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REVIEW ARTICLE

The Role of Akt Signalling Pathway in Neurological and Cardiovascular Pathologies

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ABSTRACT

The PI3K/Akt/mTOR signalling pathway plays a crucial role in several biological processes, including cell proliferation, survival, and apoptosis, as well as regulates numerous signalling pathways, including JNK, NF-κB, and ERK pathways. The recent proliferation of signal transduction studies in neurological and cardiovascular diseases/injuries sheds light on Akt-dependent pathogenesis. The downregulation of the Akt signalling pathway 24 hours post-injury prevents neurogenesis and promotes the progression of severe secondary injuries, including neuroinflammation, scar formation, and neuronal and glial necrosis, following traumatic brain and spinal cord injury, suggesting designing therapeutic approaches within a 24-hour window post-injury. Similarly, the downregulation of the Akt signalling pathway in myocardial infarction lowers cardiovascular protection, limits neurovascularization, and inhibits cell survival. Following myocarditis, the Akt signalling network is upregulated, leading to aggravated inflammation, and increased myocardial damage. Also, the upregulation of the PI3K/Akt/mTOR pathway in chordoma promotes tumor progression and invasion, leading to neuronal damage and impaired physiological functions. Future therapeutics that target the aberrant expression of key players in the PI3K/Akt/mTOR signalling pathway present a promising approach to treating several neurological and cardiovascular pathologies. This narrative review discusses the role of PI3K/Akt/mTOR signalling pathway in traumatic central nervous system injuries (brain and spinal cord), cardiac injury (myocardial infarction), inflammatory disease (myocarditis), and rare neurological cancer (chordoma) along with therapeutic targets that are known to prevent worsened outcomes and promote recovery following those conditions.

Keywords: PI3K/Akt/mTOR Signalling Pathway, Traumatic Spinal Cord Injury, Traumatic Brain Injury, Myocardial Infarction, Myocarditis, Chordoma.

INTRODUCTION

The Akt signalling is essential for cell survival, the cell cycle, and proliferation and is regulated by the phosphorylation of several growth factors and receptors that transduces the signal to transcription factors (i.e., activated Akt acts as a secondary messenger).[1,2] Akt is made from v-Akt and Akt-8 and has 68% homology with PKA and 73% homology with PKC; this high homology rate leads Akt to be termed as PKA/PKC-associated kinase.[3] Akt is divided into three homologous subtypes encoded by distinct genes: Akt1/PKB, Akt2/PKB, and Akt3/PKB, where each isoform has a pleckstrin homology (PH) domain at the N-terminus, and a central fragment, with a regulatory domain at the C-terminus, as well as a kinase catalytic domain.[2] The kinase catalytic domain has homologous regions to PKA and PKC where the Thr308 site and Ser473 (located on the C-terminal) site are needed for complete activation of Akt.[4] Despite their similarities, the three Akt subtypes conduct diverse physiological functions; Akt1, for example, is ubiquitously expressed and involved in cell formation, apoptosis, size, proliferation, angiogenesis, and tumour cell invasiveness.[1,2,5,6] Akt2 is present in insulin-sensitive tissues, as well as mammalian skeletal muscle and adipose tissue, and has been proven to regulate glucose homeostasis and cell growth and proliferation, while Akt[3] is related to the brain (i.e., required for brain size and malignant glioma cell survival), lung, heart, kidney, testis, and skeletal muscle.[1,5,6] Akt is the primary mediator of the Akt signalling pathway, resulting in phosphorylation of downstream targets, and is active in various biological pathways like cAMP, p27 inhibition, pathways that comprise upstream PI3K and PTEN, and downstream TSC2, FOXO, eIF4E, activating

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PI3P and mTOR (Figure 1).[5,7] Furthermore, several negative regulators, such as PTEN, prevent the activation of the Akt signalling pathway by hydrolysing PIP-3 to PIP-2, decreasing downstream p-Akt activity (Figure 1).[5,8]

The PI3K and Akt signalling pathway is enhanced by EGF, sonic hedgehog, IGF-1, insulin, and calmodulin; conversely, Akt can be antagonized by PTEN, glycogen synthase kinase 3β, and the HB9 transcription factor.[9,10] PI-(3,4,5)-P3 is necessary for the Akt activation and attracts Akt from the cytoplasm, causing ring-phosphorylation and conformational changes to the Akt via a combination of PDK1 and PI-(3,4,5)-P3.[11] PDK2 phosphorylates the Akt hydrophobic terminal, and double-phosphorylated Akt separates from the membrane, resulting in a cellular reaction with the substrate that includes PDK2, ILK, mTORC, and DNA-PK. The PI3K/Akt pathway is activated by PI-(3,4,5)-P3, Akt conformational alterations, and double-phosphorylation of Akt. PTEN transforms PI-(3,4,5)-P3 into a different compound inhibiting the Akt pathway (Figure 1). However, when PTEN is inhibited, the Akt pathway activates again; furthermore, carboxyl-terminal modulator protein C may decrease Akt phosphorylation and impede the PI3K/Akt signalling pathway.[2,12] Overall, the activation of Akt pathways promotes genetic stability, cell survival, NO production, glucose uptake, neuroregeneration, and NF-κB pathway, and inhibition of cellular apoptosis, neuroprotection, JNK, and ERK pathways (Figure 1).

In this narrative review, we elaborate on the role of PI3K/Akt/mTOR signalling pathways in life-changing and life-threatening neurological and cardiovascular pathologies, including traumatic brain injury, traumatic spinal cord injury, myocardial infarction, myocarditis, and chordoma. These findings have reshaped our insights into Akt signalling network-mediated pathogenesis and highlight its differential regulation in cell survival/death (i.e., traumatic injuries), cell inflammation (i.e., viral infection), and uncontrollable cell proliferation (i.e., cancer). We expect the studies of Akt signalling and neurological and cardiovascular pathologies to provide deeper insight into the pathogenesis and progression of diseases while providing opportunities for exploring novel therapies.

AKT SIGNALLING PATHWAY IN NEUROLOGICAL PATHOLOGIES

Downregulated Akt Signalling Pathway in Traumatic Brain Injury

Traumatic brain injury (TBI) is a life-threatening event that results in motor and cognitive dysfunction, long-term disability, and/or death due to the inability of cerebral tissue to repair and regenerate following blunt (i.e., blows or jolts) or invasive sharp objects (i.e., bullets) trauma.[13] Along with its striking annual prevalence of 200 per 100,000 people and mortality rate of 18 per 100,000 people worldwide, it has affected more than 2.5 million people in the United States alone.[13–15] Hence, ensuring its place in one of the most heavily researched diseases globally, with the common aim of saving mankind.[13] The sudden mechanical damage initiates the primary mechanism of TBI, which involves deformities in the brain tissue, hemorrhage, contusion, diffuse axonal injury, necrosis, the release of cytokines and chemokines, and the leakage of crucial ions, proteins, fluid, and immune cells' transmigration due to the dysfunctioning of the vascular and blood-brain barrier.[13] This distortion in brain anatomy and increased intracranial pressure induces the activation of secondary injuries such as oxidative stress, excitotoxicity, and demyelination leading to inflammation, apoptosis, autoimmune reaction, and neurodegeneration.[13] The onset of secondary injuries has been debated in the literature with a range of hours to days post-primary injury, which causes gradual alteration in neurotransmitters (i.e., dopamine and serotonin), metabolic disorders, and morphological changes of mitochondria.[13,16] The delayed occurrence of secondary injuries provides an opportunity for therapeutic intervention to prevent neurological deficits, including cognitive decline, impairment in neurological functions, psychological alterations, and long-term disability.[13] Alteration of several signalling pathways, including PI3K/Akt/mTOR, is associated with the onset of secondary injuries and promotes neuronal death following TBI; hence, it presents a promising therapeutic target for preclinical and clinical trials.[13,17]

The Akt signalling pathway plays a key role as a survival signalling pathway by blocking apoptosis through the activation of Ser87, XIAP, and PRAS40 while inhibiting YAP.[18] The alteration in Akt kinase expression initiated at 15 mins, rapidly increased till 4 hours, peaked between 4 to 24 hours, and started to significantly subside after 72 hours post-TBI.[18,19] Interestingly, the induction of the Akt pathway was observed in the lesion side/ipsilateral hemisphere (i.e., injured hippocampus and cerebral cortex) while no significant alteration in the contralateral hemisphere of the brain.[18,20] In the hippocampus (dentate gyrus, CA1, and CA3 regions), the hallmarks of Akt hyperactivation (specific to the hippocampus), including mTORC1 complex (i.e., comprising GβL, Rictor, and mTOR) dependent phosphorylation of ribosomal protein S6 and mTORC2 complex (i.e., comprising GβL, Raptor, and mTOR) associated Ser473 phosphorylation was observed at 15 to 24 hours and 4 hours post-TBI, respectively (Figure 2).[18,21] Moreover, a decreased expression of phospho-Akt (p-Akt) along with phosphorylated phosphatase and tensin homolog deleted on chromosome 10 (p-PTEN) was observed in cortical and CA3 hippocampal neurons following TBI, which may have caused excessive inflammation in and around the lesion site of the brain and eventually worsening the condition of the patient.[22]

Following traumatic brain injury, the inhibition of the Akt signalling pathway occurs, resulting in inflammation and cerebral necrosis, while its therapeutic upregulation leads to neurogenesis. Several studies have shown a strong relationship

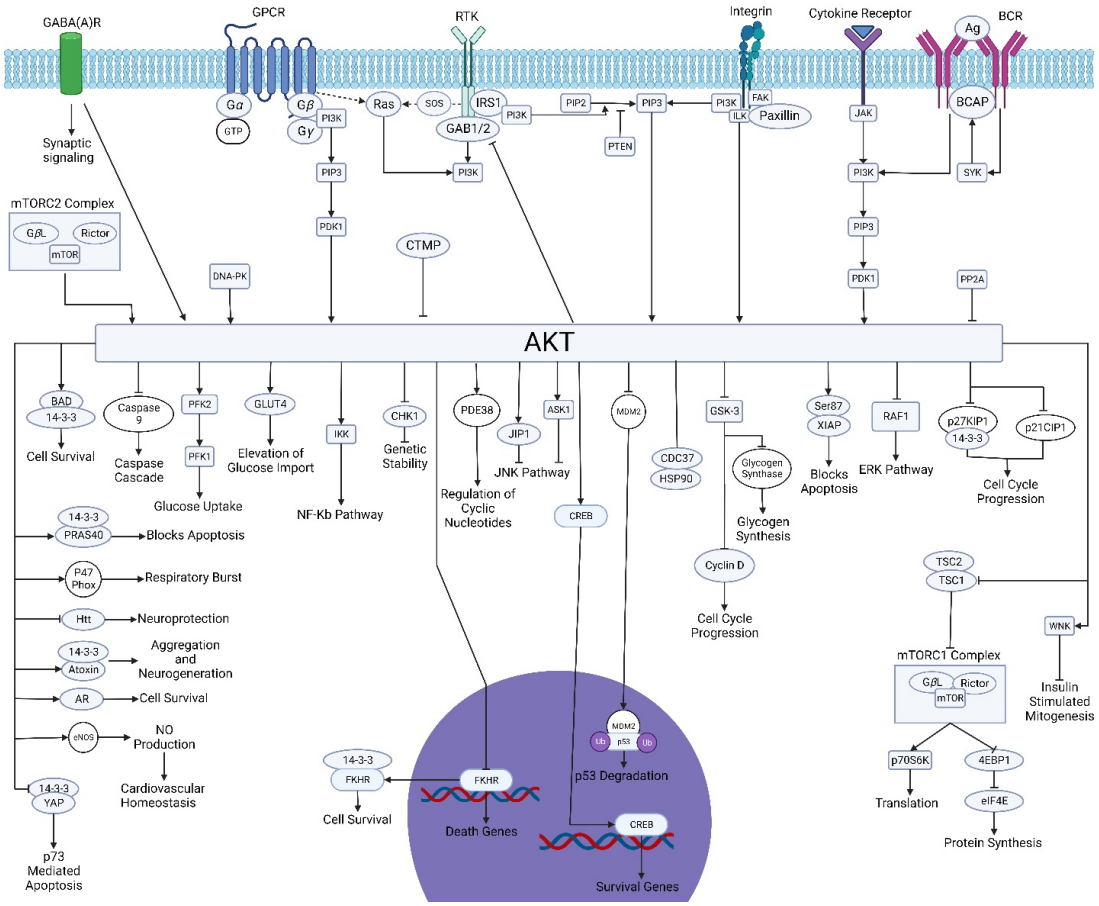

Figure 1. An Overview of the Akt Signalling Pathways Network. Akt signalling cascades are activated by the stimulation of gamma-aminobutyric acid (GABA) receptors, G-protein-coupled receptors (GPCR), receptor tyrosine kinases (RTKs), B-cell receptor, integrin, and cytokine receptors through neurotransmitter GABA, inflammatory cytokines, and growth factors. The set of adaptors (G$\alpha/\beta/\gamma$, IRS1, GAB1/2, FAK, ILK, JAK, and BCAP) links the activated receptor to other factors (SOS, PI3K, and PIP3) leading to signal transduction through small GTP-binding proteins such as Ras. The Akt is the central mediator of every pathway that transduces the signal downstream to dictate cell functioning and alteration in gene expression through the mediating of transcription factors such as FKHR and CREB. The figure was created in BioRender (BioRender.com).

between the inhibition of the Akt signalling pathway with the progression of inflammation and cerebral necrosis as well as lowering the effects of neuroprotective medications such as valproic acid that acts by inhibiting histone-deacetylases to delay apoptosis in degenerating neurons.[23,24] Research conducted at The State University of New Jersey and Harvard Medical School showed the role of activating Akt and mTORC1 pathways in improving memory and learning, reducing neuron apoptosis, and showed no effect on inflammation, while the inhibition of those pathways yielded no beneficial effects following TBI.[18,20] A 14-day-long TBI treatment using Simvastatin, a cholesterol-lowering medication, promoted the upregulation of Akt signalling, causing increased expression of growth factors and neurogenesis, leading to improved cognition.[18,25] In the research conducted at the Washington University School of Medicine, the use of Rapamycin, an immunosuppressant medication, inhibits the mTORC1 signalling to reduce neuron apoptosis and posttraumatic epilepsy in mice following four weeks of treatment post-TBI (i.e., the specific model of TBI was controlled cortical impact as the mTORC1 pathway was hyperactivated following injury.[18,26] Furthermore, Stachydrine activated the Akt pathway and stimulated the expression of Akt/PI3k/m-TOR proteins that had anti-apoptotic and anti-inflammatory effects following TBI.[23,27] Another TBI treatment using a volatile anesthetic, Sevoflurane, activated the Akt signalling pathway that reduced inflammation, blocked programmed cell death, and controlled autophagy responses.[28–31]

Despite the crucial role of the Akt signalling pathway in preventing cell death and inflammation, it is also involved in maintaining the blood-brain barrier (BBB) to treat TBI.[32] The activation of the Akt signalling pathway leads to the inhibition of BBB-weakening RhoA proteins, thereby increasing the integrity of the BBB.[32] To conclude, the recent proliferation of TBI studies suggests that the appropriate timing of therapeutic interventions and targeting the activation of Akt/mTOR/PI3K pathways could lead to recovery from TBI and provide insights into novel drug discovery for TBI.[18,19,33] Furthermore, the activation of Akt interacts with several other signalling

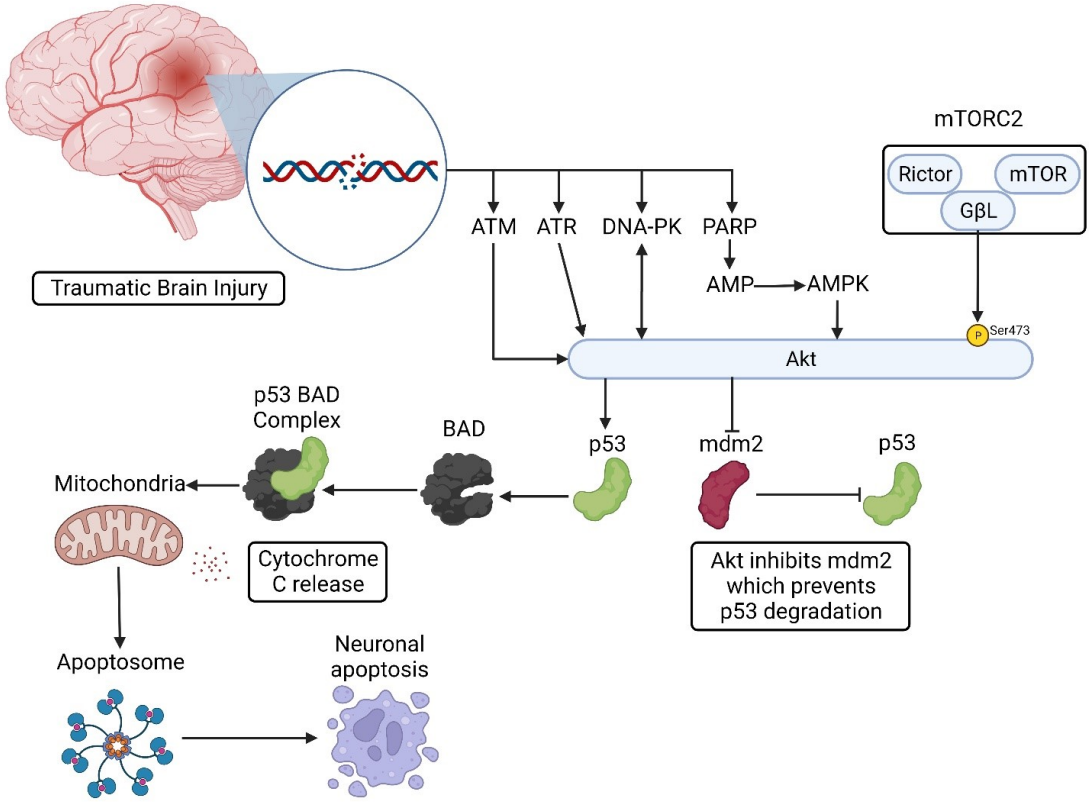

Figure 2. The Akt Signalling Pathway in Traumatic Brain Injury. The Akt signalling pathway is activated by ATM, ATR, DNA-PK, PARP, and mTORC2 when DNA damage occurs due to traumatic brain injury. mTORC2 is composed of Rictor, mTOR, and GβL and it phosphorylates the Ser473 residue of Akt. These proteins activate the Akt signalling pathway till 24 hours post-injury, which inhibits mdm2. This promotes the p53 survival and binds to BAD to form a p53-BAD complex, which triggered cytochrome C release and the formation of an apoptosome leading to neuronal apoptosis. The figure was created in BioRender (BioRender.com).

pathways following TBI that further inhibited neuronal cell death, cytotoxicity, and inflammation: downregulation of ERK pathway via inhibition of Raf1 and JNK pathway via inhibition of ASK1 and binding with JIP1, while upregulation of NF-κB pathway via activation of IKKs and overexpression to promote Akt expression.[34] Conversely, the NF-κB pathway is known to be activated in innate neurodegenerative diseases, including Alzheimer's disease, to promote neuroinflammation and neuronal apoptosis. It should be noted that the crosstalk of NF-κB and Akt signalling pathways is highly complex and context-dependent; hence, further investigation is required.

Downregulated Akt Signalling Pathway in Traumatic Spinal Cord Injury

Traumatic spinal cord injury (SCI) induces physical damage to the superstructure of neural circuits and vascular networks, impairing sensorimotor and autonomous functions.[35] Despite the advancement in neuroscience research, the inability of the spinal cord to undergo innate regeneration and no currently available treatments lead to a compromise in the patient's independence and personal, social, and economic aspects of life.[35] Globally, the annual incidence rate of 60 cases per 1 million and mortality rate of 19% of SCI patients emerges the need to understand the pathogenesis and the development of novel therapeutic strategies to treat SCI.[35] The pathological and physiological alterations following SCI comprise the primary and secondary injury cascades that determine the severity of neuronal loss, scar formation, and subsequent behavioral dysfunction below the injury site.[35] The primary injury comprises mechanical injury (i.e., compressive, and shearing forces) and vasculature disruptions that cause neuronal and glial cell death, neurogenic shock, structural damage (i.e., myelin sheath, axon and axonal connections, and nerve membrane), ionic imbalance, the release of inflammatory mediators (i.e., cytokines), and synaptic alteration (i.e., neurotransmitter levels).[35] The primary injury is inevitable and irreversible; hence, the treatment following SCI must focus on inhibiting harmful secondary injury cascade to promote neuroplasticity.[35–38] The secondary injury cascade is characterized by ischemia/hemorrhage (i.e., excessive ROS and Ca^{+2} production), inflammation (i.e., astrogliosis, infiltration of lymphocytes in the lesion, activation of monocytes), and excitotoxicity (i.e., excess level of glutamate, oxidative stress due to Ca^{+2} overproduction, and apoptosis) that gradually leads to cystic cavitation, glial scar formation, and complex apoptosis-associated signal transduction systems.[35]

The activation of PI3K and Akt signalling pathways plays a significant role in neuron and glial cell survival and cell cycle progression by limiting the apoptotic cell signalling triggered by injury-induced growth-inhibiting extracellular matrix.[35] The activated PI3K kinase dimer can be transferred to the cytomembrane's interior surface for promoting PIP3 or the conversion of PIP2 to PIP3, which phosphorylates and activates the Akt kinase.[35] Several cascades are involved in activated Akt-mediated blocking of apoptosis: activation of the Ser87 and XIAP along with PRAS40 and inhibition of YAP.[35] Interestingly, the activated Akt is also known to inhibit cell survival, and cell cycle progression cascades through the inhibition of BAD, p21CIP1, p27KIP1, FKHR, and GSK-3 (Figure 3).[35] The inhibition of cell survival-promoting FKHR transcription factor could be explained due to its additional role in death genes that outweighs its beneficial role; however, the mystery behind inhibiting other cell proliferating cascades remains unexplored.[35]

The recent proliferation of cell signalling studies suggests the activation of PI3K and Akt signalling pathways is critical for protecting neural tissue from ischemia and anoxia neuron damage, boosting cell proliferation, preventing neuronal apoptosis in the spinal cord by regulating the permeability of the blood-spinal cord barrier (BSCB) and regulating autophagy through medications such as Baicalin.[39–42] Despite the importance of Akt in SCI, it has a remarkable contribution to autophagy regulation that was previously thought to stabilize neuronal microtubules through promoting degradation of the microtubule-destabilizing protein (i.e., superior-cervical ganglia protein 10).[42] The Akt-mediated autophagy modulation is known to improve gait post-SCI through axon regeneration and attenuated axon retraction.[42] Moreover, autophagy promotes BSCB restoration and integrity by preventing the loss of tight and adherents junction proteins following SCI; hence, future research should emphasize the relationship between autophagy and apoptosis (i.e., crosstalk of signal transduction).[42] The impact of altered autophagy following neurotrauma shows discrepancies throughout the literature; however, its involvement in the removal of accumulating pro-inflammatory factors helps reduce the prolonged inflammation following SCI and has consistently improved axonal regeneration and locomotor functionality.[42]

Exploring the transcriptomic studies, the cytoplasmic Akt, PI3K, and pAkt had an upregulated expressional pattern for the first 24 hours post-SCI, and then it gradually decreased over time, which strengthens the concept of secondary injuries in promoting spinal cord healing at the initial stage and has a detrimental effect at the prolonged stage (i.e., after 24 hours post-SCI).[35] In accordance with Dobkin's 'window stage' hypothesis, these findings suggest the presence of a vital phase (i.e., within 7 to 14 days) following spinal cord damage that is a critical period for the effective restoration of the defense system through ectogenic intervention treatments (i.e., drug therapy and stem cell transplantation).[35] During this vital phase, those treatments will not just avoid the adverse environment of the acute secondary injury phase but also generate a favorable microenvironment for tissue repair, stem cell regeneration, and therapeutic action, therefore preventing the formation of glial scars and promoting functional recovery.[35]

Furthermore, olfactory ensheathing cells (OECs) promote neuroplasticity/neuroregeneration following SCI, acting as a possible candidate for SCI cell transplant treatment.[43] Previous research has shown that activating the PI3K/Akt pathway can boost vascular endothelial cell proliferation and migration through the VEGF-A or PDGF-AA cascade.[43–46] The research emphasizing the association between activated OECs and the PI3K/Akt signalling pathway revealed the participation of the PI3K/Akt signalling pathway in pro-angiogenic events generated by the incorporation of conditioned medium (i.e., extracted from activated OEC) into the vascular endothelial cell, which suggest the involvement of PI3K/Akt pathway in promoting the effectiveness of various neurotherapeutics.[43]

AKT SIGNALLING PATHWAY IN CARDIOVASCULAR PATHOLOGIES

Downregulated Akt Signalling Pathway in Myocardial Infarction

Myocardial infarction (MI), one of the leading causes of death, has an annual prevalence of 3 million people worldwide and an annual mortality of more than 1 million in the United States alone.[47] Myocardial infarction, categorized into non-ST-segment elevation and ST-segment elevation, results in irreversible damage to the cardiac tissue due to oxygen deprivation and may lead to arrhythmias due to impaired heart function.[47,48] The narrowing of coronary arteries, coronary microembolization, and transient occlusion results in non-ST-segment elevation MI, while the ST-segment elevation MI is caused by complete and prolonged epicardial coronary occlusion leads to insufficient collateral circulation.[48] An effective strategy for dealing with these issues is restoring blood flow to hypoxic-ischemic tissue, rescuing the tissue in that area, and preventing it from further stress damage and cell-programmed death.[49] The most common methods for treating MI are thrombolysis, heparin with tPA, balloon angioplasty (PCI), and coronary artery bypass grafting.[49] While these treatments help reduce the death rate of MI, there is a high risk of subsequent hemorrhages and coronary restenosis that can further complicate the patient's condition.[49] Despite those clinically available treatments, the innate recovery of cardiac tissue following MI remains questionable; hence, exploring therapeutic options to promote innate cardiac repair and regeneration would be beneficial to save many people's lives.

Regarding the pathogenesis and therapeutic opportunities for myocardial infarction, the upregulation of the Akt signalling pathway is known to be advantageous for the repair and re-

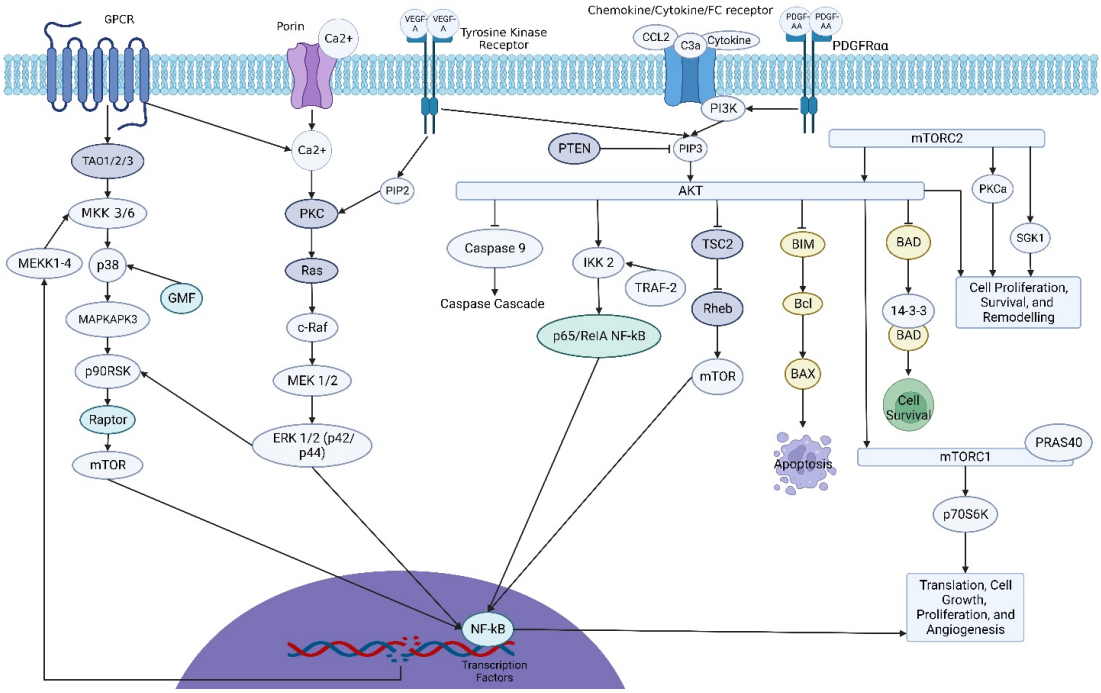

Figure 3. The Akt Signalling Pathway in Traumatic Spinal Cord Injury. The Akt signalling pathway is activated by PIP3, which is activated by PI3K. Akt then begins to initiate survival pathways by inhibiting caspase cascades, apoptosis, and activation of transcription factors that promote survival and growth pathways. It is also involved in activating Raptor and mTOR, which also triggers transcription factors for growth and survival. Furthermore, you have Tyorsine kinase receptors which bind VEGF-A wrestling in activation of PIP2 which then activates PKC leading to the PKC pathway depicted. This PKC pathway is also activated by a porin. There is also a PDGFR$\alpha\alpha$ which binds PDGFAA dimer which leads to the activation of PI3K which is also activated by the Chemokine/Cytokine/FC receptor. This leads to PIP3 and then Akt activation. The figure was created in BioRender (BioRender.com).

generation of cardiomyocytes.[50] Research conducted by Feng et al. demonstrated that the aerobic and resistance exercise-induced upregulation of IGF-1/IGF-1R-phosphatidylinositol 3-kinase (PI3K) and Akt signalling pathway resulted in protein synthesis, increased expression of myogenic regulatory factors, reduced protein degradation, and inhibited the apoptosis of myocytes following MI.[51] In cardiac tissue, the overexpression of PI3K kinase dimer resulted in the conversion of PIP2 to PIP3 lipid that binds to the PH domain of Akt kinase, causing a conformational change, which exposes the Ser473 and Thr308 sites of the Akt kinase.[52] The PDK1 and PDK2 phosphorylate the Ser473 and Thr308 sites, which allows for the Akt-based regulation of cardiac recovery following myocardial infarction.[53] The activation of Akt/PI3K pathways promotes the proliferation of endothelial cells in MI patients leading to angiogenesis due to the accumulation of myeloid cells, transducing pro-inflammatory signals, collagen production, and activation of the JAK/STAT pathway.[54,55] Moreover, activating the PI3K, Akt, and MAPK pathways promotes the production of functional vasculatures, which aid in the organization and development of complex blood vessel networks for efficient oxygen and nutrition delivery.[56,57]

Following MI, the therapeutic activation of the Akt signalling pathway resulted in the activation of the Notch signalling pathway that, in response, promoted the overexpression of PI3K and Akt signalling pathway; hence, several therapeutics are designed to take advantage of the Notch signalling pathway activation through Oestrogen receptor β.[50,58] This inter-activation and crosstalk between the two pathways establish a positive feedback loop, which is essential for cardiovascular protection, regulating cardiac regeneration, promoting neurovascularization, and improving angiogenesis.[59,60] Moreover, when targeted by platelet-derived growth-factor-BB, the Akt phosphorylation accomplished through Notch leads to the upregulation of ERK1/2 (i.e., MAPK signalling pathway) that promotes vascular endothelial cell migration and recruitment.[50,61]

Several studies have studied the involvement of various kinds of RNAs in cell proliferation and recovery through their interaction with Akt and PTEN signalling pathways following MI.[50] Recent proliferation in studies emphasizing the importance of long non-coding RNAs revealed that the binding of small nucleolar RNA host gene 1 binds to PTEN and forms a positive feedback loop with Akt, PTEN, and c-Myc to induce cardiomyocyte proliferation.[50,62] Here, the Akt pathway not only aids in regeneration but also promotes cell survival in the myocardium through increasing anti-apoptotic signals and reducing inflammation.[63] This effect is consistent with medication such as Rosuvastatin that activates the PI3K and Akt pathways, where the medication successfully reduces the caspase-3 levels due to active Akt pathways and inhibits NF-κB p65.[63]

Around the globe, stem cells (i.e., especially Human-Induced Pluripotent Stem Cells (hiPSC)) have received great attention as one of the best regenerative therapeutics following MI or other cardiac disorders. Human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) are known to improve myocardial recovery by replacing the injured cardiomyocytes; however, they are significantly more prone to hypoxia due to the downregulation of the Akt signalling pathway following MI.[64] The treatment with thymosin β4 (Tb4) activated the integrin-linked kinase that promoted the Akt signalling pathway, which resulted in the activation of transcription factors responsible for the overexpression of caspase inhibitors in hiPSC-CMs that protected them from hypoxia-induced cellular damage.[64]

Following myocardial infarction, nerve growth factor (NGF) poly (lactic-co-glycolic acid) (PLGA) nanoparticles exerted a protective effect on human umbilical cord mesenchymal stem cell (hUCMSC) and enhanced the paracrine effects of hUCMSCs on protecting cardiomyocyte and promoting angiogenesis through the regulation of the TrkA (tyrosine kinase A) and PI3K/Akt signalling pathways.[65] To further investigate the role of those pathways in the NGF-induced protection of hUCMSCs, the inhibition of TrkA or Akt signalling pathways using K252a or MK-2206, respectively, led to the complete failure of the anti-apoptotic effect of NGF and the subsequent angiogenesis (i.e., reversed the effects of NGF).[65] Research conducted at Duke University demonstrated a similar role of the Akt signalling pathway in inhibiting hypoxia-induced apoptosis and ventricular remodeling, limiting infarct size, and promoting cardiac/ventricular function (i.e., effectively contracting cardiomyocytes) following Akt-overexpressing mesenchymal stem cells (Akt-MSCs) therapy for myocardial infarction.[66] Lastly, the inhibition of Akt activity through nitrosylation increased the infarct size and reduced the capillary density, hence, delaying the revascularization and subsequent cardiac recovery.[67]

Upregulated Akt Signalling Pathway in Myocarditis

In the nineteenth century, the term "myocarditis" was first used in medical literature to characterize disorders of the heart muscle that were not connected with valve abnormalities.[67] The currently accepted definition of myocarditis refers to the heart muscle inflammation characterized by necrosis, inflammatory cell infiltration (i.e., monocyte and lymphocyte infiltration, pro-inflammatory chemokines, cytokines, and autoantibodies) in the myocardial interstitium, fibrosis, and edema.[68] Certain medical conditions are known to elevate the risk of developing myocarditis, including diabetes, AIDS, HIV, autoimmune disorders, and viral, bacterial, parasitic, and fungal infections.[68] Myocarditis, a silent illness with few physiological symptoms, is one of the top causes of unexplained sudden death (i.e., accounting for around 20% of cases) in the age group under 40 years, young athletes, US Air Force recruits, and elite Swedish orienteers.[68]

The recent proliferation of cardiology studies demonstrated that inhibiting the PI3K/Akt pathway significantly reduced the development of myocarditis (i.e., myocarditis patients had significantly increased p-Akt levels) (Figure 4), hence, protein kinase B (Akt) is an essential therapeutic target for the development, progression, and inhibition of myocarditis.[68–71] When testing the effect of inhibiting and activating the PI3K and Akt signalling pathway, it was found that lowering Akt phosphorylation using LY294002 (a PI3K inhibitor) promoted apoptosis in Coxsackievirus (CVB) 3 infected cells, decreased myocardial damage, and improve cardiac function in experimental autoimmune myocarditis animals.[72,73] Moreover, the CVB3 infection-induced autophagic response aggravated in Akt1-overexpressing cells through direct inhibition of Akt, hence, suppressing the disease progression, while Akt-/- mice increased the occurrence of experimental autoimmune encephalomyelitis.[68,74,75] Several transcriptomic studies (i.e., RNA-Seq and microarray) showed the activation of the Akt signalling pathway in myocarditis, causing alterations to genes related to the Akt network.[76,77]

Some naturally occurring compounds such as salidroside, curcumin, and Scutellaria baicalensis Georgi are known to inhibit PI3K/Akt/GSK-3β, PI3K/Akt/NF-κB, and Akt/p38 signalling pathways, respectively, from sepsis and CVB3-myocarditis.[72,73,78–81] Hence, those compounds act as natural antiviral agents that can help downregulate the mRNA levels of myocarditis-promoting signalling pathways, and their administration within 48 hours post the onset of symptomatic infection yields the best results.[81] Andrographolide, a labdane diterpenoid, downregulates the levels of p-PI3K and p-Akt while causing no alteration to the PI3K and Akt levels, indicating that this compound inhibits myosin-induced proliferation.[82,83] Also, andrographolide appears to suppress the formation of experimental autoimmune myocarditis, which may be related to its ability to inhibit the Akt signalling pathway and its anti-inflammatory effects.[83] SC79, an Akt phosphorylation activator, and Akt-PH domain translocation inhibitor, is known to counter the effects of this compound.[83] Contradictorily, the constitutive Akt activation in a healthy heart increased cardiomyocyte growth/size and resulted in concentric left ventricular hypertrophy, whereas Akt knockout mice had smaller heart sizes.[84] Furthermore, Akt activation elevated the expression of angioprotein-2 and VEGF in cardiomyocytes leading to increased cardiac capillary density and physiological hypertrophic remodeling.[85] Therefore, future research should emphasize the impact of Akt downregulation during myocarditis on cardiomyocyte regenerability, function, and cellular structure.

UPREGULATED AKT SIGNALLING PATHWAY IN CHORDOMA

Chordoma, a slow-growing and invasive malignant tumor, arises from the remnants of the non-disintegrating notochord cells post-birth in proximity to the tailbone (i.e., sacral tumor)

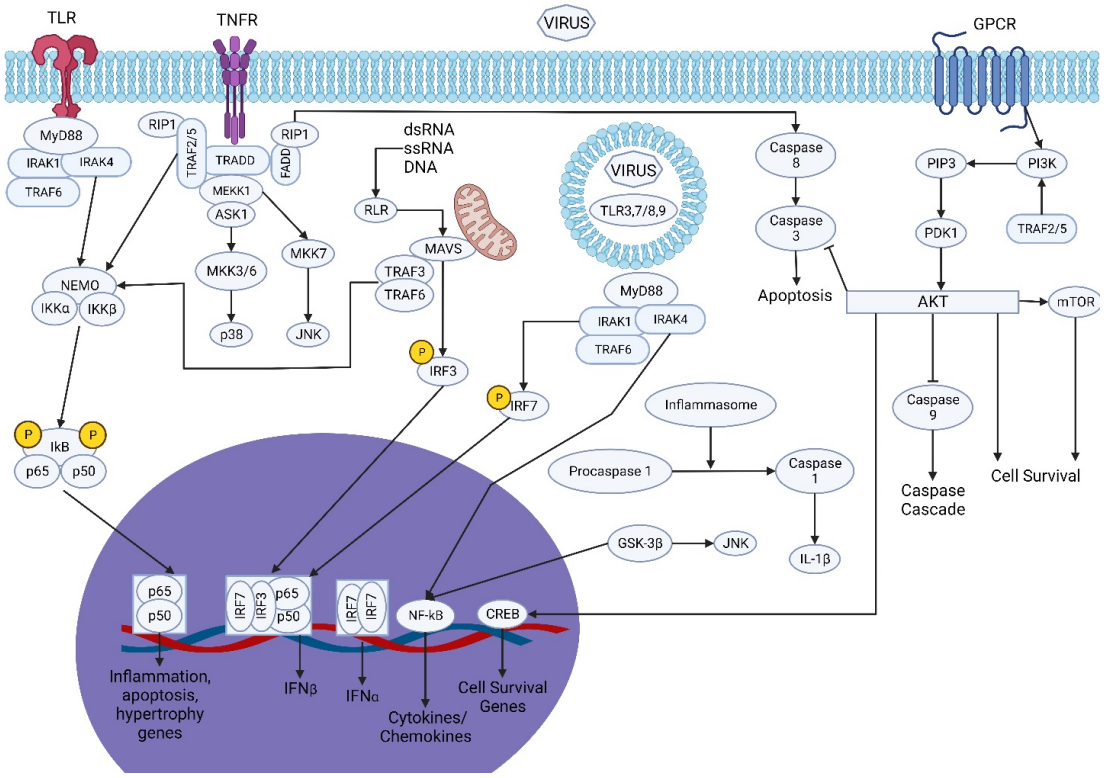

Figure 4. The Akt Signalling Pathway in Myocarditis. An Akt signalling pathway is also involved in myocarditis by promoting cell survival pathways. It does this by inhibiting caspase cascades via the inhibition of caspase 9 which also helps with the inhibition of caspase 3. This helps the cell survive and is also assisted by the Akt activation of mTOR. Furthermore, Akt activates transcription factors that are involved in cell survival which help prevent cell death, protein degradation, increased protein synthesis, and increased myogenic regulatory factors to deal with myocarditis. Furthermore, IRAK4 (which is activated with MyD88, IRAK1, and TRAF6) leads to the activation of the NF-κB transcription factor which leads to the release of cytokines and chemokines. This NF-κB activity is also promoted by GSK-3β which also signals to JNK for its pathway. The figure was created in BioRender (BioRender.com).

and articulation of the spine and skull (i.e., clival tumor).[86] Patients are usually diagnosed with chordoma in their 50s and 60s (i.e., accounting for 95% of cases); hence, its detection and diagnosis mostly occur at the severe stage due to no clinically relevant presentation at previous stages.[86] In some cases, such as children's chordomas, the tumor grows at a prominent rate accounting for 5% of cases with high prevalence in female children than male children.[86]

The focus on the association of PI3K/Akt/mTOR pathway and chordoma initially developed with the numerous chordoma patients demonstrating tuberous sclerosis syndrome, which involved the alteration of TSC1/2 genes (i.e., critical downstream effectors of PI3K/Akt/mTOR pathway).[86] Further genomic investigation of chordoma tissue revelated the activation of the PI3k/Akt/mTOR pathway; hence, the regulation of PI3k, Akt, and mTOR is crucial to lessen the severity and pathogenesis of chordoma.[87] To evaluate those therapeutic targets, several molecular, pre-clinical, and clinical studies have shown excellent outcomes in restricting chordoma growth via inhibiting cellular proliferation and promoting apoptosis.[86]

Throughout the literature, the molecular evidence pertaining to the expression of certain proteins, signalling pathway activity, chromosomal alteration, and mutations plays a key role in the development of chordoma. Chromosomal aberrations are unique for chordoma, including the loss of PI3KCA, mTOR, and PTEN at 3q26, 1p36.2, and 10q23 harboring gene regions, respectively.[88–91] The mTOR, RPS6, and S6 have shown gene copy number variation, while it is not observed TSC1/2 suggesting the involvement of other mechanisms for inactivating the TSC1/2 complex (i.e., promotes mTOR pathway).[89] Moreover, 20% of patients showed biallelic inactivation of the TSC1/2 complex (i.e., germline TSC1/2 mutation), abolishing its mTOR-inhibiting effect.[86] Nonsense germline TSC1 mutation was also detected in chordoma patients with a family history of tuberous sclerosis (TSC), which led to the termination of translation.[91] In addition, somatic mutations in Rheb, PI3KCA, PTEN, and mTOR are mainly absent (i.e., a mutation in 1-5% of cases); hence, it is not the primary reason for aberrant signalling regulation. [89,92–94] The lack of TSC1/2 mutations and high expression of Akt, p-Akt, and TSC1/2 proteins suggest the Akt-induced phosphorylation of TSC2 that causes the inactivation of TSC1/2 complex instead of genetic mutation.[85,95,96] Compared to fetal nucleus pulposus tissue, significant expression of p-Akt was observed, which is associated with activation of the Akt signalling pathway and decreased survival

rate.[90] Also, PI3K, mTOR, p-mTOR (> 50% of samples), p-p70S6K (> 50% of samples), p-RPS6K, p-PKD-1, PTEN (correlated with the degree of bone invasion), 4E-BP1, p-4E-BP1, and eIF-4E was differentially expressed in chordoma.[89,95–99] The p-mTOR and p-p70S6K (i.e., better than p-mTOR) have been adequate biomarkers for PI3K/Akt/mTOR pathway activation that demonstrated the upregulation of those pathways in 46-65% of chordoma.[95] Hypermethylation of several cancer-related gene loci in chordoma samples suggested regulating several cellular proliferative pathways, including PI3K/Akt/mTOR pathway.[93,100] Moreover, transcriptomic studies showed: 1) the association between expression of brachyury in tumors and activity of the PI3K/Akt signalling pathway, 2) clival and sacral chordomas had considerably differing expression levels of the PI3K/ACT signalling pathway, and 3) highly expressed YBX1 triggered the EGFR/Akt pathway in chordoma.[101–103]

Numerous prospective therapies are supported by the abundance of pre-clinical research that shows both their *in-vitro* and *in-vivo* efficacy. Treatment with rapamycin, an mTOR complex 1 (mTORC1), has shown: 1) tumor suppressive effects (i.e., decreased tumor volume-cell number, growth, and proliferation), 2) lowered the p-Akt and p-P70S6K levels, 3) delayed the initiation of tumor formation in zebrafish, and 4) increased the survival rate of tumor-bearing fish.[104] Wortmannin, a PI3K inhibitor, lowered the p-Akt levels and brachyury mRNA expression in chordoma cell lines, U-CH1 and U-CH2, respectively.[105] PI-103, a dual PI3K/mTOR inhibitor, decreased cell proliferation and promoted apoptosis while showing tumor-suppressive effects when combined with chemotherapy drugs.[94] In U-CH2, Ly2094002 suppressed the brachyury mRNA expression, while it was also observed in BEZ235 treatment along with its impact on inhibiting cell growth and brachyury protein expression.[105] β-β-dimethylacrylshikonin possesses antitumor activity by lowering the Akt, p-Akt, and p-Erk levels in chordoma cell lines.[106] Antagomirs, inhibiting miR-140-3p and miR-155-5p, promoted the PTEN protein expression that significantly downregulated the PI3K-Akt-mTOR signalling and tumor-cell proliferation.[107] MLN0128, an ATP-competitive dual MTORC1/2 inhibitor, suppressed the activity of the PI3k/Akt/mTOR signalling pathway, while LY294022, a PI3K inhibitor, showed no effect on tumor growth (i.e., mTOR, not activated by PI3K but through Ras oncogene).[108,109]

In terms of clinical evidence, several case reports on the use of rapamycin (slowed chordoma recurrence by six times post-surgery and treatment for ten months), imatinib, and sirolimus (89% improvement in patients and reached stable disease state), everolimus (promoted stable disease state following slight progression during four months of PDGFR inhibitor treatment), and temsirolimus showed positive results for treating chordoma patients.[104,110] A phase 2 clinical study evaluated the impact of imatinib and everolimus treatment for progressively advanced chordoma in 43 adult patients.[111] Although the data demonstrated minimal anticancer activity, certain patients with highly phosphorylated mTOR effectors had better treatment outcomes, indicating a link between mTOR pathway activation and responsiveness to imatinib plus everolimus therapy.[111]

CONCLUSION

Traumatic brain injury, especially the secondary injury following primary physical trauma, results in a wide range of physiological/functional impairments due to neuronal and glial apoptosis, neuroinflammation, excitotoxicity, mitochondrial dysfunction, and axonal damage. Within 24 hours of the onset of TBI, the Akt kinase is significantly upregulated, promoting cell survival and an innate preventive mechanism against the physical trauma; however, the Akt signalling pathway is significantly downregulated after 24 hours leading to severe secondary injury pathologies. This suggests that the therapeutic upregulation of the Akt signalling pathway can be extremely beneficial if performed within 24 hours post-TBI to promote neurogenesis, prevent cell programmed death, control autophagy, and reduce neuroinflammation. Moreover, the crosstalk of the Akt signalling network suggests the role of the downregulation of ERK and JNK pathways and the upregulation of the NF-κB pathway in promoting recovery following TBI. A similar observation of downregulated Akt signalling pathway following 24 hours post-injury inhibits recovery in traumatic spinal cord injury. In cardiovascular injuries such as myocardial infarction, the PI3K/Akt signalling pathway is downregulated; however, the therapeutics upregulation is known to limit infarct size, promote cardiovascular protection and neurovascularization, improve angiogenesis, and increase the efficiency of stem cell therapy. Following myocarditis, the therapeutic inhibition of several Akt signalling networks promoted cardiac regeneration and reduced myocardial damage: PI3K/Akt/GSK-3β, PI3K/Akt/NF-κB, and Akt/p38. Interestingly, the activation of the Akt signalling pathway in myocarditis led to an increase in cardiomyocyte size, resulting in ventricular hypertrophy and lowered cardiac output. Moreover, the pre-clinical and clinical research suggested that the upregulation of the PI3K/Akt/mTOR pathway in chordoma aggravated the invasion and progression of cancerous tissue. In conclusion, the PI3K/Akt/mTOR pathway is downregulated in traumatic injuries (i.e., cell apoptosis) and upregulated in cancer (i.e., uncontrollable cell proliferation) and inflammatory traumas (i.e., cell size growth). Several therapeutic drugs can module the aberrant activity of the PI3K/Akt/mTOR pathway through upregulating or downregulating Akt mRNA expression (Figures 5 and 6) and through activating or inhibiting the PI3K/Akt/mTOR pathway, which can be used to treat several neurological and cardiovascular diseases.

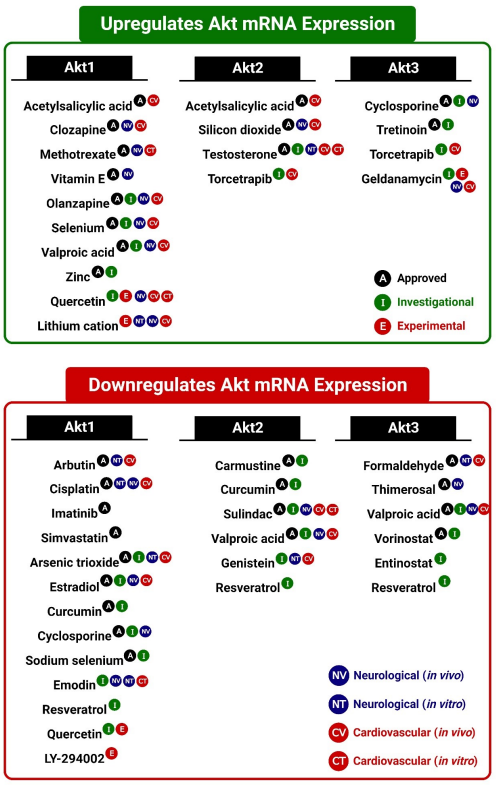

Figure 5. Comprehensive Overview of Akt mRNA Expression-Modulating Drugs. List of approved, investigational, and experimental drugs that are categorized based on their regulatory effect (i.e., upregulate or downregulate) on Akt mRNA expression. Data for the figure was obtained from DrugBank.[112] The figure was created in BioRender (BioRender.com).

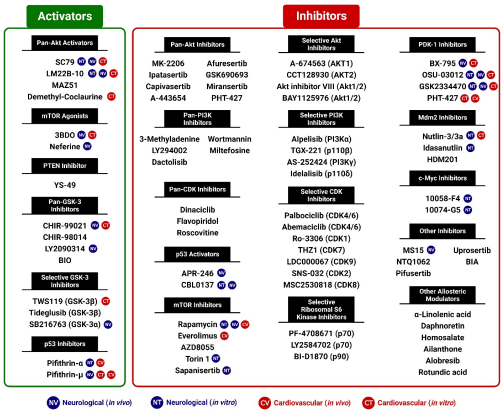

Figure 6. Comprehensive Overview of Akt Signalling Pathway Activators and Inhibitors in Cardiovascular and Neurological Research. List of drugs that act as pan-Akt activators, mTOR agonists, PTEN inhibitors, pan/selective GSK-3 inhibitors, and p53 inhibitors to activate the Akt signalling pathway. List of drugs that act as pan/selective Akt, pan/selective PI3K, pan/selective CDK, mTOR, selective ribosomal S6 kinase, PDK-1, Mdm2, c-Myc, and other inhibitors along with p53 activators and allosteric modulators that deactivate/inhibit the Akt signalling pathway. The activators/inhibitors are divided into 3 categories based on their application in literature: cardiovascular *(in vivo/in vitro)*, neurological *(in vivo/in vitro)*, and potential candidates. Data for the figure was obtained from IUPHAR/BPS Guide to Pharmacology[113] and PubMed literature search. The figure was created in BioRender (BioRender.com).

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