WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 18, 419-431. Review Article ISSN 2277– 7105

HEDGEHOG-GLI SIGNALING IN NEURODEGENERATION BY 3-NITRO PROPIONIC ACID INDUCED: NEUROGENESIS AND BEYOND

Susheela Kumari[1]*, Palvi Sharma[2], Kiran Thakur[3], Shalini Chauhan[4] and Pooja Sharma[5]

[1,3]Associate Professor, Abhilashi College of Pharmacy, Nerchowk, Mandi, HP, 175008.
[2,4]Assistant Professor, Abhilashi College of Pharmacy, Nerchowk, Mandi, HP, 175008.

Article Received on
01 Sept. 2023,
Revised on 21 Sept. 2023,
Accepted on 11 October 2023
DOI: 10.20959/wjpr202318-29971

***Corresponding Author**
Susheela Kumari
Associate Professor,
Abhilashi College of Pharmacy, Nerchowk,
Mandi, HP, 175008.

ABSTRACT

The hedgehog (Hh) pathway is one of a few that regulate the number and kind of cells generated during development in organisms ranging from Drosophila to humans. The hedgehog (SHH) signaling pathway is primarily convoluted in smooth muscle differentiation, adult tissue homeostasis, cell proliferation, tissue repair following injury, embryonic gut development, and tissue polarity during vertebrate and invertebrate development. A number of cellular and molecular pathways are involved in the process of reviving from neurodegeneration damage or injury. One of these is the Hedgehog pathway. The Hedgehog (Hh) signaling pathway is the most common signal transduction pathway in mammalian cells. The pathway has also been associated with several cancer as one of its component is *PTCH* Cause the Basal cell Nevus Syndrome. **Aim:** The aim of this review is about the involvement of hedgehog gli signaling in Neurodegeneration. **Objective:** The objective of this review is to know about the appliance and method of Involvement of hedgehog signaling in Neurodegeneration. In this commentary, we present data that there is the possibility of hedgehog – Gli signaling in Neurodegeneration induced by 3-NP. We Also briefly discuss about the various markers of Neurodegeneration.

KEYWORDS: Neurodegeneration, Hedgehog-Gli, 3-Nitropropionic acid.

INTRODUCTION

Hedgehog (Hh) is one of the few signaling mechanisms that is frequently utilized for intercellular conversation during development. For the Maturation of almost all organs in mammals, as well as for reanimation and equanimity Hh is required. Furthermore, Hh signaling is disrupted in a variety of cancers.[1,2] The hedgehog SHH Smooth muscle differentiation, mature tissue homeostasis, cell proliferation, tissue repair after damage, embryonic gut development, and tissue polarity during vertebrate and invertebrate development are the main signaling pathways that are intricate. Signal intermediaries for the SHH pathway constitutes the GLIoma-Associated Oncogene Homolog (GLI).) family of zinc-finger transcription components and Smoothened (SMO).[3]

Hedgehog (Hh) signalling is crucial for the management of several cellular processes, including embryonic development. Hepatocellular carcinoma, among other human malignancies, has been linked to anomalous activation of Hh signalling. (HCC). In this research, we investigated the molecular mechanisms and pathobiological roles of the Hh signalling pathway in HCC cells.

The progressive degeneration and loss of functioning of neurons, including neuronal death, is defined as degeneration. It is the persistent deterioration of a person's intellectual skills, as memory. This degradation can be attributable to anatomical alterations that hinder preventing neurons' (brain cells') regular function or causing cell death. It is a characteristic of a group of disorders known as "neurodegenerative diseases." Among the most well-known are Frontotemporal Lobar Degeneration (FTLD), Huntington's disease, Alzheimer's disease, Parkinson's disease, and Vascular Cognitive Impairment (VCI), and Amyotropic Lateral Sclerosis (ALS). Genetic mutations cause a small percentage of neurodegenerative disorders (5%). The surviving cases are believed to be the result of toxic protein build up in the brain, as well as a malfunction of the brain's "energy-producing components" (mitochondria), which produces toxic molecules that damage neurons.[4] The major cause of neurodegenerative disorders is ageing. Both mitochondrial DNA mutations and oxidative stress influence to ageing. Protein degradation offers therapeutic alternatives for both avert aberrant protein synthesis and breakdown. Increased autophagy may potentially help to remove protein clumps linked to dementia.[5] The frequent occurrence of neurological conditions like Parkinson's disease and Alzheimer's disease (PD) has increased as global populations have aged (AD) has increased dramatically. Increased tissue oxidative damage, accelerated tau

protein phosphorylation, accumulation of bizarre protein fragments, prolonged inflammatory cytokine production increasing cell atrophy, elevated inflammatory lipid mediators, and apoptosis, decreased neurotransmitter production, decreased mitochondrial and axonal transport are all common features of neurodegenerative illnesses. (Figure 1)

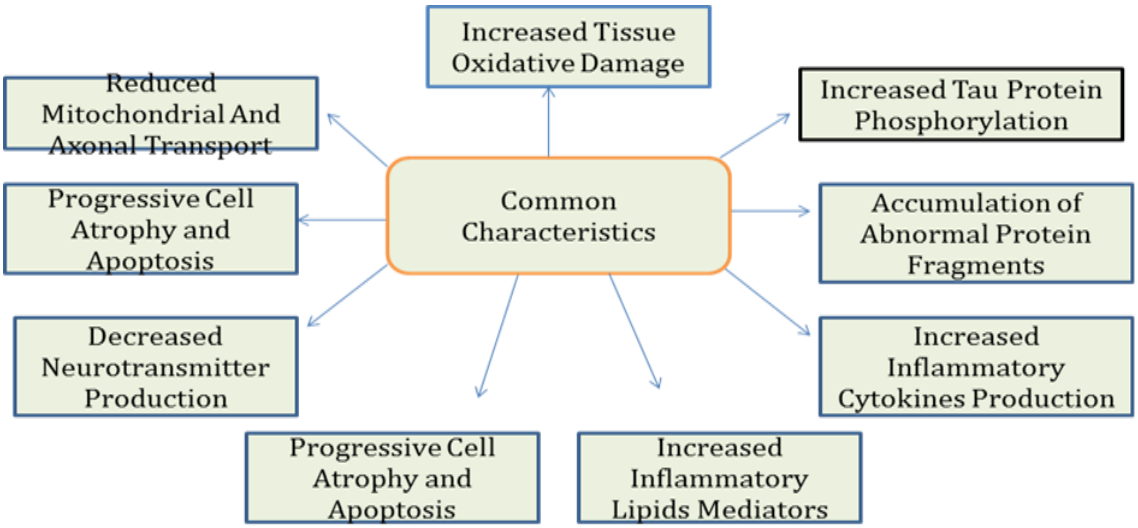

Figure 1: Common characteristics of neurodegeneration.

The process of recovering from harm or injury resulting in neurodegeneration involves numerous cellular and molecular pathways. The Hedgehog route is one of them. The most prevalent signal transduction route in mammalian cells is the hedgehog (Hh) signaling pathway.[6,7] In 1980, Nusslein –Volhard and Weischaus discovered this pathway by genetically screening factors influencing Drosophila embryonic patterning[8]. Sonic hedgehog (Shh), Indian hedgehog (Ihh), and desert hedgehog (Dhh) are three vertebrate that attach to the patched receptor protein. The Sonic Hedgehog (Shh) pathway is vital in the formation of the central nervous system (CNS). Desert hedgehog (Dhh) is another ligand required for proper peripheral nervous system formation (PNS). Ihh (Indian hedgehog) regulates chondrocyte differentiation, proliferation, and maturation, especially during endochondrial ossification.[9]

Tissue damage or brain injuries regulate The generation of Hh molecules and activate their signalling as part of the tissue repair process. These findings sparked further investigation into activating the Gli- mediated process, which could kick start neurogenesis and aid in the recovery from neurodegenerative diseases.[10,11]

Neurodegeneration: Neurodegeneration is the progressive loss of neurons, and this neuronal loss is accompanied by an extracellular and intracellular buildup of misfolded proteins, a characteristic of many neurodegenerative proteinopathies. The Major Neurodegenerative disease is (Figure 2) Alzheimer, Parkinsonism, Huntington's, Frontotemporal Lobar degeneration (FTLD), corticobasal Degeneration (CBD), Amyotrophic Lateral Sclerosis (ALS), Spinocerebellar Ataxia, Spinal Bulbar Muscular Atropy, Progressive Supranuclear Palsy (PSP).

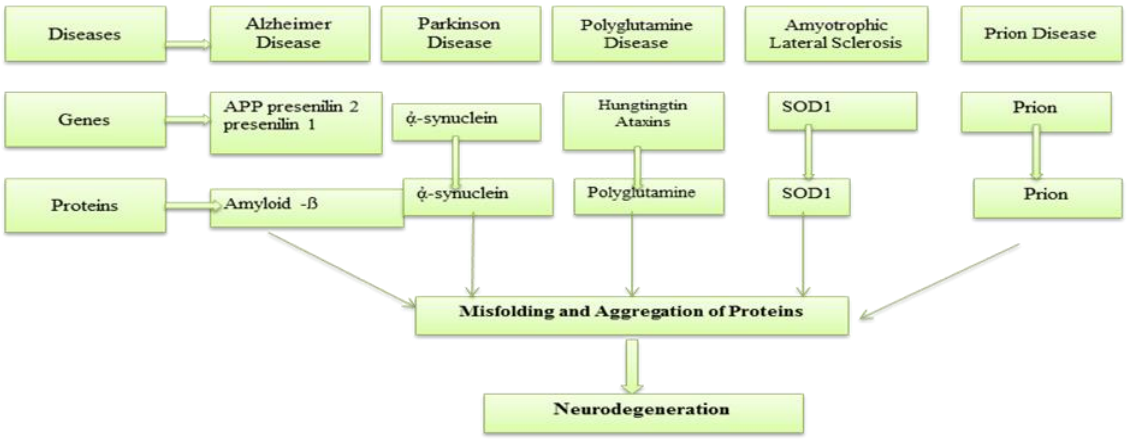

Figure 2: Diseases leading to neurodegeneration.

Mechanism of neurodegeneration:

A number of neurodegenerative diseases follow almost common characteristics and ends up in neurodegeneration. They affect different areas of brain and they can be distinguished according to their associated pathological markers. Mechanism involved in neurodegeneration are as follow:

a) Genetics

b) Protein misfolding

c) Intracellular Mechanism

- Protein Degradation Pathway
- Membrane Destruction
- Axonal Transport
- Mitochondrial Dysfunction

d) Induced Cell Death

- Apoptosis (Type I)
- Autophagic (Type II)
- Cytoplasmic (Type III)

a) Genetic mutation:

Genetic mutations, the majority of which are located in unconnected genes, are the root cause of a number of neurodegenerative diseases. The mutant gene has a similar trait in many of the diseases: a triad of the nucleotide CAG repetition. CAG is an abbreviation for the amino acid glutamine. A polyglutamine (polyQ) tract is generated by the CAG recite. Polyglutamine illnesses are those that manifest this. The CAG– polyglutamine disorder family consists of nine members: spine and bulbar muscular atrophy (SBMA), Huntington disease, dentatorubral pallidoluysian atrophy, and six spino cerebellar ataxias[12]

b) Protein misfolding:

β- amyloid aggregation: - The cerebral cortex, hippocampus, and Meynert's basal nucleus are mostly afflicted by Alzheimer's disease. The production of a peptide (protein) called amyloid beta (beta amyloid, Aß) that builds up into On blood arteries and the brain's extracellular synapses, there are amyloid plaques (senile plaques), eventually causing neurodegeneration, which is thought to be the key event causing AD. Aß peptides have the potential to cause cerebral vasoconstriction.[13] It has been established that Aß inhibits mitochondrial activity in PC12 cells and human neuroblastoma cells.[14] A first sketch resulting from the amyloid chain of events in AD would be: Amyloid plaque development, neuronal death, dementia, and Aß formation.

Amyloid Precursor Protein undergoes enzymatic clipping to produce amyloid beta peptide, a normal neuron membrane protein (APP). The amyloid beta peptide comes in two varieties: one with 40 amino acids and the other with 42 amino acids. The secretases are the enzymes that break down APP. Alpha- secretase and beta-secretase are the two enzymes that combat one another to break APP at first. When alpha- secretase cleaves APP, no Aß is formed. If beta- secretase cleaves APP, It is even more cleaved by gamma- secretase to generate either Aß40, which is soluble and usually harmless, or Aß42, which clusters united to form insoluble amyloid plaques. Aß42 fibrils create amyloid plaques when they group together. Aß40 and Aß42 are generated intracellularly but cause harm when transferred outside of cells. Aß40 is more prevalent in cerebral plaques compared to neuritic plaques, where Aß42 is the most prevalent amyloid-beta.[15].

Polyglutamine disease: The polyQ expansion causes dominant toxicity, which leads to gradual neuronal dysfunction and loss.[16] Through improper protein interaction, polyglutamine-expanded proteins interfere with the activity of nuclear proteins including

histone acetyltransferase (HAT), resulting in transcriptional dysregulation in a family of neurodegenerative diseases. PolyQ illnesses are currently classified into nine forms, including spinocerebellar ataxias (SCAs) and Huntington's disease (HD).[17] Different polyQ diseases are characterised by the production of polyQ oligomers and clusters in the cytosol and nucleus, which leads to neural cell loss in the brain cortex and striatum, in addition to the development of mutant huntingtin's intranuclear inclusions. Postsynaptic signaling, Protein trafficking, vesicle transit, apoptosis and transcription, are all regulated by huntingtin. As a result, several intracellular processes are disrupted due to the normal protein's loss of function and mutant huntingtin's.[18]

c) Intracellular mechanism:

Protein deterioration pathways: Both Parkinson's, Huntington's diseases linked to intracellular harmful protein buildup. Protein aggregation illnesses are diseases induced by protein aggregation. The substantia nigra, the dorsal motor nucleus of the vagus, and the Meynert basal nucleus are all affected by Parkinson's disease.[19] The buildup of misfolded proteins is most likely a critical event in the neurodegeneration of Parkinson's disease. Pathogenic mutations can either directly cause aberrant protein conformations (as with -synuclein) or affect the cellular machinery's capacity to identify and eliminate misfolded proteins (Parkin, UCH-L1). Oxidative damage, which has been associated to mitochondrial dysfunction and aberrant dopamine metabolism, may increase misfolded protein conformations.[20]

Mitochondrial dysfunction: The disruption of brain processes and the development of severe neurodegenerative conditions have both been related to alterations in cholesterol homeostasis because cholesterol has a crucial role to perform in the control of membrane biophysical properties and cell functions through modulation of signaling cascades. However, it is controversial whether the levels of total cholesterol are elevated or diminished in AD, despite the fact that changes in cholesterol homeostasis have been related to neurodegenerative disease.[21] Cellular elements recognized by the immune receptors of microglia are known as damage-associated molecular patterns (DAMPs), and they can cause or exacerbate neuroinflammation in neurodegenerative diseases. Numerous studies have shown a connection between inflammation-mediated mitochondrial malfunction, including that caused by cardiolipin, mitochondrial DNA, and mitochondrial transcription factor A(TFAM). After minor mitochondrial damage, a subtype of EV called mitochondrial-derived

vesicles (MDVs) is created. These EVs fuse with multivesicular bodies and are then released into the extracellular environment as EVs. mtDAMPs, which can trigger an immune response and the release of pro-inflammatory cytokines, are especially abundant in MDVs. Importantly, mounting data confirms the link between inflammation, EV release, and mitochondrial dysfunction[22]

Axonal transport: Multiple neurodegenerative illnesses have been associated with axonal transport abnormalities. Genetic mutations producing axonal transport defects in neurodegenerative disorders are associated with changes in microtubules, kinesin, neurofilaments, dynein and cargoes. Frequently, this causes microtubule instability, impaired adaptor protein recruitment, abnormal motor protein function, and absence of motor protein binding[23]

d) Programmed cell death:

A non-apoptotic type of planned cell death known as ferroptosis, Pyroptosis, Autophagy has recently been discovered. It is characterized by an intracellular buildup of lipid peroxides that is iron-dependent and eventually results in oxidative stress and cell death.[24][25] Neurons may be particularly susceptible to cell loss in NDD due to a number of innate characteristics. There are several reasons for this, including: (1) their post-mitotic nature, which leads to (i) a slow buildup of DNA damage due to ageing, lipids, proteins, and organelles; and (ii) their inability to replicate and replenish the neural cell population; (2) their enormous energy demands, primarily because they need to maintain synaptic activity and the oxidative phosphorylation that results in the production of ROS; and (3) their dendrites and long axons.[26]

Hedgehog pathway

One of the few pathways, the hedgehog (Hh) pathway, controls the quantity and type of cells produced during growth in organisms ranging from Drosophila to human beings. Sonic hedgehog (Shh), the most popular Hh-pathway ligand, has been observed to contribute to the central nervous system's development in the brain, whereas desert hedgehog (Dhh), another ligand, is necessary for proper peripheral nervous system creation (PNS).[27]

Regulation of hedgehog pathway: A distinct mechanism that involves Patched (Ptc) and Smoothened, two of Hh's receptor subunits, delivers the Signal from Hh to the cytosol, to make a sequence of restrictive contacts (Smo). Numerous cellular proteins in Drosophila are

implicated in the transduction of the Hh signal; however, There are no mammalian homologs of Cubitus interruptus (Ci), transcription factor (Gli (1-3), or the Ci/Gli-associated protein, Suppressor of Fused (Su). This mechanism is dormant in the lack of ligand protein; however, in the presence of ligand protein, it attaches to the receptor protein (Ptch) and activates the smoothened seven-transmembrane GPCR (Smo). Supressor of Fused (SUFU)[28] is a negative regulator of the hedgehog pathway that receives the signal from activated smoothened and releases the Gli protein, which subsequently enters the nucleus for transcription. The Gli-controlled genes trigger downstream signals and contribute to cellular proliferation and differentiation[29](Figure 3)

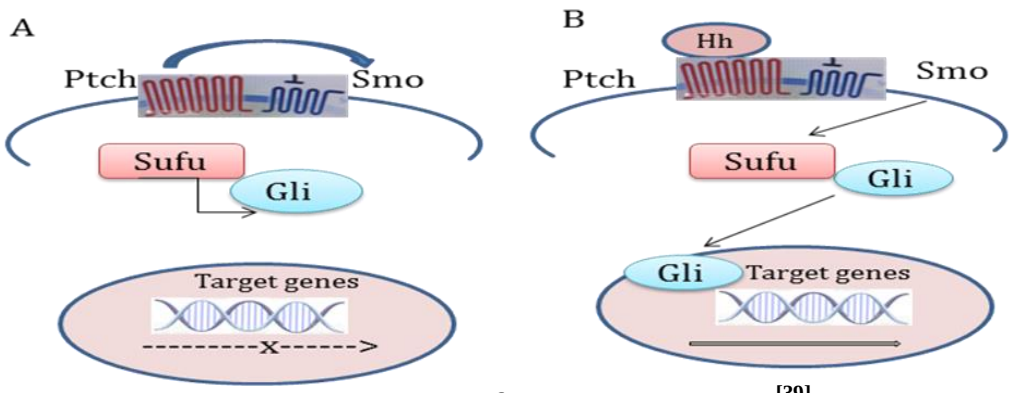

Figure 3: Regulation of hedgehog pathway.[39]

A. In the absence of ligand, transmembrane Patched (Ptch) inhibits the activity of Smo. Gli entry into the nucleus is prevented due to SuFu. Transcriptional activity is repressed.

B. In certain cancers, ligand binds to Ptch; relieves inhibition of Smo. Smo becomes active. Smo signals to activate Gli Transcription factor. Gli translocates to the nucleus; activates target gene expression.

Gli proteins: With roughly 1000 amino acids, the Gli proteins are zinc-finger transcription factors that contain activator and repressor activities. Cubitus interruptus (Ci), a fly Gli related protein, has the ability to operate as both an activator and a repressor. Gli1 is transcriptionally inactive in the absence of Hedgehog signalling, although Gli2 and Gli3 can be produced. The Gli code transforms in the presence of Hh ligands and Smoothened (Smo), a transmembrane protein, is activated, Gli1 is triggered transcriptionally, possibly by pre-existing Gli2 or Gli3, Gli2 turns into an activator, and Gli3 is not further altered. The interaction of the Hh receptor to Ptch, a 12-transmembrane protein receptor, initiates Hh signaling.[30]

Hedgehog Gli signalling pathway in embryonic development: The hedgehog pathway provides cells with the information they need to properly develop the embryo. Proteins from the genus of produced signalling molecules known as hedgehogs (Hh) have been recognized as essential organisers of tissue patterning in studies. In 1992, it was found in Drosophila.[31] Three Hh genes in humans have been found as being related: Sonic, Indian, and Desert hedgehog (Shh, Ihh and Dhh).[6] During animal embryonic development, hedgehog signalling affects cell differentiation and organ creation.[5] It performs a role in the development of several organs, including the Pancreas, cerebellum, gut, and skin.[32][33][3] Hh-GLI1 also act as mitogens, controlling cellular proliferation, longevity, and organogenesis in several anatomical locations of vertebrates, and as a ventral neural tube induction signal, growth of the somatic ventral structures and the anterior-posterior axis of the extremities.[34]

Hedgehog-Pathway in repair mechanisms in adults: Once development is complete, the expression of Hh ligands, Ptc, Smo, and Gli1 in healthy normal tissues diminishes to low levels, at least in rodents. Almost a decade prior, evolutionary scientists hypothesised that adult tissue may reactivate networks like the Hh pathway to promote lesion healing. By encouraging endogenous stem cells to multiply and differentiate, as happens within the embryo, more Hh protein may be capable to restore functional tissue. Shh regulates the proliferation and survival of cerebral precursor cells and helps cells survive. Gli1 transcription, an injectable Hh agonist at concentrations that raise spinal cord operation, boosts the number of neural progenitor cells in adult rats following spinal cord injury.[35] The Hedgehog pathway is also implicated in a variety of disorders and repair mechanisms, including neurodegenerative diseases, acute brain damage, Parkinson's disease, peripheral neuropathy, ischemia, heart vessel maintenance, hair follicle cycling, cancer, and other diseases and repair.[36][37][38]

CONCLUSION

The finding from the present literature demonstrate that there may be the involvement of Hedgehog–Gli in Neurodegeneration induced. Hedgehog pathway is regulated in the cytoplasm by release of GLI protein which causes transcription in the nucleus. The small compartment controls the Hh signalling's primary effectors, the GLI proteins and the unfavourable regulator SUFU. Signal transmission in the hedgehog in vertebrates is crucial for the growth and upkeep of the majority of tissues.

Hh ligand reactions are highly sensitive to changes in cell structure, and disruption of a number of cell components reduces the response. Disruptions of particular cell proteins, however can also cause the pathway to function in an unnecessary manner, and Some proteins may undergo particular modifications that either improve or impair Hh signal transduction. To construct the main cell, dozens, if not thousands, of amino acids are needed; Because Hh signalling plays so many vital roles, mutations in cell genes jointly affect human health in a significant way. The GLI proteins, which are the primary Hh signalling effectors, and the SUFU negative regulator are controlled by the cell. Among these approaches Hedgehog has a novel approach of relevance for neurodegeneration.

REFERENCES

1. Davis FG, Kupelian V, Freels S, McCarthy B, Surawicz T. Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups. Neuro-oncology, 2001; 1, 3(3): 152-8.
2. Bangs F, Anderson KV. Primary cilia and mammalian hedgehog signalling. Cold Spring. Harbor perspectives in biology, 2017; 1, 9 (5): a028175.
3. Bambakidis NC, Horn EM, Nakaji P, Theodore N, Bless E, Dellovade T, Ma C, Wang X, Preul MC, Coons SW, Spetzler RF. Endogenous stem cell proliferation induced by intravenous hedgehog agonist administration after contusion in the adult rat spinal cord. Journal of Neurosurgery: Spine, 2009; 1, 10(2): 171-6.
4. Skovronsky DM, Lee VM, Trojanowski JQ. Neurodegenerative diseases: new concepts of pathogenesis and their therapeutic implications. Annu. Rev. Pathol. Mech. Dis, 2006; 28, 1: 151-70.
5. Varjosalo M, Taipale J. Hedgehog: functions and mechanisms. Genes & development, 2008; 15, 22(18): 2454-72.
6. McMahon AP, Ingham PW, Tabin CJ. 1 Developmental roles and clinical significance of Hedgehog signaling.
7. Ohashi T, Oguro Y, Tanaka T, Shiokawa Z, Shibata S, Sato Y, Yamakawa H, Hattori H, Yamamoto Y, Kondo S, Miyamoto M. Discovery of pyrrolo [3, 2-c] quinoline-4-one derivatives as novel hedgehog signaling inhibitors. Bioorganic & medicinal chemistry, 2012; 15, 20(18): 5496-506.
8. Han JB, Hua YQ, Chen LY, Liu LM. Advances in Smoothened-targeting therapies for pancreatic cancer: implication for drug discovery from herbal medicines. Zhong xi yi jie he xue bao= Journal of Chinese integrative medicine, 2012; 1, 10(3): 256-63.

9. Huycke TR, Eames BF, Kimmel CB. Hedgehog-dependent proliferation drives modular growth during morphogenesis of a dermal bone. Development, 2012; 1, 139(13): 2371-80.
10. Galvin KE, Ye H, Wetmore C. Differential gene induction by genetic and ligand-mediated activation of the Sonic hedgehog pathway in neural stem cells. Developmental biology, 2007; 15, 308 (2): 331-42.
11. Hynes M, Porter JA, Chiang C, Chang D, Tessier-Lavigne M, Beachy PA, Rosenthal A. Induction of midbrain dopaminergic neurons by Sonic hedgehog. Neuron, 1995; 1, 15(1): 35-44.
12. Stoyas CA, La Spada AR. The CAG–polyglutamine repeat diseases: a clinical, molecular, genetic, and pathophysiologic nosology. Handbook of clinical neurology, 2018; 1, 147: 143-70.
13. Niwa K, Porter VA, Kazama KE, Cornfield D, Carlson GA, Iadecola C. Aβ-peptides enhance vasoconstriction in cerebral circulation. American Journal of Physiology-Heart and Circulatory Physiology, 2001; 1, 281(6): H2417-24.
14. Pereira C, Santos MS, Oliveira C. Mitochondrial function impairment induced by amyloid β-peptide on PC12 cells. Neuroreport, 1998; 1, 9(8): 1749-55.
15. Best B. Alzheimer's disease– Molecular Mechanisms. Retrieved on March, 1990; 27: 2014.
16. Bilen J, Liu N, Burnett BG, Pittman RN, Bonini NM. MicroRNA pathways modulate polyglutamine-induced neurodegeneration. Molecular cell, 2006; 6, 24(1): 157-63.
17. Paulson HL, Shakkottai VG, Clark HB, Orr HT. Polyglutamine spinocerebellar ataxias—from genes to potential treatments. Nature Reviews Neuroscience, 2017; 18(10): 613-26.
18. Argueti-Ostrovsky S, Alfahel L, Kahn J, Israelson A. All Roads Lead to Rome: Different Molecular Players Converge to Common Toxic Pathways in Neurodegeneration. Cells, 2021; 10 (9): 2438.
19. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders?. Neurology, 2007; 30, 68(5): 326-37.
20. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron, 2003; 11, 39(6): 889-909.
21. Arenas F, Garcia-Ruiz C, Fernandez-Checa JC. Intracellular cholesterol trafficking and impact in neurodegeneration. Frontiers in molecular neuroscience, 2017; 17, 10: 382.

22. Deus CM, Tavares H, Beatriz M, Mota S, Lopes C. Mitochondrial Damage-Associated Molecular Patterns Content in Extracellular Vesicles Promotes Early Inflammation in Neurodegenerative Disorders. Cells, 2022; 1, 11(15): 2364.
23. Guo W, Dittlau KS, Van Den Bosch L. Axonal transport defects and neurodegeneration: Molecular mechanisms and therapeutic implications. In Seminars in cell & developmental biology, 2020; 1 (99: 133-150). Academic Press.
24. Xu Y, Zhao J, Zhao Y, Zhou L, Qiao H, Xu Q, Liu Y. The role of ferroptosis in neurodegenerative diseases. Molecular Biology Reports, 2023; 50(2): 1655-61.
25. Qiu Z, Zhang H, Xia M, Gu J, Guo K, Wang H, Miao C. Programmed Death of Microglia in Alzheimer's Disease: Autophagy, Ferroptosis, and Pyroptosis. The Journal of Prevention of Alzheimer's Disease, 2023; 5: 1-9.
26. Wilson DM, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. Cell, 2023; 16, 186(4): 693-714.
27. Dellovade T, Romer JT, Curran T, Rubin LL. The hedgehog pathway and neurological disorders. Annu. Rev. Neurosci., 2006; 21, 29: 539-63.
28. Aikin RA, Ayers KL, Thérond PP. The role of kinases in the Hedgehog signalling pathway. EMBO reports, 2008; 9(4): 330-6.
29. Tremblay MR, Lescarbeau A, Grogan MJ, Tan E, Lin G, Austad BC, Yu LC, Behnke ML, Nair SJ, Hagel M, White K. Discovery of a potent and orally active hedgehog pathway antagonist (IPI-926). Journal of medicinal chemistry, 2009; 23, 52(14): 4400-18.
30. Muller B, Basler K. The repressor and activator forms of Cubitus interruptus control Hedgehog target genes through common generic gli-binding sites. Development, 2000; 15, 127(14): 2999-3007.
31. Armas-López L, Zúñiga J, Arrieta O, Ávila-Moreno F. The Hedgehog-GLI pathway in embryonic development and cancer: implications for pulmonary oncology therapy. Oncotarget, 2017; 1, 8(36): 60684.
32. Lee MY, Sun L, Veltmaat JM. Hedgehog and Gli signaling in embryonic mammary gland development. Journal of mammary gland biology and neoplasia, 2013; 18(2): 133-8.
33. Ramalho-Santos M, Melton DA, McMahon AP. Hedgehog signals regulate multiple aspects of gastrointestinal development. Development, 2000; 15, 127(12): 2763-72.
34. Ingham PW, McMahon AP. Hedgehog signaling in animal development: paradigms and principles. Genes & development, 2001; 1, 15(23): 3059-87.

35. Omenetti A, Diehl AM. The adventures of sonic hedgehog in development and repair. II. Sonic hedgehog and liver development, inflammation, and cancer. American Journal of Physiology-Gastrointestinal and Liver Physiology, 2008; 294(3): G595-8.
36. Amankulor NM, Hambardzumyan D, Pyonteck SM, Becher OJ, Joyce JA, Holland EC. Sonic hedgehog pathway activation is induced by acute brain injury and regulated by injury-related inflammation. Journal of Neuroscience, 2009; 19, 29(33): 10299-308.
37. Kusano KF, Allendoerfer KL, Munger W, Pola R, Bosch-Marce M, Kirchmair R, Yoon YS, Curry C, Silver M, Kearney M, Asahara T. Sonic hedgehog induces arteriogenesis in diabetic vasa nervorum and restores function in diabetic neuropathy. Arteriosclerosis, thrombosis, and vascular biology, 2004; 1, 24(11): 2102-7.
38. Nagase T, Nagase M, Machida M, Fujita T. Hedgehog signalling in vascular development. Angiogenesis, 2008; 11(1): 71-7.