Therapeutic Approaches to Disorders of Sonic Hedgehog Signaling

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Background

- The Sonic Hedgehog (SHH) signaling pathway is critical in embryonic development through the regulation of cell differentiation and proliferation. Notably, the SHH mitogen is critical in neurodevelopment by regulating developmental patterning, tissue growth, tissue repair, and homeostasis in neural tissue.

- CEP290 is critical to the specialized proximal region of the cilia.

- Glucocorticoids interact with transcription factors to regulate CEP290.

- Chronic upregulation of SHH pathway through haploinsufficiency.

- In diseases where SHH is downregulated or there is a deficiency, the purpose of this review on therapeutic approaches to SHH is to: provide foundational information on human disorders affecting SHH signaling pathways.

- Table 1. Diseases and phenotypes caused by SHH signaling dysregulation.

- There are several diseases characterized by the dysregulation of SHH. Disruption of a singular SHH-associated gene is pleiotropic and can lead to multiple phenotypic expressions.

- The phenotypes associated with disorders of SHH signaling affect multiple organ systems ranging from renal deficits in individuals with Joubert syndrome to cardiac deficits in individuals with Down syndrome.

- epidermolysis bullosa (EB), Hirschsprung disease (HSCR), and Down syndrome (DS) are examples of SHH-related disorders.

- Chronic upregulation of SHH through genetic mechanisms.

- Acute upregulation of SHH through addition of Sonic soaking bead implantation.

- Acute upregulation of SHH through SHH soaked bead implantation.

- The phenotypes associated with disorders of SHH signaling affect multiple organ systems ranging from renal deficits in individuals with Joubert syndrome to cardiac deficits in individuals with Down syndrome.

- References

- The authors provide a comprehensive review of the existing literature on therapeutic approaches to SHH.

- The authors note that there are still several safety concerns about upregulation of SHH signaling that limit its use in humans.

- The authors highlight that while some developmental effects of trisomy in Ts65Dn mice can be rescued with targeted therapies, this is an area that requires further research.

- The authors emphasize the importance of understanding the neurobiology of SHH signaling for the development of effective treatments.

Conclusion

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Bibliography


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Figure 3. Schematic overview of canonical Sonic Hedgehog Signaling pathway.

Figure 4. Schematic representation of acute and chronic therapeutic approaches to Shh pathway upregulation in mice.