patients with neurological disorders. J Neurochem. 1982;38(5):1475-1482. [DOI][PubMed]
49. Bennison SA, Blazejewski SM, Liu X, Hacohen-Kleiman G, Sragovich S, Zoidou S, et al. The cytoplasmic localization of ADNP through 14-3-3 promotes sex-dependent neuronal morphogenesis, cortical connectivity, and calcium signaling. Mol Psychiatry. 2023;28(5):1946-1959. [DOI][PubMed][PMC]
50. Khan S, Barve KH, Kumar MS. Recent advancements in pathogenesis, diagnostics and treatment of Alzheimer's disease. Curr Neuropharmacol. 2020;18(11):1106-1125. [DOI]
51. Twarowski B, Herbet M. Inflammatory processes in Alzheimer's disease: Pathomechanism, diagnosis and treatment: A review. Int J Mol Sci. 2023;24(7):6518. [DOI]
52. Sathe G, Na CH, Renuse S, Madugundu AK, Albert M, Moghekar A, et al. Quantitative proteomic profiling of cerebrospinal fluid to identify candidate biomarkers for Alzheimer's disease. Proteomics Clinical Apps. 2019;13(4):1800105. [DOI]
53. Do AN, Ali M, Timsina J, Wang L, Western D, Liu M, et al. CSF proteomic profiling with amyloid/tau positivity identifies distinctive sex-different alteration of multiple proteins involved in Alzheimer's disease. MedRxiv [Preprint]. 2024. [DOI]
54. Park H, Lee YB, Chang KA. miR-200c suppression increases tau hyperphosphorylation by targeting 14-3-3γ in early stage of 5xFAD mouse model of Alzheimer's disease. Int J Biol Sci. 2022;18(5):2220-2234. [DOI][PubMed][PMC]
55. Hayes MT. Parkinson's disease and Parkinsonism. Am J Med. 2019;132(7):802-807. [DOI]
56. Ostrerova N, Petrucelli L, Farrer M, Mehta N, Choi P, Hardy J, et al. Alpha-Synuclein shares physical and functional homology with 14-3-3 proteins. J Neurosci. 1999;19(14):5782-5791. [DOI][PubMed][PMC]
57. Kawamoto Y, Akiguchi I, Nakamura S, Honjyo Y, Shibasaki H, Budka H. 14-3-3 proteins in lewy bodies in Parkinson disease and diffuse lewy body disease brains. J Neuropathol Exp Neurol. 2002;61(3):245-253. [DOI]
58. McFerrin MB, Chi X, Cutter G, Yacoubian TA. Dysregulation of 14-3-3 proteins in neurodegenerative diseases with Lewy body or Alzheimer pathology. Ann Clin Transl Neurol. 2017;4(7):466-477. [DOI]
59. Nichols RJ, Dzamko N, Morrice NA, Campbell DG, Deak M, Ordureau A, et al. 14-3-3 binding to LRRK2 is disrupted by multiple Parkinson's disease-associated mutations and regulates cytoplasmic localization. Biochem J. 2010;430(3):393-404. [DOI][PubMed][PMC]
60. Martinez Fiesco JA, Beilina A, Alvarez de la Cruz A, Li N, Metcalfe RD, Cookson MR, et al. 14-3-3 binding maintains the Parkinson's associated kinase LRRK2 in an inactive state. Nat Commun. 2025;16:7226. [DOI]
61. George G, Valiya Parambath S, Lokappa SB, Varkey J. Construction of Parkinson's disease marker-based weighted protein-protein interaction network for prioritization of co-expressed genes. Gene. 2019;697:67-77. [DOI][PubMed]
62. Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. Natural products in drug discovery: Advances and opportunities. Nat Rev Drug Discov. 2021;20(3):200-216. [DOI]
63. Li J, Sun Y, Li G, Cheng C, Sui X, Wu Q. The extraction, determination, and bioactivity of curcumenol: A comprehensive review. Molecules. 2024;29(3):656. [DOI][PubMed][PMC]
64. Mao Z, Zhong L, Zhuang X, Liu H, Peng Y. Curcumenol targeting YWHAG inhibits the pentose phosphate pathway and enhances antitumor effects of cisplatin. Evid Based Complement Alternat Med. 2022;2022:3988916. [DOI][PubMed][PMC]
65. Oyabambi AO, Areola ED, Olatunji LA, Soladoye AO. Uric acid is a key player in salt-induced endothelial dysfunction: The therapeutic role of *Stigma maydis* (corn silk) extract. Appl Physiol Nutr Metab. 2020;45(1):67-71. [DOI][PubMed]
66. Zhang H, Jiang H, Zhao M, Xu Y, Liang J, Ye Y, et al. Treatment of gout with TCM using turmeric and corn silk: A concise review article and pharmacology network analysis. Evid Based Complementary Altern Med. 2022;2022:3143733. [DOI]
67. Diener C, Keller A, Meese E. Emerging concepts of miRNA therapeutics: From cells to clinic. Trends Genet. 2022;38(6):613-626. [DOI]
68. Huang W. microRNAs: biomarkers, diagnostics, and therapeutics. In: Huang J, Borchert GM, Dou D, Huan J, Lan W, Tan M, Wu B, editors. Bioinformatics in microRNA research. New York: Springer; 2017. p. 57-67. [DOI]
69. Schreiber SL, Crabtree GR. The mechanism of action of cyclosporin A and FK506. Immunol Today. 1992;13(4):136-142. [DOI]
70. Konstantinidou M, Zingiridis M, Pennings MAM, Fragkiadakis M, Virta JM, Revalde JL, et al. Scaffold-hopping for molecular glues targeting the 14-3-3/ERα complex. Nat Commun. 2025;16:6467. [DOI]
71. De Vries-van Leeuwen IJ, da Costa Pereira D, Flach KD, Piersma SR, Haase C, Bier D, et al. Interaction of 14-3-3 proteins with the estrogen receptor alpha F domain provides a drug target interface. Proc Natl Acad Sci U S A. 2013;110(22):8894-8899. [DOI][PubMed][PMC]

72. Katz LS, Visser EJ, Plitzko KF, Pennings MAM, Cossar PJ, Tse IL, et al. Molecular glues of the regulatory ChREBP/14-3-3 complex protect beta cells from glucolipotoxicity. Nat Commun. 2025;16(1):2110. [DOI][PubMed][PMC]
73. Liu Y, Bai J, Li D, Cang Y. Routes to molecular glue degrader discovery. Trends Biochem Sci. 2025;50(2):134-142. [DOI]
74. Larasati YA, Solis GP, Koval A, Korff C, Katanaev VL. A personalized 14-3-3 disease-targeting workflow yields repositioning drug candidates. Cells. 2025;14(8):559. [DOI][PubMed][PMC]
75. Kay DF, Raza HG, Doveston RG, Leney AC. Hydrogen-deuterium exchange mass spectrometry for molecular glue characterization. Adv Sci. 2025;12(41):e08543. [DOI][PubMed][PMC]
76. Lee JXT, Tan WR, Low ZS, Lee JQ, Chua D, Yeo WDC, et al. YWHAG deficiency disrupts the EMT-associated network to induce oxidative cell death and prevent metastasis. Adv Sci. 2023;10(31):e2301714. [DOI][PubMed][PMC]
77. Raungrut P, Wongkotsila A, Champoochana N, Lirdprapamongkol K, Svasti J, Thongsuksai P. Knockdown of 14-3-3γ suppresses epithelial–mesenchymal transition and reduces metastatic potential of human non-small cell lung cancer cells. Anticancer Res. 2018;38(6):3507-3514. [DOI]
78. Vilmont V, Nowakowski RS, Zhou Y. Role of the YWHAG gene mutations in developmental and epileptic encephalopathy. Front Neurosci. 2025;19:1641250. [DOI][PubMed][PMC]
79. Cho E, Park J, Hwang EM, Kim HW, Park JY. 14-3-3γ haploinsufficiency leads to altered dopamine pathway and Parkinson's disease-like motor incoordination in mice. Mol Brain. 2023;16(1):2. [DOI][PubMed][PMC]
80. Oh HS, Urey DY, Karlsson L, Zhu Z, Shen Y, Farinas A, et al. A cerebrospinal fluid synaptic protein biomarker for prediction of cognitive resilience versus decline in Alzheimer's disease. Nat Med. 2025;31(5):1592-1603. [DOI][PubMed][PMC]
81. Li ZK, Liao JL, Luo MR, Fang SJ, Huang WZ, Zhang DY. Neuro-tumor interactions: Multi-dimensional mechanisms of neurotransmitter regulation in tumor immune evasion and metabolic reprogramming. World J Clin Oncol. 2025;16(10):108954. [DOI][PubMed][PMC]
82. Wang X, Fan Y, Wang Q, Shu X, Lin J, Guo J, et al. Tumor-infiltrating nerves: Unraveling the role of cancer neuroscience in tumorigenesis, disease progression, and emerging therapies. Discov Oncol. 2025;16(1):1209. [DOI][PubMed][PMC]
83. Wang X, Yan Y, Li L, Li T, Thakur A, Zhang K, et al. The influence of neuro-tumor interactions on tumorigenesis and therapeutic response. Exp Hematol Oncol. 2026;15(1):18. [DOI][PubMed][PMC]
84. Fraser KB, Moehle MS, Daher JPL, Webber PJ, Williams JY, Stewart CA, et al. LRRK2 secretion in exosomes is regulated by 14-3-3. Hum Mol Genet. 2013;22(24):4988-5000. [DOI]
85. Schapansky J, Nardozzi JD, LaVoie MJ. The complex relationships between microglia, alpha-synuclein, and LRRK2 in Parkinson's disease. Neuroscience. 2015;302:74-88. [DOI][PubMed][PMC]
86. Ma Y, Li C, Huang Y, Wang Y, Xia X, Zheng JC. Exosomes released from neural progenitor cells and induced neural progenitor cells regulate neurogenesis through miR-21a. Cell Commun Signal. 2019;17(1):96. [DOI][PubMed][PMC]
87. Winkler F, Venkatesh HS, Amit M, Batchelor T, Demir IE, Deneen B, et al. Cancer neuroscience: State of the field, emerging directions. Cell. 2023;186(8):1689-1707. [DOI]
88. Mancusi R, Monje M. The neuroscience of cancer. Nature. 2023;618(7965):467-479. [DOI]
89. Hanahan D, Monje M. Cancer hallmarks intersect with neuroscience in the tumor microenvironment. Cancer Cell. 2023;41(3):573-580. [DOI][PubMed][PMC]
90. Yaniv D, Mattson B, Talbot S, Gleber-Netto FO, Amit M. Targeting the peripheral neural-tumour microenvironment for cancer therapy. Nat Rev Drug Discov. 2024;23(10):780-796. [DOI][PubMed][PMC]
91. Stevers LM, Wolter M, Carlile GW, Macdonald D, Richard L, Gielkens F, et al. Macrocycle-stabilization of its interaction with 14-3-3 increases plasma membrane localization and activity of CFTR. Nat Commun. 2022;13(1):3586. [DOI]
92. Meng EC, Goddard TD, Pettersen EF, Couch GS, Pearson ZJ, Morris JH, et al. UCSF ChimeraX: Tools for structure building and analysis. Protein Sci. 2023;32(11):e4792. [DOI]
93. Bai Q, Yu J, Li Y, Ma J, Gou Y. MicroRNA-182 promoted esophageal squamous cell carcinoma cell growth and metastasis via targeting YWHAG. J BUON. 2018;23(5):1439-1447. [PubMed]
94. Chen G, Zhang Z, Li Y, Wang L, Liu Y. LncRNA PTPRG-AS1 promotes the metastasis of hepatocellular carcinoma by enhancing YWHAG. J Oncol. 2021;2021:3624306. [DOI][PubMed][PMC]
95. Wang P, Deng Y, Fu X. miR-509-5p suppresses the proliferation, migration, and invasion of non-small cell lung cancer by targeting YWHAG. Biochem Biophys Res Commun. 2017;482(4):935-941. [DOI][PubMed]
96. Yoo JO, Kwak SY, An HJ, Bae IH, Park MJ, Han YH. miR-181b-3p promotes epithelial-mesenchymal transition in breast cancer cells through Snail stabilization by directly targeting YWHAG. Biochim Biophys Acta. 2016;1863(7 Pt A):1601-1611. [DOI][PubMed]
97. Zhou X, Wang Z, Xu B, Ji N, Meng P, Gu L, et al. Long non-coding RNA NORAD protects against cerebral ischemia/reperfusion injury induced brain damage, cell apoptosis, oxidative stress and inflammation by regulating miR-30a-5p/YWHAG. Bioengineered. 2021;12(2):9174-9188. [DOI][PubMed][PMC]
98. Perdigão-Henriques R, Petrocca F, Altschuler G, Thomas MP, Le MT, Tan SM, et al. miR-200 promotes the mesenchymal to epithelial transition by suppressing multiple members of the Zeb2 and Snail1 transcriptional repressor complexes. Oncogene. 2016;35(2):158-172. [DOI][PubMed]

Publisher's Note