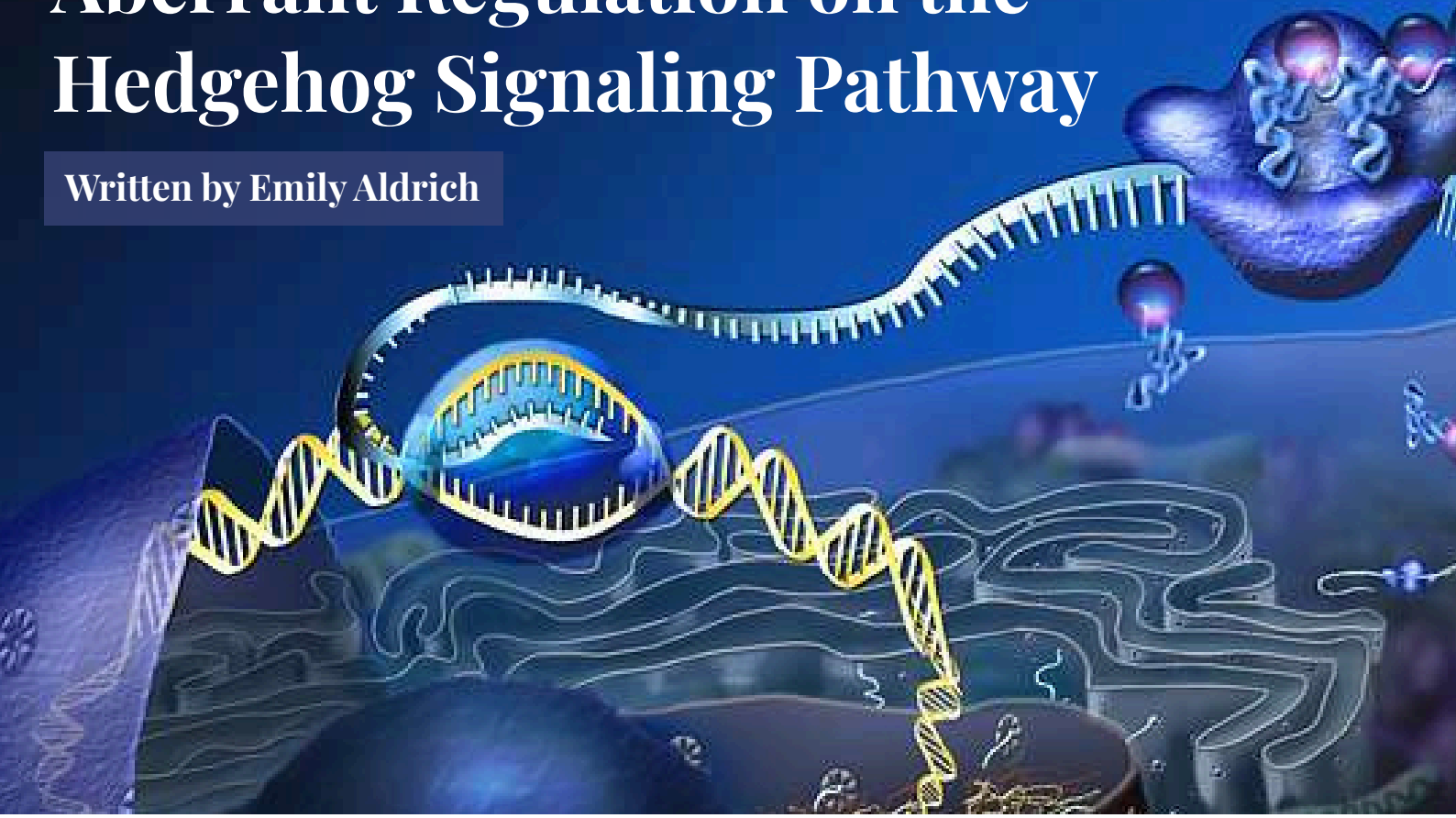
The Detrimental Effects of Aberrant Regulation on the Hedgehog Signaling Pathway

Written by Emily Aldrich



What is Sonic Hedgehog?

The Hedgehog (Hh) signaling pathway is a conserved neural pathway that plays an important role in the embryonic development of both invertebrates and vertebrates. This pathway was originally discovered in the species Drosophila melanogaster, the common fruit fly, and is found among a variety of species. The signal transmission from cell membranes are regulated by the Hh signaling pathway and dictate embryonic development. There are three main Hedgehog ligand proteins that regulate the transcription of target genes for this pathway. The three types of Hedgehog in the mammalian body are Sonic Hedgehog (Shh), important in the specification of cells in the nervous system, Desert Hedgehog (Dhh) which is seen in the hormone-producing gonad glands involved in reproduction, and Indian Hedgehog (Ihh) which plays a role in skeletal development (Carballo et al., 2018). All of the components in the Hh pathway are found in the primary cilium, which is an immobile organelle that juts out from the side of a cell and can sense the surrounding environment (Gigante & Caspary, 2020). When the pathway is regulated, typical development can occur. However, the dysregulation of the Hh signaling pathway may lead to a variety of diseases and disorders, including tumorigenesis of medulloblastoma, the most common malignant brain tumor.

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The Signal Transduction Pathway of Sonic Hedgehog

The Shh pathway is most commonly activated by canonical signaling, in which there are ligand-dependent interactions or receptor-induced signalings. Without the glycoprotein Shh, this signaling pathway does not occur. Smoothened (Smo) is a GPCR-like transmembrane protein that is usually inhibited by another transmembrane protein called Patched (Ptch 1) when the glycoprotein Shh is absent. Gli transcription factors are present in the cilia in a complex with Kif7, an IFT-kinesin that moves necessary materials toward the cilium during cellular signaling. Additionally, the

repressor factor Sufu promotes the truncation of Gli proteins, in which Gli proteins are shortened and turned into the GliR repressor form. This inhibits the transcription of Shh target genes (Traiffort et al., 2012). During Shh canonical signaling, the glycoprotein Shh binds to and inactivates Ptch 1, which, in turn, activates Smo. When this protein is activated, it accumulates at the primary cilium. This accumulation relieves the inhibition that Sufu exerts on Gli proteins, which allows them to turn into the GliA activated form, and move into the nucleus to activate the transcription of Shh target genes. Each target gene has a specific function. For example, Gli1 and Ptch1 are involved in pathway feedback, Cyclin-D1 and Myc promote cell proliferation, and CCND2 and CCNE1 regulate the cell cycle. In addition, bcl2 regulates apoptosis, AGN1/2 are involved in angiogenesis, SNAIL is involved with epithelial-to-mesenchymal transitions, and NANOG and SOX2 regulate the self-renewal of stem cells.

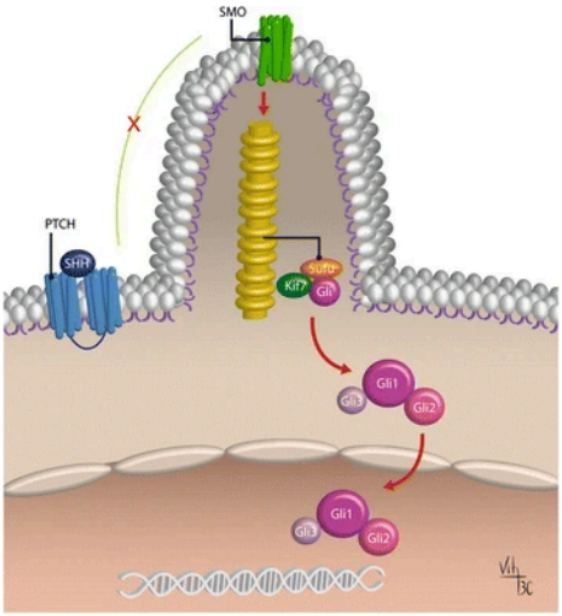

Figure 1. Canonical activation of the sonic hedgehog (Shh) signaling pathway occurring at the primary cilium (Adapted from Robbins et al., 2012).

Dysregulation of Hh Signaling Pathway

When the Hh signaling pathway is not carefully controlled, the effects on the development of cells and tissues can be very harmful. The aberrant activation of the Hh signaling pathway is caused either by mutations in pathway-related genes or by the excessive expression of Hh signaling molecules. This uncontrolled activation is what leads to tumorigenesis. The Shh pathway plays a particularly important role in regulating neural development in the cerebellum, a part of the brain linked to motor learning and coordination. Aberrant activation of this pathway is linked to pathway-activating mutations in Ptc (a protein found in Drosophila, the common fruit fly, that is similar to Ptch in humans), Sufu, or Smo, which all have key roles in the regulation of the Hh signaling pathway. It has been seen in mice medulloblastoma brain tumor stem cells that there is markedly higher Gli1 expression than in the normal stem cells. These cells do not undergo apoptosis (programmed cell death). Instead, they continue to proliferate when they are not supposed to. This suggests that there is a lack of protective mechanisms in place for these malignant stem cells, whereas non-malignant stem cells are able to control excessive proliferation in response to signals that promote mitosis. Interestingly, only 25% of medulloblastomas displaying abnormally high Hh signaling pathway activation have been found with mutations in Ptc, Sufu, or Smo (Traiffort et al., 2012). This means that there are other genetic pathways associated with Hh signaling that play a role in the development of cancer cells. Tumor suppressors are genes that regulate cell growth in order to prevent the development of cancer. Without them, cells will not perform apoptosis and instead continuously divide uncontrollably. Tumor suppressors such as Ren(KCTD11), Numb, and p53 have suppressive effects on Gli-dependent activation of Hh target genes. The activity of these tumor suppressors may decrease and lead to unregulated Glli protein activation, contributing to cancer development.

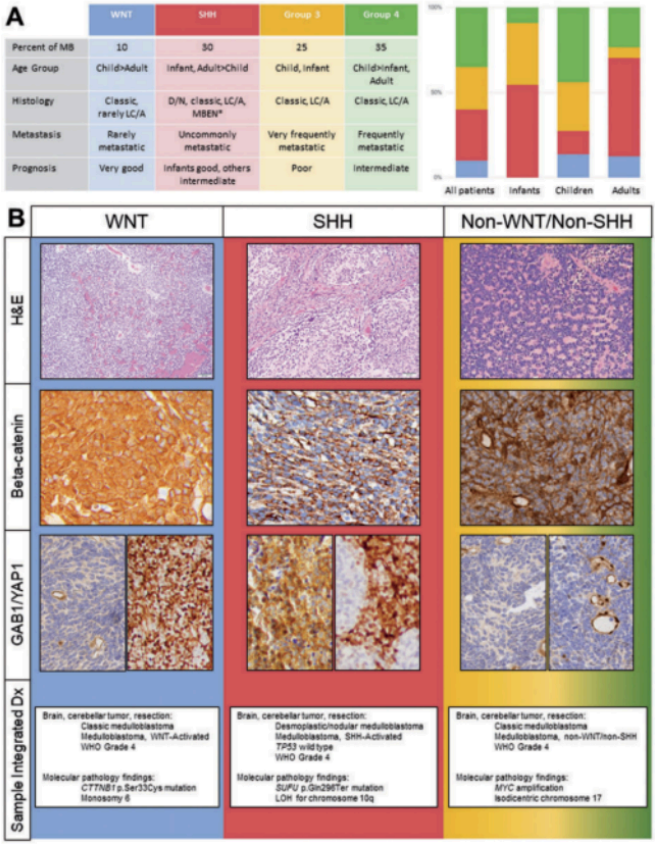

Figure 2. Medulloblastoma subgroups and the histological characteristics (Cotter & Hawkins, 2021).

Research for Improvement and Treatments

The findings of how the Hh signaling pathway works and its involvement in tumorigenesis have opened up the possibilities of developing methods of molecular targeting

and tumor prevention associated with the pathway. Several studies support the hypothesis that malignant tumors are initiated and maintained by cancer stem cells (Tan et al., 2006; Xie et al., 2022). Specific neuronal cancer stem cells can be found in a niche, where neurons and glial cells are generated from stem cells or progenitor cells. The niche provides signals that regulate whether the stem cells should differentiate, remain dormant, or actively divide. Shh is very important for determining cell fate and patterning during embryo development. It was discovered that the level of Shh signaling pathway activation in adulthood played an important role in regulating the balance between dormant and activated neuron stem cells (Carballo et al., 2018). Currently, the standard treatment for most brain tumors is the removal of the majority of the tumor, followed by chemotherapy and radiotherapy. Researchers are currently trying to determine alternative treatments involving the inhibition of the Shh pathway activation in cancer stem cells. There is great interest in targeted Hh signaling pathway inhibition (HPI) as a type of treatment for aggressive cancer cells when radiotherapy and surgery are not effective (Skoda et al., 2018). There have been multiple HPI molecules identified that act at different levels of the Hh pathway. One group is Hh ligand inhibitors, HPIs that inhibit the binding of the Hh protein to Ptch receptors, keeping Smo inhibited and therefore the rest of the pathway blocked from activating target genes. This includes Cyclopamine, Vismodegib, and Sonidegib. Another group is Smo antagonists which bind to a specific site on the Smo receptor that prevents the downstream activation of the Hh signaling cascade. However, clinical studies have shown that the use of Smo inhibitors can induce development of mutations that lead to treatment resistance. Moreover, Shh medulloblastomas are highly mutated tumors, and it is not uncommon for these tumors to develop a resistance to Smo inhibition, as they present alterations in downstream Shh pathway genes such as Sufu and Gli2. This turned researchers to Gli-based inhibitors, which is an alternative group of Shh antagonists that act directly in Gli to block transcription factors. This includes NVPLDE-225 and BMS-833923, which are currently being tested in brain tumors (Carballo et al., 2018). While most of the HPIs that have entered clinical trials mainly target Smo, the resistance to these inhibitors have lead to the discovery of new HPIs that may be essential to bypass these resistance mechanisms and control the tumorigenesis of medulloblastoma.

A Gateway Into the Future

The Hh signaling pathway plays a critical role in healthy embryonic development, putting into action a multitude of target genes that are needed for the initial stages of development. There are many steps in the transduction pathway leading to expression of target genes. Mutations that form can cause this highly regulated pathway to either activate uncontrollably or become inhibited at the wrong times. When this occurs, continuous and inappropriate cell division can lead to the rapid growth of tumors in the body. With the knowledge that scientists have today about the Hh signaling pathway, there is great potential for certain treatments and therapies that can inhibit the aberrant regulation of the Hh pathway, either from ligand-dependent or ligand-independent signaling inhibition. Further research into which pathway mechanisms are most likely to elicit a strong response to inhibition can provide a greater understanding of the Hh pathway, and can be used to create better, more effective, and safer anti-cancer therapies.

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About the Author

Emily Aldrich is a Freshman majoring in Neuroscience with minors in Linguistics and Psychology on the pre-med track. Emily joined Brain Matters to gain a deeper understanding of the brain through exploring current research topics in neuroscience. In her free time, she enjoys listening to music, reading, and spending time with friends.