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# The multifaceted functions of $\beta$ -arrestins and their therapeutic potential in neurodegenerative diseases

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Arrestins are multifunctional proteins that regulate G-protein-coupled receptor (GPCR) desensitization, signaling, and internalization. The arrestin family consists of four subtypes: visual arrestin1,  $\beta$ -arrestin1,  $\beta$ -arrestin2, and visual arrestin-4. Recent studies have revealed the multifunctional roles of  $\beta$ -arrestins beyond GPCR signaling, including scaffolding and adapter functions, and physically interacting with non-GPCR receptors. Increasing evidence suggests that  $\beta$ -arrestins are involved in the pathogenesis of a variety of neurodegenerative diseases, including Alzheimer's disease (AD), frontotemporal dementia (FTD), and Parkinson's disease (PD).  $\beta$ -arrestins physically interact with  $\gamma$ -secretase, leading to increased production and accumulation of amyloid-beta in AD. Furthermore,  $\beta$ -arrestin oligomers inhibit the autophagy cargo receptor p62/SQSTM1, resulting in tau accumulation and aggregation in FTD. In PD,  $\beta$ -arrestins are upregulated in postmortem brain tissue and an MPTP model, and the  $\beta$ 2AR regulates SNCA gene expression. In this review, we aim to provide an overview of  $\beta$ -arrestin1 and  $\beta$ -arrestin2, and describe their physiological functions and roles in neurodegenerative diseases. The multifaceted roles of  $\beta$ -arrestins and their involvement in neurodegenerative diseases suggest that they may serve as promising therapeutic targets.

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## INTRODUCTION

### $\beta$ -arrestin1 versus $\beta$ -arrestin2

**Expression patterns.**  $\beta$ -arrestin1 and  $\beta$ -arrestin2 share 78% sequence similarity and thus share many functions, including regulating receptor desensitization<sup>1,2</sup>, internalization<sup>3–6</sup>, and signaling<sup>7,8</sup>. Double knockout of both  $\beta$ -arrestin1 and  $\beta$ -arrestin2 results in neonatal death<sup>9</sup>, while knockout of only one isoform results in a relatively normal phenotype<sup>10,11</sup>, indicating that one  $\beta$ -arrestin can functionally compensate for the loss of the other.  $\beta$ -arrestin1 and  $\beta$ -arrestin2 are ubiquitously expressed in most mammalian cell types and tissues<sup>12,13</sup>, including but not limited to epithelial<sup>14,15</sup>, endothelial<sup>16–18</sup>, and smooth muscle cells<sup>19</sup>.  $\beta$ -arrestins are also highly expressed in the brain<sup>20</sup>. Overall,  $\beta$ -arrestin1 is more abundant in the adult brain than  $\beta$ -arrestin2, with as much as a tenfold expression difference<sup>21</sup>, and the immunodensity of  $\beta$ -arrestin2 in the human brain decreases by 3–5% per decade<sup>22</sup>. However, expression patterns and cellular functions may vary depending on the specific brain region. For example,  $\beta$ -arrestin1 and  $\beta$ -arrestin2 have equal expression patterns in striatal medium spiny neuron (MSN) populations in both the direct and indirect dopamine pathways. Within the striatum,  $\beta$ -arrestin2 expression is higher in cholinergic interneurons than in parvalbumin interneurons or MSNs<sup>23</sup>. The prefrontal cortex exhibits higher  $\beta$ -arrestin2 expression than the striatum, whereas the levels of  $\beta$ -arrestin1 are similar between the two regions in the rat brain<sup>24</sup>.  $\beta$ -arrestin1 and  $\beta$ -arrestin2 are highly

expressed in the pyramidal cell layers of the cingulate, somatosensory, and motor cortex, as well as in the CA1–CA3 regions and granular layer of the hippocampus and dentate gyrus (DG).  $\beta$ -arrestin1 also plays a role in neurogenesis and the proliferation of neural precursor cells in the subgranular zone and DG of the adult hippocampus<sup>25</sup>. Moderate to high expression is found in the hypothalamus and thalamic nuclei. Moderate expression is found in the periaqueductal gray, mesencephalic trigeminal nucleus, and locus coeruleus of the brainstem<sup>20</sup>.

**Intracellular localization.**  $\beta$ -arrestin1 is found in both the cytoplasm and nucleus, whereas  $\beta$ -arrestin2 is mainly found in the cytoplasm<sup>26–28</sup>. This differential cellular location is due to localization signal sequences. Both  $\beta$ -arrestin1 and  $\beta$ -arrestin2 contain a nuclear localization signal (NLS) in their N-terminus, which is required for nuclear import<sup>26,28</sup>. However, only  $\beta$ -arrestin2 contains a C-terminal leucine residue nuclear export signal (NES), which allows  $\beta$ -arrestin2 to exit the nucleus. Given its N-terminal NLS and C-terminal NES,  $\beta$ -arrestin2 shuttles between the cytoplasm and nucleus. Although  $\beta$ -arrestin2 is able to enter, its NES predominates and does not allow it to persist in the nucleus. This shuttling activity is important for the regulation of the E3 ubiquitin ligase Mdm2 and the protein kinase JNK3, which in turn regulate transcription factor activity<sup>29</sup>. Free cytoplasmic  $\beta$ -arrestins translocate to the plasma membrane upon agonist-induced receptor stimulation and/or act as scaffolding proteins<sup>30</sup>.

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**Differential interaction with GPCRs.**  $\beta$ -arrestins interact with hundreds of GPCRs and participate in various signaling pathways to carry out their diverse cellular functions. These GPCRs include but are not limited to adrenergic, dopaminergic, opioid, cholinergic, and glutaminergic receptors. Many of these receptor- $\beta$ -arrestin interactions are preferential for specific isoforms via biased agonist/ligand-induced recruitment. On a structural level, selective binding to receptors is indirectly mediated by the C-terminal region, directly mediated by the N-terminal region, and can also be mediated by the central domains of the  $\beta$ -arrestin protein<sup>31</sup>. GPCRs are categorized into six classes (A through F) according to functional and sequence similarities<sup>27,32–34</sup>. Currently, Class A GPCRs, also known as the “rhodopsin-like family”, are the largest and most diverse group of GPCRs<sup>35</sup>. The remaining classes, B through F, are classified as the secretin family, metabotropic glutamate receptors, fungal mating pheromone receptors, cyclic adenosine monophosphate receptors, and Frizzled and Smoothened receptors<sup>32–34</sup>. Generally, many Class A GPCRs tend to display a preference for  $\beta$ -arrestin2 over  $\beta$ -arrestin1, whereas Class B GPCRs lack such selectivity<sup>27</sup>. For example, it is well documented that  $\beta$ -arrestin2 has a dramatically greater affinity for beta-2 adrenergic receptor ( $\beta$ 2AR) binding than  $\beta$ -arrestin1<sup>36,37</sup> and translocates to the  $\beta$ 2AR much more efficiently<sup>27</sup>. Similarly, evidence supports differential affinity between  $\beta$ -arrestin1 and  $\beta$ -arrestin2 with dopamine receptor isoforms.  $\beta$ -arrestins participate in dopaminergic signaling via interaction with dopamine 1 and dopamine 2 receptors (D1R and D2R). This protein-receptor interaction occurs at the third cytoplasmic loop and C-terminal domain of the D1R and D2R. Given the structural similarities between  $\beta$ -arrestin1 and  $\beta$ -arrestin2, and between D1R and D2R, both isoforms of  $\beta$ -arrestin can interact with both isoforms of the dopamine receptor. However,  $\beta$ -arrestin1 and  $\beta$ -arrestin2 display agonist-induced preferential interactions with D2R<sup>38</sup> and D1R<sup>39</sup>, respectively, in rodent striatal neurons. This preference infers a functional difference given that D1R typically complexes with Gs to stimulate adenylyl cyclase activity, while D2R typically complexes with Gi to inhibit adenylyl cyclase activity.

Among the opioid receptors, both  $\beta$ -arrestin isoforms interact with the Class A mu-opioid receptor (mOR) and regulate its diffusion and mobility.  $\beta$ -arrestin1 has been implicated in facilitating mOR dephosphorylation and potentially promoting its resensitization by mediating its ubiquitination. In contrast,  $\beta$ -arrestin2 is prominently involved in promoting receptor desensitization by recruiting various signaling proteins and promoting receptor internalization<sup>40–45</sup>. However,  $\beta$ -arrestin1 plays a greater role in mOR internalization than  $\beta$ -arrestin2, and  $\beta$ -arrestin1 knockdown suppresses, whereas  $\beta$ -arrestin2 knockdown increases, adenylyl cyclase activity<sup>46</sup>. Similarly, the delta-opioid receptor (dOR) engages in differential interactions with  $\beta$ -arrestins, as high-internalizing dOR agonists facilitate  $\beta$ -arrestin1 recruitment, whereas low-internalizing dOR agonists facilitate  $\beta$ -arrestin2 recruitment<sup>47</sup>. The dOR is also involved in the nuclear localization of  $\beta$ -arrestin1, as agonist-induced activation of dOR leads to the translocation of  $\beta$ -arrestin1 to the nucleus, where it can then stimulate transcription and histone acetylation<sup>48</sup>. This same induction of  $\beta$ -arrestin1 nuclear trafficking is not observed in agonist-stimulated mOR or  $\beta$ 2AR.

Some Class B GPCRs known to interact with  $\beta$ -arrestins include, but are not limited to, the angiotensin II type 1A receptor (AT1aR), the muscarinic acetylcholine receptor (mAChR), and the parathyroid hormone 1 receptor (PTH1R).  $\beta$ -arrestin1 and  $\beta$ -arrestin2 are equally recruited to AT1aR in response to ligand activation. However,  $\beta$ -arrestin2 has the ability to induce a much greater affinity shift for certain biased agonists than  $\beta$ -arrestin1. Thus, although the two isoforms interact with AT1aR, their interactions may have different functions<sup>49</sup>.  $\beta$ -arrestin1 and  $\beta$ -arrestin2 are involved in the arrestin-dependent internalization of the M2

mAChR. While knockout of both  $\beta$ -arrestins in mouse embryonic fibroblasts dramatically diminishes mAChR internalization, the presence of either  $\beta$ -arrestin isoform can rescue mAChR internalization, indicating a lack of selectivity for either isoform<sup>50</sup>. Both  $\beta$ -arrestin1 and  $\beta$ -arrestin2 are recruited to the active PTH1R; however, small structural or conformational differences in the isoforms likely contribute to differential interactions with PTH1R conformations.  $\beta$ -arrestin1 preferably binds to and stabilizes the “hanging” PTH1R conformation to promote receptor internalization via interaction with distal receptor phosphorylation sites, whereas  $\beta$ -arrestin2 is unable to do so. Rather,  $\beta$ -arrestin2 preferably stabilizes the “core” PTH1R conformation via interaction with proximal receptor phosphorylation sites<sup>51</sup>. A summary of the similarities and differences between  $\beta$ -arrestin1 and  $\beta$ -arrestin2 can be found in Table 1.

## PHYSIOLOGICAL FUNCTIONS OF $\beta$ -ARRESTINS

### $\beta$ -arrestins in GPCR signaling

$\beta$ -arrestin1 and  $\beta$ -arrestin2 play a significant role in regulating GPCR function<sup>52</sup> (Fig. 1). GPCRs interact with three main regulatory proteins: guanine nucleotide-binding proteins (G-proteins), G-protein-coupled receptor kinases (GRKs), and arrestins<sup>53</sup>. GPCR agonists activate heterotrimeric G-proteins by inducing a conformational change in the receptor. Upon activation, the  $\alpha$  and  $\beta\gamma$  subunits of the G-protein dissociate, triggering the activation of secondary messenger-generating enzymes. As a result, the cell may undergo a variety of physiological changes<sup>53</sup>. However, there is a system that immediately opposes the effects of G-protein activation, beginning with the phosphorylation of the activated receptor by a GRK<sup>52</sup>. This first step sequentially leads to  $\beta$ -arrestin binding to the phosphorylated receptor, as receptor phosphorylation increases the binding affinity between  $\beta$ -arrestin and the receptor. G-protein coupling is physically inhibited by  $\beta$ -arrestin binding, resulting in homologous desensitization of the receptor<sup>52</sup> (Fig. 1). Overall, this is an established paradigm of the mechanisms of GPCRs, which was discovered when studying the  $\beta$ 2AR<sup>54</sup>.

Along with desensitization, the binding of  $\beta$ -arrestins to GRK-phosphorylated receptors also facilitates GPCR sequestration or internalization (Fig. 1).  $\beta$ -arrestins can function as adapter proteins because they contain two motifs in the R2 domain of their C-terminus: the clathrin binding motif LIEF and AP-2 binding motif RXR<sup>52,55</sup>. These motifs allow them to create a linkage between the GPCR and clathrin-dependent endocytic machinery<sup>52</sup>. The interaction between the  $\beta$ 2 adaptin subunit of AP-2 recruits activated  $\beta$ -arrestins to the clathrin pit via the RXR motif, which is found in the autoinhibitory C-terminus of all arrestin subtypes<sup>56–58</sup>. However, interactions between clathrin and  $\beta$ -arrestins can also occur due to the presence of the LIEF motif within the autoinhibitory segment of  $\beta$ -arrestin1 and  $\beta$ -arrestin2<sup>4,57,59</sup>. The inactive C-terminal ‘tail’ of  $\beta$ -arrestin acts as an autoinhibitory segment bound to a groove in the N-terminus<sup>14,57</sup> and, as a result, masks AP-2 and clathrin binding motifs. When the C-terminus is phosphorylated, however, it will displace this autoinhibitory tail segment, allowing for interaction between  $\beta$ -arrestin, AP-2, and clathrin. This interaction results in the recruitment of GPCRs to clathrin-coated pits<sup>57,60,61</sup>.

$\beta$ -arrestin1 is basally phosphorylated by ERK1 and ERK2 at Ser-412 and is dephosphorylated at the plasma membrane prior to receptor binding<sup>62,63</sup>. This finding was confirmed by the expression of a dominant-negative MEK1 mutant (K97A) in HEK293 cells, resulting in a ~70% reduction in phosphorylated  $\beta$ -arrestin1<sup>62</sup>.  $\beta$ -arrestin1 dephosphorylation is required for binding to clathrin and internalization of  $\beta$ 2AR<sup>63</sup>, and MEK1 K97A increases this interaction, leading to receptor sequestration by increasing dephosphorylated  $\beta$ -arrestin1<sup>62</sup>. Expression of a constitutively active MEK1 S218D/S222D mutant reduces receptor sequestration, which is enhanced by overexpression of

**Table 1.** Comparison of  $\beta$ -arrestin1 and  $\beta$ -arrestin2.

	<b><math>\beta</math>-arrestin1</b>	<b><math>\beta</math>-arrestin1 and <math>\beta</math>-arrestin2</b>	<b><math>\beta</math>-arrestin2</b>
Structure	Does not contain a C-terminal NES.	Share 78% sequence similarity <sup>1,2</sup> . Contain an N-terminal NLS for nuclear import <sup>26,28</sup> .	Contains a C-terminal NES, allowing for nuclear-cytoplasmic shuttling <sup>29</sup> .
Expression patterns	Up to 10x more abundant in the brain than $\beta$ -arrestin2 <sup>21</sup> .	Universally expressed in most mammalian cell types and tissues, and highly expressed in the brain <sup>12,13,20</sup> .	
	Protein concentration increases with age in the rat brain <sup>21</sup> .	Expression patterns are influenced by age.	Protein concentration decreases with age in the rat brain <sup>21</sup> , with an average immunodensity decrease of 3–5% per decade in the human brain <sup>22</sup> .
	Similar expression in the prefrontal cortex and striatum in the rat brain <sup>24</sup> .	Equal expression in striatal MSNs of direct and indirect dopamine pathways <sup>23</sup> . High expression in the pyramidal cells of the cortex and hippocampus <sup>20</sup> .	Higher expression in the prefrontal cortex compared to striatum in the rat brain <sup>24</sup> .
Class A GPCR interactions		Highly involved in the regulation of Class A GPCR signaling while similarly recruited by Class B GPCRs <sup>27</sup> .	Greater affinity for class A GPCRs compared to that of $\beta$ -arrestin1 <sup>27</sup> .
	There is very little research on the $\beta$ -arrestin1- $\beta$ 2AR interaction despite the known high affinity between $\beta$ -arrestin2 and the $\beta$ 2AR.	Most $\beta$ 2AR ligands trigger a similar degree of $\beta$ -arrestin recruitment to the $\beta$ 2AR <sup>180</sup> .	Tenfold more efficient at internalizing the $\beta$ 2AR, and 100-fold greater amount of $\beta$ -arrestin1 is needed to match $\beta$ -arrestin2-driven $\beta$ 2AR internalization <sup>37</sup> . Significantly higher binding affinity for the $\beta$ 2AR than $\beta$ -arrestin1 <sup>36,37</sup> .
	Preferentially interacts with the D2R dopamine receptor isoform <sup>38</sup> .	Interact with D1R and D2R to participate in dopaminergic signaling <sup>38,39</sup> .	Preferentially interacts with the D1R dopamine receptor isoform <sup>39</sup> .
Class B GPCR interactions	Knockdown suppresses adenylyl cyclase activity <sup>46</sup> . High internalizing dOR agonists facilitate $\beta$ -arrestin1 recruitment to the dOR <sup>47</sup> . $\beta$ -arrestin1 plays a greater role in mOR internalization compared to $\beta$ -arrestin2 <sup>46</sup> .	Interact with opioid family receptors (mOR and dOR) and play a potentially neuroprotective role <sup>181</sup> .	Knockdown enhances adenylyl cyclase activity <sup>46</sup> . Low-internalizing dOR agonists facilitate $\beta$ -arrestin2 recruitment to the dOR <sup>47</sup> .
		Equal interaction with the AT1aR with equal recruitment and binding affinity, albeit with slightly different conformations <sup>49</sup> .	Causes a greater affinity shift in response to certain agonists compared to $\beta$ -arrestin1 <sup>49</sup> .
	Preference for binding to and stabilizing the “hanging” PTH1R conformation <sup>51</sup> .	Equally recruited to the mAChR in response to ligand activation <sup>50</sup> . Equally recruited to the active PTH1R <sup>51</sup> .	Preference for binding to and stabilizing the “core” PTH1R conformation <sup>51</sup> .

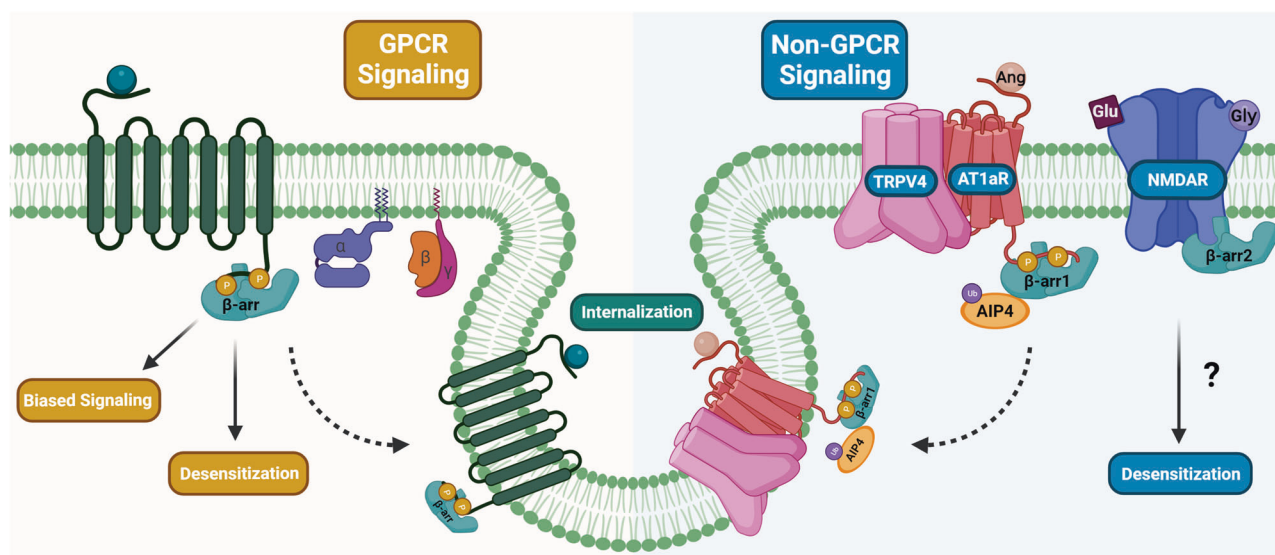
$\beta$ -arrestin1<sup>62</sup>. However, overexpression of  $\beta$ -arrestin2 with MEK1 S218D/S222D has no effect on receptor sequestration<sup>62</sup>, suggesting that ERKs only modulate the function of  $\beta$ -arrestin1 and not  $\beta$ -arrestin2, as  $\beta$ -arrestin2 does not have a comparable Ser-412 site.

$\beta$ -arrestin2 also functions as an adapter protein and recruits Mdm2, an E3 ubiquitin ligase that ubiquitinates both  $\beta$ 2AR and  $\beta$ -arrestin2<sup>64</sup>. Loss or inactivation of Mdm2 inhibits the internalization, but not degradation, of  $\beta$ 2AR<sup>64</sup>, indicating that the ubiquitination of  $\beta$ -arrestin2 is required for proper receptor internalization. Furthermore, the expression of a  $\beta$ 2AR mutant without lysine residues, which prevents ubiquitination, led to improper degradation of the receptor<sup>64</sup>. These results indicate that  $\beta$ -arrestin2 and GPCR ubiquitination play distinct roles in receptor internalization and degradation. The  $\beta$ 2AR can be catalytically ubiquitinated by other unidentified E3 ligases, but this still requires the presence of  $\beta$ -arrestin2 for proper internalization<sup>4,64</sup>. This is because  $\beta$ -arrestin2 quickly binds in response to accumulated GRK2-mediated phosphorylated receptors and immediately dissociates upon agonist removal<sup>65</sup>. This

fast-acting mechanism of  $\beta$ -arrestin2 is necessary for rapid signaling control in cells such as neurons. Clathrin and AP-2 are two integral proteins of clathrin-coated pits where GPCR internalization occurs<sup>4</sup>.

### **$\beta$ -arrestins in biased signaling**

As previously described, classic GPCR signaling involves agonist binding to the receptor, leading to the activation of heterotrimeric G-proteins and downstream second messenger signaling. After phosphorylation of the receptor C-terminus by GRKs,  $\beta$ -arrestins are recruited and bind to the receptor, leading to the steric hindrance of further G-protein signaling. However,  $\beta$ -arrestin proteins can simultaneously trigger another separate set of downstream signals<sup>66,67</sup> (Fig. 1). This is known as “ $\beta$ -arrestin-biased signaling.” Agonist testing has determined that certain ligands may be biased toward G-protein and/or  $\beta$ -arrestin signaling, leading to different downstream signaling processes<sup>66,67</sup>. Additionally,  $\beta$ -arrestin-biased ligands may simultaneously inhibit G-protein signaling while promoting  $\beta$ -arrestin signaling<sup>66,67</sup>. This concept of receptor bias could be used to



**Fig. 1 Physiological functions of  $\beta$ -arrestins.**  $\beta$ -arrestins bind to the phosphorylated C-terminus of GPCRs, leading to desensitization, internalization, and  $\beta$ -arrestin-biased signaling. Upon binding to GPCRs,  $\beta$ -arrestin inhibits G-protein coupling, thereby desensitizing the receptor and promoting clathrin-mediated internalization. Additionally,  $\beta$ -arrestins perform inhibitory functions outside of GPCR binding.  $\beta$ -arrestin1 serves as an adapter protein by recruiting the E3 ubiquitin ligase AIP4 to the TRPV4 and AT1aR complex, resulting in internalization of the complex.  $\beta$ -arrestin2 is also involved in suppressing spinal cord NMDAR signaling. However, the precise mechanism by which  $\beta$ -arrestin2 downregulates spinal cord NMDAR signaling has yet to be fully elucidated. Created with BioRender.com.

prevent the off-target effects of certain drugs, therefore leading to a reduction in side effects.

While many different receptor types have been found to be capable of biased signaling, one of the most studied are  $\beta$ -adrenergic receptors ( $\beta$ -ARs). Indeed, most known agonists of  $\beta$ 2AR exhibit  $\beta$ -arrestin bias and demonstrate similar G-protein signaling activity<sup>68,69</sup>. Three  $\beta$ 2AR agonists show clear  $\beta$ -arrestin bias: isoetharine, clenbuterol, and ethylnorepinephrine<sup>68</sup>. Interestingly, all three biased agonists contain an ethyl substitution on the  $\alpha$ -carbon<sup>68</sup>, indicating that biased ligands may have similar structures. Further investigation into the biased ligands of  $\beta$ -ARs has revealed an important role of  $\beta$ -arrestin-biased signaling in cognitive functions.  $\beta$ -arrestin-biased signaling through the  $\beta$ -adrenergic signaling pathway is required for memory reconsolidation<sup>70</sup>, suggesting a novel target for drug therapies.

$\beta$ -arrestin-biased signaling has also been observed in dopamine receptors. Novel D2R agonists that are  $\beta$ -arrestin biased can exert antipsychotic effects without off-target motor side effects<sup>71</sup>. This finding was confirmed by a lack of response in  $\beta$ -arrestin2 knockout mice<sup>71</sup>. Moreover, structural studies may be able to determine which compounds are able to induce  $\beta$ -arrestin-biased activity<sup>72</sup>. Further testing of a  $\beta$ -arrestin-biased D2R ligand showed promise in the treatment of schizophrenia by acting as both an agonist and antagonist in different brain regions, leading to a broader effect on symptoms<sup>24</sup>. These data support the use of  $\beta$ -arrestin-biased agonists for more specific pharmacological targeting, as they may be able to reduce side effects and increase effectiveness.

### $\beta$ -arrestins in non-GPCR signaling

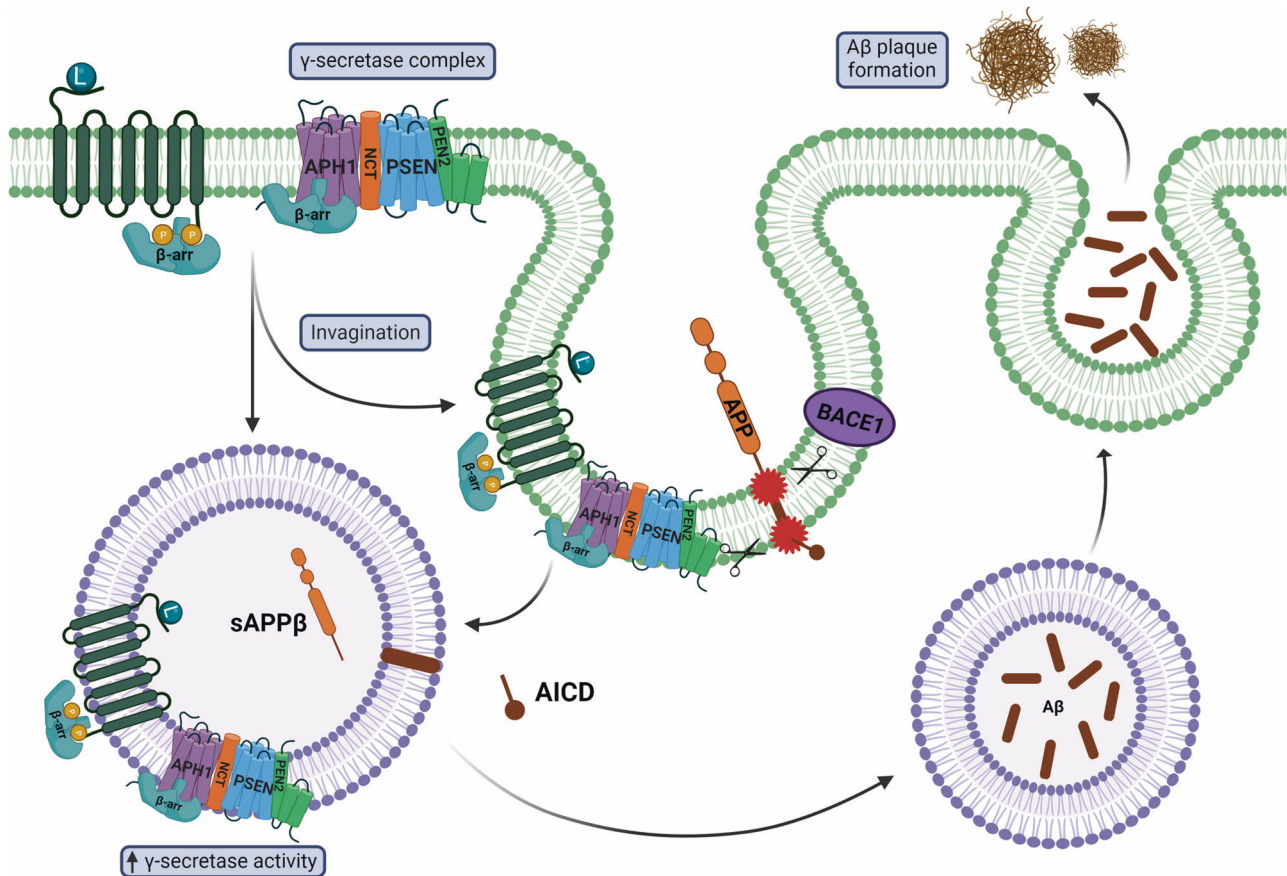
$\beta$ -arrestins are multifunctional proteins that regulate various non-GPCR signaling pathways<sup>73</sup>.  $\beta$ -arrestin1 plays a role in focal adhesion kinase (FAK) activation via C-X-C chemokine receptor type 4 (CXCR4), a GPCR, resulting in chemotaxis<sup>74</sup>. This interaction is facilitated by STAM1 binding to  $\beta$ -arrestin1, thereby creating a structural conformation specific for CXCR4 activation<sup>74</sup>. These data highlight a mechanism by which the non-GPCR functions of  $\beta$ -arrestin1 may contribute to the downstream regulation of GPCRs.  $\beta$ -arrestin1 also acts as an adapter in the regulation of TRPV4, a mechanosensitive  $\text{Ca}^{2+}$  channel.  $\beta$ -arrestin1 is recruited

to TRPV4 and the AT1aR complex via angiotensin stimulation<sup>75</sup> (Fig. 1).  $\beta$ -arrestin1 then acts as an adapter for the E3 ubiquitin ligase AIP4, which ubiquitinates TRPV4, resulting in downregulation of the ion channel<sup>75</sup>. This pathway serves as an excellent example of the critical function  $\beta$ -arrestins play as adapters, recruiting E3 ligases and subsequently facilitating the ubiquitination of adjacent receptors<sup>76</sup>.  $\beta$ -arrestin2 also regulates TRPV1, a cation channel in the transient receptor potential family.  $\beta$ -arrestin2 forms a complex with the phosphodiesterase PDE4D5, resulting in the desensitization of TRPV1<sup>77</sup>. These findings further indicate that the scaffolding properties of both  $\beta$ -arrestins play a significant regulatory role outside of the scope of GPCRs.

$\beta$ -arrestin2 also interacts with N-methyl-D-aspartate receptors (NMDARs) in the spinal cord dorsal horn<sup>78</sup> (Fig. 1). NMDARs are glutamate-sensitive ion channels composed of GluN1 and GluN2 or GluN3<sup>79</sup>. NMDARs mainly function at excitatory synapses, regulating sodium and calcium influx and potassium efflux in the central nervous system<sup>80</sup>. Their activation requires glutamate and either glycine or D-serine binding<sup>80</sup>.  $\beta$ -arrestin2 knockout mice display prolonged GluN2B-dependent late-phase mechanical allodynia and early-phase analgesia<sup>78</sup>. In contrast, overexpression of  $\beta$ -arrestin2 resolves chronic neuropathic pain<sup>78</sup>. This finding suggests that  $\beta$ -arrestin2 may also serve as a regulator of spinal cord NMDARs associated with the duration of pain through the desensitization of NMDARs; however, the specific mechanism behind this signaling pathway is unclear, and it remains to be tested whether there is a direct interaction between  $\beta$ -arrestin2 and NMDARs<sup>78</sup>.

$\beta$ -arrestin2 functions in multiple antiproliferative pathways by regulating the type III transforming growth factor beta (TGF- $\beta$ ) receptor and maternal embryonic leucine-zipper kinase (MELK).  $\beta$ -arrestin2 regulates TGF- $\beta$  function via receptor internalization, resulting in decreased TGF- $\beta$  signaling<sup>81,82</sup>. MELK plays a role in cell cycle regulation, proliferation, and apoptosis. Additionally, overexpression of MELK impacts various cancer types, such as glioblastomas<sup>82</sup>. The interaction between  $\beta$ -arrestin2 and MELK influences the function of the active MELK kinase domain, promoting the antiproliferative MELK pathway<sup>82</sup>. However, the exact nature of the interactions between  $\beta$ -arrestin2 and MELK has yet to be elucidated.  $\beta$ -arrestins also play a role in regulating





**Fig. 2 β-arrestins in Alzheimer's disease.** In AD, β-arrestins directly bind to the APH1 subunit of γ-secretase, which subsequently leads to an increase in γ-secretase enzymatic activity. Amyloid precursor protein (APP) is cleaved by γ-secretase and BACE1, leading to the production of toxic Aβ. The enhanced gamma-secretase activity within endosomes further contributes to the increased production of toxic Aβ peptides. Endosomes containing Aβ are exocytosed, leading to the formation of extracellular Aβ plaques. Created with BioRender.com.

transcription factors via Smoothened (Smo). β-arrestins play a role in Sonic Hedgehog (Shh) signaling through Smo, a GPCR. Both β-arrestin1 and β-arrestin2 mediate the interaction between Smo and Kif3A, a kinesin motor protein, allowing Smo to localize to the primary cilia and activate Gli<sup>83</sup>. This pathway is supported by a study showing that Smo localization to primary cilia in NIH3T3 cells is disrupted after transfection with β-arrestin1 and β-arrestin2 siRNA<sup>83</sup>. These studies indicate that β-arrestin2 plays a significant role in the regulation of proliferative pathways such as MELK and that both β-arrestins aid in the regulation of Shh, independent of GPCR binding.

β-arrestin1 and β-arrestin2 exist in monomer, homo- and hetero-oligomer forms<sup>84,85</sup>. β-arrestin oligomers are formed by bridging binding sites located on the N- and C-terminal globular domains, and binding is facilitated by inositol hexakisphosphate (IP6)<sup>85</sup>. β-arrestin oligomers have previously been proposed as an inactive, "resting" state; however, multiple studies have highlighted their unique functional roles. While β-arrestin monomers are mostly thought to act on GPCRs, β-arrestin2 oligomers have been shown to still bind to AT1aR after stimulation with the same kinetics as monomers<sup>84</sup>, suggesting that oligomers play functional roles. Disturbing the NES of β-arrestin2 results in the accumulation of both endogenous and mutant β-arrestin2 in the nucleus<sup>84</sup>. However, co-expression of β-arrestin1 and β-arrestin2 allows β-arrestin1 to be exported from the nucleus, suggesting that hetero-oligomers help maintain the correct subcellular localization of β-arrestins. A previous study showed that β-arrestin2 oligomers interact with the oncoprotein Mdm2 and promote its nuclear export, enhancing the antiproliferative effects of p53<sup>86</sup>. However,

β-arrestin2 oligomerization mutants reduce their interaction with Mdm2, which inhibits p53 downstream effects<sup>86</sup>, suggesting that β-arrestin2 oligomers regulate cell proliferation and survival. β-arrestin1 and β-arrestin2 oligomers also disrupt autophagy machinery by preventing p62/SQSTM1 self-interaction, leading to the accumulation of pathological tau in FTD<sup>87,88</sup>. β-arrestin1 can also associate with microtubules and compete with tau for microtubule binding, leading to microtubule destabilization in FTD<sup>88</sup>. These results indicate that the differing conformations of β-arrestins allow them to participate in unique cellular functions.

## ROLE OF β-ARRESTINS IN NEURODEGENERATIVE DISEASES

### β-arrestins in Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the accumulation of toxic intracellular tau tangles and extracellular amyloid-beta (Aβ) plaques in the brain<sup>89</sup>. Interestingly, β-arrestin1 and β-arrestin2 mRNA and protein levels are elevated in postmortem brain tissues from AD patients<sup>90–93</sup>. Overexpression of β-arrestin1 or β-arrestin2 increases Aβ production in cultured cells and primary neurons in vitro, and genetic ablation of *Arrb1* or *Arrb2* reduces Aβ accumulation in the *APP/PS1* mouse model of AD<sup>91,92</sup>. Moreover, compared to their *APP/PS1* littermates, *APP/PS1;Arrb1*<sup>−/−</sup> mice exhibit improved learning and memory in the novel object recognition and Morris water maze tests<sup>91</sup>. Furthermore, siRNA knockdown of β-arrestin1 in CRND8 mice, an APP mouse model with Swedish and Indiana mutations, significantly reduces the Aβ plaque burden in the hippocampus<sup>91</sup>. β-arrestin1 and β-arrestin2

modulate A $\beta$  levels by directly interacting with the  $\gamma$ -secretase complex<sup>91,92</sup> (Fig. 2). Specifically,  $\beta$ -arrestin1 and  $\beta$ -arrestin2 bind to the anterior pharynx defective 1 (APH1) subunit of the  $\gamma$ -secretase complex<sup>91,92</sup>, and disruption of this interaction reduces A $\beta$  production in vitro<sup>91</sup>. It was recently revealed that APH1A contains GRK-mediated phosphorylation barcodes in its C-terminus, which regulate the recruitment and interaction with  $\beta$ -arrestin2<sup>94</sup>, thereby regulating A $\beta$  levels.

APP cleavage, A $\beta$  production, and  $\gamma$ -secretase activity can be altered via  $\beta$ 2AR and G-protein-coupled receptor 3 (GPR3).  $\beta$ -arrestin2 has a higher binding affinity for both  $\beta$ 2AR and GPR3 than  $\beta$ -arrestin1, and treatment with the  $\beta$ 2AR agonist isoproterenol in APPsw HEK293 cells increases A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> levels<sup>95</sup>. However, cotreatment with the  $\beta$ 2AR antagonists propranolol and isoproterenol eradicates the increase in secreted A $\beta$  levels, while propranolol treatment alone has no effect<sup>95</sup>. Pretreatment of the  $\gamma$ -secretase inhibitor L895,458 alongside isoproterenol does not alter secreted A $\beta$ <sup>95</sup> levels, indicating that  $\beta$ 2AR modulates A $\beta$  levels in a  $\gamma$ -secretase-dependent manner. Furthermore, stimulation of  $\beta$ 2AR increases the production of A $\beta$  in late endosomes and lysosomes<sup>95</sup>. Isoproterenol treatment also enhances the colocalization of RAB7 and PS1 in endosomes<sup>95</sup>, and acidic environments enhance  $\gamma$ -secretase activity, leading to an increase in A $\beta$  production<sup>96</sup>. Knockdown of  $\beta$ -arrestin2, but not  $\beta$ -arrestin1, prevents the internalization of  $\beta$ 2AR after A $\beta$  or isoproterenol treatment in mouse embryonic fibroblasts (MEFs)<sup>97</sup>. Additionally,  $\beta$ -arrestin2 V54D, a mutant incapable of inducing  $\beta$ 2AR internalization, is also unresponsive to A $\beta$  or isoproterenol treatment in HEK293 cells<sup>97</sup>, further suggesting that  $\beta$ 2AR internalization is primarily reliant on  $\beta$ -arrestin2.

Additionally, GPR3 overexpression increases A $\beta$  levels, and GPR3 knockdown reduces A $\beta$  levels in vitro<sup>98,99</sup>. Inhibition of  $\gamma$ -secretase eliminates GPR3's effect on A $\beta$  production in HEK293 cells and mouse primary hippocampal neurons<sup>98</sup>. Transduction of GPR3 in the APP/PS1 hippocampus increases A $\beta$  levels without altering  $\gamma$ -secretase expression levels, and APP/PS1;Gpr3<sup>+/-</sup> and APP/PS1;Gpr3<sup>-/-</sup> mice exhibit significantly reduced A $\beta$  levels compared to APP/PS1 littermates. These results suggest that GPR3 is also dependent on  $\gamma$ -secretase for A $\beta$  regulation; however, a direct interaction has not yet been observed. Co-transfection of GPR3 and  $\beta$ -arrestin2, but not  $\beta$ -arrestin1, significantly increases A $\beta$  levels in vitro, and knockdown of  $\beta$ -arrestin2 suppresses GPR3-induced A $\beta$  production<sup>99</sup>. Point mutations in GPR3 impair Gs coupling (DRY-AYY) and eliminate  $\beta$ -arrestin recruitment (Q302\*), while a point mutation that removes a putative GRK site (S237A) enhances GPR3- $\beta$ -arrestin2 interaction<sup>99</sup>. GPR3 Q302\* also failed to increase A $\beta$ <sup>99</sup>, suggesting that the GPR3- $\beta$ -arrestin2 interaction is required to stimulate A $\beta$  production. GPR3 colocalizes with APP in rat hippocampal neurons and with  $\beta$ -arrestin2 in neuronal cell bodies and endosomes<sup>99</sup>. Overexpression of  $\beta$ -arrestin2 or the GPR3 S237A variant significantly enhances, while DRY-AYY and Q302\* variants reduce GPR3-APP interaction, and  $\beta$ -arrestin1 overexpression has no effect<sup>99</sup>. This finding correlates with  $\beta$ -arrestin2 recruitment to GPR3, suggesting that GPR3- $\beta$ -arrestin2 binding is needed to enhance A $\beta$  production. G-protein-biased GPR3 mice, which retain G-protein signaling while eradicating  $\beta$ -arrestin2 signaling, crossed with APP knock-in mice exhibit significantly reduced A $\beta$  levels and neuroinflammation<sup>100</sup>, further supporting that  $\beta$ -arrestin2 signaling is required for GPR3-mediated A $\beta$  production.

Neuroinflammation is another hallmark of AD, and GPCRs on microglia can promote or reduce A $\beta$  pathology<sup>101</sup>. A $\beta$  can directly bind to multiple GPCRs located on microglia and regulate APP processing<sup>102</sup>. Furthermore, treatment with various modulators of microglial GPCRs can result in a wide range of effects on neuroinflammation, A $\beta$  pathology, and neurotoxicity<sup>101</sup>. GRKs have also been implicated in the pathogenesis of AD. GRK2 is upregulated in the brain in early-stage AD<sup>103</sup>, and in vitro A $\beta$

treatment reduces membrane-associated GRK2 and GRK5, which promotes GPCR dysfunction<sup>104</sup>. In vivo studies revealed a similar reduction in active GRK2 and GRK5 levels in CRND8 AD mice<sup>104</sup>, and membrane-associated GRK5 levels are reduced, while cytosolic levels are increased, in aged APPsw mice<sup>105</sup>. Total GRK2 levels are increased in peripheral blood samples from AD patients<sup>106</sup>, and A $\beta$  can induce tau phosphorylation at Ser-214 via a GRK2/ $\beta$ 2AR/PKA signaling pathway<sup>107</sup>. These studies reveal key connections between A $\beta$ , microglial GPCRs, and GRKs in the pathogenesis of AD. However, further research is needed on the specific role of  $\beta$ -arrestins in neuroinflammation and GRK dysfunction in the context of AD.

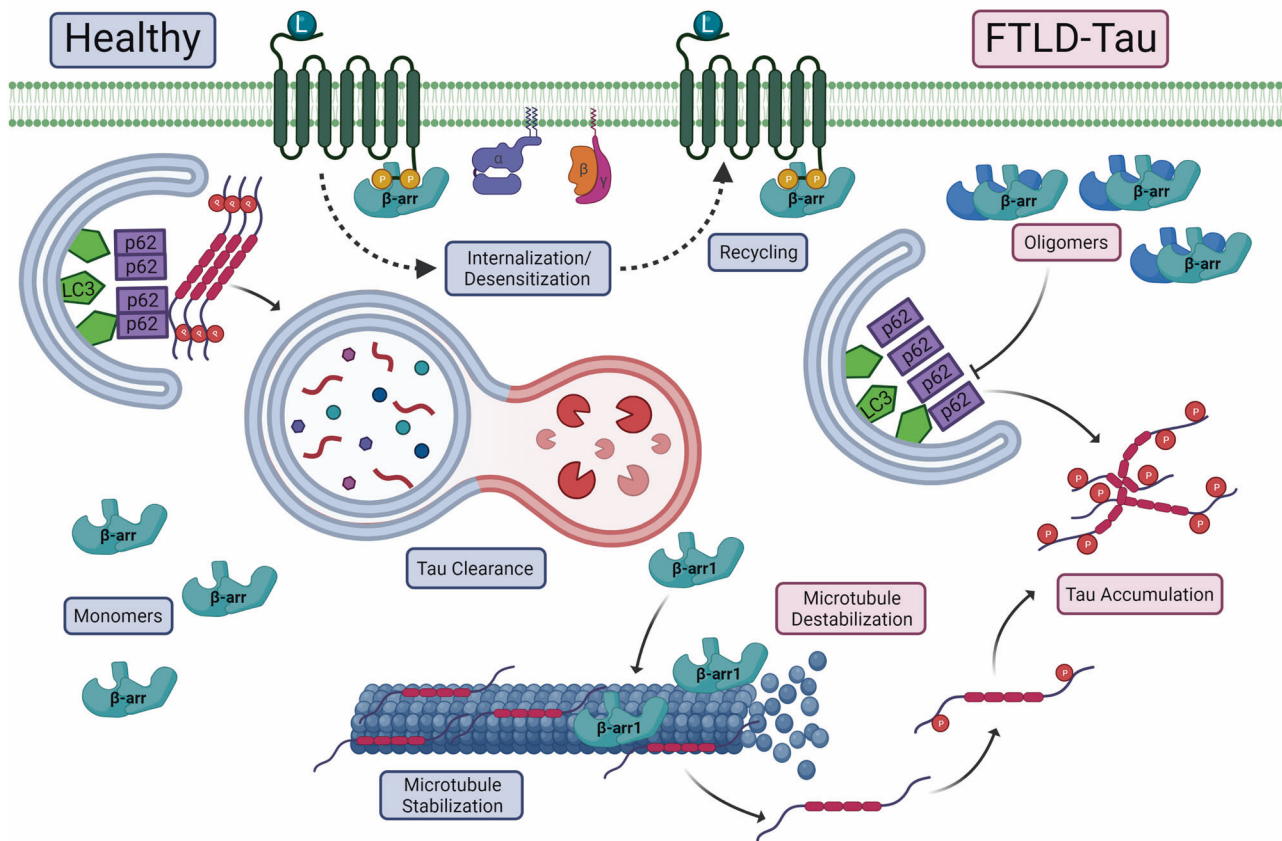
Current AD therapies include cholinesterase inhibitors, NMDA antagonists, and immunotherapies. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine prevent the degradation of acetylcholine and butyrylcholine, thereby increasing levels in the brain<sup>108</sup>. Cholines can bind to multiple receptor types, including nicotinic and muscarinic acetylcholine receptors, in which the latter is a type of GPCR. NMDA antagonists such as memantine regulate glutamate signaling in the brain by inhibiting non-GPCR NMDA receptors<sup>109</sup>. Immunotherapies for the treatment of AD include recently FDA-approved aducanumab and lecanemab, which are A $\beta$  monoclonal antibody treatments<sup>110</sup>. However, the role of  $\beta$ -arrestins in current AD therapies has not been explored, outside of their canonical role in regulating GPCR signaling.

### $\beta$ -arrestins in frontotemporal dementia

Frontotemporal dementia (FTD) is an ill-defined group of neurodegenerative diseases largely characterized by frontotemporal lobar degeneration (FTLD)<sup>111</sup>. First described as Pick's disease, FTD has been difficult to clinically define due to the wide range of presentations and pathologies. FTD differs from AD in both the brain regions that degenerate and the lack of A $\beta$  pathology<sup>112</sup>. Despite challenges with clinically diagnosing FTD, there are currently two major classifications of FTD based on pathology: FTLD-tau and FTLD-TDP, which are characterized by tauopathy and TDP-43 proteinopathy, respectively<sup>113</sup>. Despite being a significant cause of dementia, FTD is not as well studied as AD, and the role of  $\beta$ -arrestins in FTD is poorly understood, with only two studies investigating  $\beta$ -arrestins in FTLD-tau. However, both  $\beta$ -arrestin1 and  $\beta$ -arrestin2 levels are elevated in FTLD-tau patients and PS19 transgenic mice, suggesting that  $\beta$ -arrestins may play a key role in FTLD-tau pathology<sup>87,88</sup>.

$\beta$ -arrestin2 overexpression increases, while  $\beta$ -arrestin2 knockdown decreases, tau and phospho-tau levels in HeLa-V5-tau cells and PS19 primary cortical neurons<sup>87</sup>. However, tau mRNA levels are not significantly altered, suggesting that  $\beta$ -arrestin2 affects tau levels at a post-translational level<sup>87</sup>. PS19;Arrb2<sup>-/-</sup> mice have decreased sarkosyl-insoluble tau and phospho-tau, and hippocampal long-term potentiation is restored in PS19;Arrb2<sup>+/-</sup> and PS19;Arrb2<sup>-/-</sup> mice compared to PS19 littermates<sup>87</sup>.  $\beta$ -arrestin2 oligomeric mutants  $\Delta$ IP6N and  $\Delta$ IP6C increase tau turnover and autophagy flux in HeLa-V5-tau cells<sup>87</sup>. Furthermore, AAV9 expression of  $\Delta$ IP6N and  $\Delta$ IP6C mutants in PS19 mice inhibits hippocampal tau accumulation in vivo<sup>87</sup>.  $\beta$ -arrestin2 also inhibits p62/SQSTM1 self-interaction (Fig. 3), while  $\Delta$ IP6N and  $\Delta$ IP6C mutants do not, suggesting that  $\beta$ -arrestin2 oligomers specifically affect autophagy via p62/SQSTM1<sup>87</sup>. These results suggest that  $\beta$ -arrestin2 oligomers may be a therapeutic target for FTLD-tau or other tauopathies.

Similarly,  $\beta$ -arrestin1 is elevated in and colocalizes with pathogenic AT8 phospho-tau in FTLD-tau patient postmortem brain tissue, with no significant difference in mRNA levels<sup>88</sup>.  $\beta$ -arrestin1 and  $\beta$ -arrestin2 knockdown reduces GPCR agonist-induced increases in tau in HeLa-V5-tau cells, suggesting that  $\beta$ -arrestins are necessary for GPCR-mediated increases in tau and phospho-tau<sup>88</sup>. Overexpression of  $\beta$ -arrestin1 reduces the amount



**Fig. 3 β-arrestins in frontotemporal dementia.** In healthy neurons, β-arrestin monomers regulate the internalization, desensitization, and recycling of GPCRs. Additionally, P62/SQSTM1-mediated autophagy remains intact due to the successful self-interaction of P62, which is required for its localization to the autophagosome formation site, resulting in efficient removal of damaged organelles and misfolded proteins. Tau is able to bind to and stabilize microtubules. However, in FTLD-Tau, β-arrestin oligomers accumulate and prevent P62/SQSTM1 self-interaction, leading to autophagy impairment. β-arrestin1 also competes with tau for microtubule binding, inducing microtubule destabilization and tau accumulation. Created with BioRender.com.

of tau bound to microtubules, suggesting that β-arrestin1 promotes tau missorting via dissociation from microtubules<sup>88</sup> (Fig. 3). Furthermore, compared to PS19 littermates, PS19;*Arrb1*<sup>-/-</sup> mice exhibit reduced tau accumulation and improved cognitive function<sup>88</sup>. Similar to β-arrestin2, β-arrestin1 inhibits p62/SQSTM1 flux by disrupting p62 self-association<sup>88</sup> (Fig. 3). The effects of β-arrestin1 and β-arrestin2 on tauopathy warrant further investigation into their mechanisms and therapeutic potential for other tauopathies outside of FTD. While multiple studies have connected GRKs to AD pathology, the roles of GRKs in FTD are not well understood. FTD therapies include selective serotonin reuptake inhibitors and antipsychotics for the management of behavioral symptoms and riluzole and dopamine for motor symptoms<sup>114</sup>. While these therapies may assist in reducing symptomatic behaviors, there are currently no treatments that target the underlying cause of the disease. Indeed, GPCR dysfunction and neuroinflammation are also hallmarks of FTD; however, the specific roles of β-arrestins in the context of FTD need to be further explored in these areas.

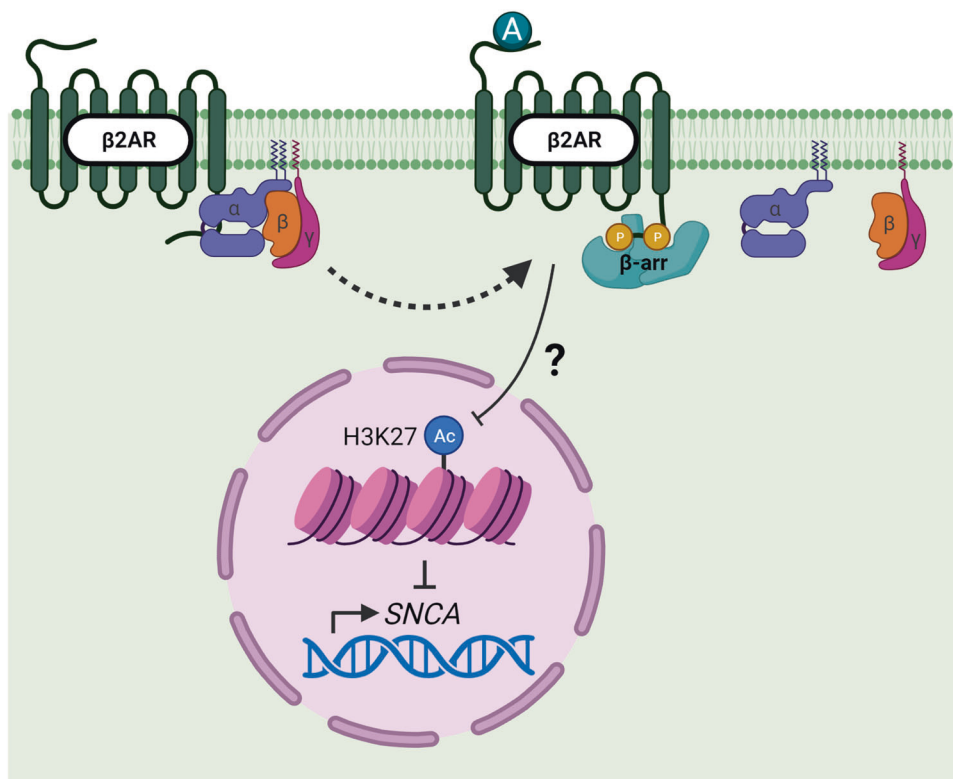
### β-arrestins in Parkinson's disease

Parkinson's disease (PD) is the second most prevalent progressive neurodegenerative disorder that affects older adults after AD<sup>115,116</sup>. Its prevalence is expected to increase nearly exponentially as the population ages, with risk peaking after 80 years of age<sup>115,117,118</sup>. The main PD hallmarks are the loss of dopaminergic neurons in the substantia nigra of the midbrain and the

accumulation of intracellular inclusions of α-synuclein protein known as Lewy bodies<sup>115,119–121</sup>. Motor symptoms of PD include bradykinesia, muscular rigidity, and resting tremors, and non-motor symptoms include olfactory dysfunction, cognitive impairment, psychiatric symptoms, and autonomic dysfunction<sup>119</sup>. Currently available therapies only treat symptoms of the disease<sup>115,119</sup>; thus, a major objective in PD research is the development of drugs that slow or halt the neurodegenerative process entirely.

GPCR signaling is involved in PD pathogenesis, as GPCRs mediate microglial activation, which can be proinflammatory and neurotoxic when active, contributing to PD pathology<sup>119,122–125</sup>. β-arrestin1 and β-arrestin2 have opposing effects on neuroinflammation and microglia, as knockout of β-arrestin1 improves, while knockout of β-arrestin2 exacerbates, PD pathological features through microglial activation and dopaminergic neuron death<sup>126</sup>. These differing effects that β-arrestin1 and β-arrestin2 have on PD pathology may be due to their regulatory effects on the inflammatory NF-κB and STAT1 pathways. Knockout of β-arrestin1 inhibits components of the NF-κB and STAT1 pathways, while β-arrestin2 knockout activates the same signaling proteins, leading to reduced and increased inflammation, respectively<sup>126</sup>. To further interpret these differing effects, the expression levels of β-arrestin1 and β-arrestin2 across immune cells should be considered<sup>19</sup>. Both β-arrestins are expressed in macrophages<sup>127</sup> and lymphocytes<sup>128</sup>. However, T cells express more β-arrestin2 than B cells<sup>128</sup>, and β-arrestin1 is highly





**Fig. 4 The  $\beta$ 2AR regulates *SNCA* gene expression.** Binding of  $\beta$ 2AR agonists (A), such as clenbuterol, to the receptor induces the dissociation of heterotrimeric G-proteins, leading to receptor phosphorylation and  $\beta$ -arrestin binding. Although the precise molecular mechanism underlying the reduction in H3K27 acetylation after clenbuterol treatment remains unknown, it has been observed that this reduction ultimately leads to a reduction in *SNCA* gene expression. However, the role of  $\beta$ -arrestins in this process has not been investigated. Created with BioRender.com.

expressed specifically in polymorphonuclear leukocytes<sup>16</sup>.  $\beta$ -arrestin expression levels across immune cells may vary in disease states. For example, typical CD4<sup>+</sup> T lymphocytes highly express nuclear  $\beta$ -arrestin1; however, in allergic asthma mouse models, CD4<sup>+</sup> T lymphocytes highly express  $\beta$ -arrestin2<sup>129</sup>. Specifics of  $\beta$ -arrestin expression patterns in proinflammatory and anti-inflammatory immune cells require further research. Additionally,  $\alpha$ -synuclein interferes with GPCR signaling<sup>130</sup>, and  $\beta$ 2AR regulates the expression of *SNCA* (Fig. 4), the gene that encodes  $\alpha$ -synuclein<sup>131</sup>. Therefore, elucidating the relationship between GPCR signaling,  $\alpha$ -synuclein, and  $\beta$ -arrestins is essential for further understanding PD pathology.

$\beta$ -arrestins mediate dopamine receptor (DAR) signaling, which contributes to PD pathogenesis<sup>132</sup>. GRKs and  $\beta$ -arrestins are upregulated in PD models, although the upregulated GRK subtype varies<sup>133,134</sup>. For example, in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) PD model,  $\beta$ -arrestin1 and GRK6 are upregulated<sup>133</sup>. However, GRK3 and GRK5 are upregulated in human postmortem tissue from Parkinson's disease with dementia (PDD) patients, while GRK6 expression is not altered. As both  $\beta$ -arrestin1 and  $\beta$ -arrestin2 demonstrate upregulated expression in PD<sup>133,134</sup>, it has been suggested that downregulating GRK and  $\beta$ -arrestin expression may serve as a therapeutic target. Post-MPTP lesioning, L-DOPA treatment reduces  $\beta$ -arrestin1 and GRK6 expression levels<sup>133</sup>. Simultaneous upregulation of GRKs and  $\beta$ -arrestins suggests that they may be expressed concurrently, although whether they colocalize has not been fully established. Interestingly, GRK2 and GRK5 can phosphorylate  $\alpha$ -synuclein at the C-terminus, and phosphorylation is regulated by factors that also regulate GPCR phosphorylation<sup>135</sup>. However, the role of  $\beta$ -arrestins in  $\alpha$ -synuclein phosphorylation by GRKs has not been investigated. While the interactions between GRKs,  $\alpha$ -synuclein, and

$\beta$ -arrestins within PD pathogenesis have not been fully elucidated, it appears that they all contribute to DAR regulation and signaling, which is an essential aspect of PD pathogenesis.

Current antiparkinsonian therapies include dopamine precursors, dopamine agonists, and adenosine receptor antagonists. Undesirable side effects of these medications may be exacerbated or alleviated by targeting  $\beta$ -arrestins. Concurrently, antiparkinsonian compounds may affect  $\beta$ -arrestins' involvement in PD progression. Thus,  $\beta$ -arrestins are a target of interest for maximizing the efficacy and reducing the side effects of PD therapies. L-DOPA or levodopa, a dopamine precursor, is a standard treatment for bradykinesia and parkinsonism in PD<sup>136</sup>. Piribedil, a D2R and D3R agonist, is another standard PD treatment typically used in conjunction with L-DOPA<sup>137,138</sup>. Another common complementary treatment, istradefylline, is an adenosine A2A receptor antagonist that is also used in combination with L-DOPA and is used to treat "off" periods between medications during which PD symptoms are heightened<sup>139</sup>. L-DOPA-induced dyskinesias (LIDs) are a side effect of L-DOPA use and are characterized by involuntary, excessive muscle movement<sup>140,141</sup>. After five to six months of treatment, approximately 50% of patients present with one or more LID, with a median prevalence of approximately 40% after four to six years of treatment, suggesting the need for LID-targeted therapies<sup>140–142</sup>. Dopaminergic presynaptic denervation in the nigrostriatal pathway, increased striatal DAR activity, and GPCR hypersensitivity contribute to LID pathogenesis<sup>143–146</sup>. Because of its role in desensitizing GPCR signaling,  $\beta$ -arrestin2 is a protein target of interest for alleviating LID symptoms<sup>147,148</sup>. Overexpression of  $\beta$ -arrestin2 reduces LID-associated symptoms, while genetic deletion of *Arb2* increases LID-associated symptoms<sup>148</sup>. In a 6-hydroxydopamine-lesioned model of PD,  $\beta$ -arrestin2 overexpression attenuates LID-associated symptoms



and decreases D1R activation and the levels of D1R-associated markers FosB, ERK1/2 phosphorylation, and DARPP-32<sup>144,149</sup>. However,  $\beta$ -arrestin2 overexpression does not affect the antiparkinsonian effects of L-DOPA. Conversely, knocking down  $\beta$ -arrestin2 promotes dyskinetic symptoms and increases ERK1/2 phosphorylation, FosB, and DARPP-32. These findings further support the notion that  $\beta$ -arrestin2 may mediate D1R activity by decreasing GPCR sensitivity and could be a possible therapeutic target for LIDs.

As previously mentioned,  $\beta$ -arrestins play a role in A $\beta$  accumulation, which is a comorbid aspect of PD pathology associated with cognitive symptoms<sup>137,150</sup>. PD treatments L-DOPA, piribedil, and istradefylline can promote A $\beta$  generation. For example, piribedil and L-DOPA stimulate A $\beta$  production in primary neurons and neuronal cells<sup>137</sup>. It has been suggested that D2R expression and activation from  $\beta$ -arrestin signaling are primarily responsible for increased  $\gamma$ -secretase activity<sup>137</sup>. Accordingly, when  $\beta$ -arrestin2 is knocked down, A $\beta$  production and  $\gamma$ -secretase activity are inhibited<sup>137</sup>. Istradefylline also promotes A $\beta$  production in vitro, but this effect is not dependent on  $\beta$ -arrestins<sup>151</sup>.  $\beta$ -arrestin2 may have differential effects on the D1R and D2R signaling pathways, and further characterization of this relationship may elucidate more specific therapies for PD.

Autophagy dysfunction is another hallmark of PD and other neurodegenerative diseases<sup>152–155</sup>. Chaperone-mediated autophagy (CMA) can degrade  $\alpha$ -synuclein, as inhibition of CMA induces the accumulation of soluble high molecular weight and detergent-insoluble species of  $\alpha$ -synuclein<sup>156</sup>. Additionally,  $\beta$ -arrestin1 and  $\beta$ -arrestin2 oligomers inhibit autophagy flux by preventing p62/SQSTM1 self-interaction, leading to the accumulation of pathological tau in FTLD<sup>87,88</sup>. While this mechanism has not yet been explored in the context of PD, it is plausible that  $\beta$ -arrestin oligomers have a similar effect on  $\alpha$ -synucleinopathy. Agonists of  $\beta$ 2AR reduce, while antagonists increase, *SNCA* gene expression by modulating H3K27 acetylation<sup>131</sup>. In a population of 4 million Norwegians, treatment with  $\beta$ 2AR agonists reduced, while antagonist treatment increased, the risk of developing PD<sup>131</sup>. Furthermore, tau is a common co-pathology seen in PD patients and patients with other Lewy body disorders<sup>157–159</sup>, and tau is required for memory and synaptic dysfunction in a mouse model of  $\alpha$ -synucleinopathy<sup>160</sup>.

### $\beta$ -arrestins in amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by motor neuron degeneration and loss. Clinical symptoms include loss of voluntary muscle use, stiffness, dyspnea, wasting, dysarthria, and eventually paralysis<sup>161,162</sup>. ALS was first identified in the late nineteenth century by Jean-Martin Charcot, and sufficiently describing the pathogenesis of the disease has since been challenging<sup>163</sup>. Current treatments aim to slow disease development and improve patient quality of life, including riluzole, a glutamatergic release inhibitor, and edaravone, a free radical scavenger that protects against oxidative stress<sup>80,164–166</sup>. Due to the aggressive nature of the condition, with an average prognosis of two to five years postdiagnosis, finding treatments that ameliorate disease progression is of paramount importance<sup>161</sup>.

*SOD1* was the first gene found to be connected to ALS, and subsequent research has linked ~700 genes to ALS risk, including *TARDBP*<sup>161,167,168</sup>, which encodes TDP-43, the accumulation of which is a hallmark of ALS pathology. Nonpathologically, TDP-43 regulates RNA transcription, stability, and splicing<sup>169,170</sup>. When TDP-43 moves from the nucleus to the cytoplasm, it can accumulate and cause neuronal death<sup>171</sup>. In addition,  $\beta$ 2AR signaling and components of the GPCR pathway, such as kinase activity, are modified in ALS<sup>122,172,173</sup>. Because of their role in GPCR signal transduction,  $\beta$ -arrestins may play a role in ALS pathogenesis.

Thus far, the role of  $\beta$ -arrestins in ALS is not well established, and research is limited to the therapeutic benefits of targeting

$\beta$ 2AR. In vivo,  $\beta$ 2AR agonists slow disease progression, as measured by reduced motor neuron loss and delayed motor symptom onset<sup>174–177</sup>. Additionally, ALS shares pathological similarities with FTLD. Namely, TDP-43 accumulation is present in both pathologies<sup>178</sup>. Within FTLD-tau,  $\beta$ -arrestin1 mediates tau accumulation through GPCR signaling<sup>88</sup>. FTLD-tau patients also have increased levels of both  $\beta$ -arrestin1 and  $\beta$ -arrestin2<sup>87,88</sup>.  $\beta$ -arrestins may induce similar  $\beta$ 2AR signal transduction in ALS as in FTLD. Furthermore, autophagic inhibition by  $\beta$ -arrestin1 and  $\beta$ -arrestin2 oligomers, as seen in the context of FTLD-tau, could also apply to ALS, as autophagy dysfunction is a common hallmark in multiple neurodegenerative diseases<sup>87,88,152,153</sup>. Overlapping aspects of FTD and ALS pathophysiology may provide evidence for the role of  $\beta$ -arrestins within ALS and may identify new therapeutic targets for the condition.

### DISCUSSION

Arrestins are multifunctional proteins that play key roles in receptor desensitization<sup>1,2</sup>, internalization<sup>3–6</sup>, and signaling<sup>1,7,8</sup> (Fig. 1). While visual arrestins are mostly expressed in the rods and cones of the retina and act on light-sensitive receptors,  $\beta$ -arrestins are ubiquitously expressed and act on a variety of receptors. Although the overall structures of arrestins are similar across the four subtypes, differences in both the N- and C-termini of arrestins differentiate receptor binding affinity between the visual arrestins and  $\beta$ -arrestins<sup>179</sup>.  $\beta$ -arrestin1 and  $\beta$ -arrestin2 share 78% sequence similarity; however,  $\beta$ -arrestin1 is localized to both the cytosol and nucleus, while  $\beta$ -arrestin2 is mostly limited to the cytosol due to its C-terminal NES<sup>27,28</sup>. Furthermore,  $\beta$ -arrestin hetero-oligomers regulate the proper localization of each  $\beta$ -arrestin<sup>84</sup>. Double knockout of both  $\beta$ -arrestin1 and  $\beta$ -arrestin2 is lethal<sup>9</sup>; however, single knockout of either  $\beta$ -arrestin protein results in a relatively normal phenotype<sup>10,11,87,88</sup>, suggesting that  $\beta$ -arrestin1 and  $\beta$ -arrestin2 can compensate for the loss of the other.

Given that nearly every aspect of metabolism is regulated by the GPCR- $\beta$ -arrestin axis, it is worth noting that GPCR dysfunction has been implicated in multiple neurodegenerative diseases. While the precise mechanisms by which GPCR dysfunction exacerbates neurodegeneration remain to be elucidated,  $\beta$ -arrestin1 and  $\beta$ -arrestin2 have been implicated in a variety of neurodegenerative diseases. Both  $\beta$ -arrestins are upregulated in the brains of AD<sup>91–93</sup>, PD<sup>133,134</sup>, and FTLD-tau<sup>87,88</sup> patients compared to normal controls, indicating that  $\beta$ -arrestins are dysregulated in neurodegenerative diseases. However, there is a clear lack of studies investigating the role of  $\beta$ -arrestins in ALS pathogenesis.  $\beta$ -arrestins directly bind to  $\gamma$ -secretase<sup>91,92</sup>, leading to an increase in toxic A $\beta$  production and accumulation in AD (Fig. 2).  $\beta$ -arrestin1 is also upregulated in an MPTP-induced model of PD<sup>133</sup>, and  $\beta$ -arrestins could be a possible therapeutic target for LIDs<sup>144</sup>. The  $\beta$ 2AR also regulates *SNCA* gene expression by modifying histone acetylation<sup>131</sup> (Fig. 4); however, the role of  $\beta$ -arrestins in this mechanism has not yet been explored. Furthermore,  $\beta$ -arrestin oligomers prevent self-interaction of the autophagy cargo receptor p62/SQSTM1<sup>87,88</sup>, resulting in the accumulation of aggregated tau in FTLD-tau (Fig. 3).  $\beta$ -arrestin1 oligomers compete with tau for microtubule binding, leading to destabilization and tau accumulation<sup>88</sup> (Fig. 3). Given that  $\beta$ -arrestin1 and  $\beta$ -arrestin2 share 78% sequence similarity<sup>1,2</sup>, it is likely that  $\beta$ -arrestin2 is also capable of competing with tau.  $\beta$ -arrestin oligomers are a promising therapeutic target, as cells deficient in oligomers exhibit the same  $\beta$ -arrestin binding capability for clathrin and AP-2<sup>85</sup>, making them indistinguishable from wild-type cells. These studies clearly demonstrate that multiple functions of  $\beta$ -arrestins contribute to neurodegenerative disease pathology, and further studies on  $\beta$ -arrestins are necessary to elucidate disease mechanisms and develop new therapeutic strategies for the prevention or treatment of neurodegeneration.

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T.R.K. and J.A.W.: conceptualization; T.R.K., S.A.K., M.B.N., B.M.M., V.K.Z., Y.K.K., and K.C.M.P.: original draft writing; T.R.K., S.A.K., M.B.N., B.M.M., V.K.Z., Y.K.K., K.C.M.P., and J.A.W.: review and editing; T.R.K. and J.A.W.: supervision; J.A.W.: funding acquisition.

## COMPETING INTERESTS

The authors declare no competing interests.

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