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### Role of Sonic Hedgehog (SHH) signaling in promoting Blood Brain Barrier (BBB) integrity in Diffuse Intrinsic Pontine Glioma (DIPG)

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#### Background:

DIPG is the most common brainstem tumor in children and is uniformly fatal. The BBB is frequently intact in DIPG and plays an active role in restricting the delivery of systemically administered conventional and biological therapies. Recent studies have shown that SHH signaling plays a major role in the maintenance of BBB integrity and this pathway is highly active in DIPG.

#### Objective:

We hypothesize that SHH signaling in DIPG plays a critical role in BBB integrity.

#### Methods:

Primary DIPG cells, astrocytes and human/mice brain microvascular endothelial cells (h/m BMVEC) were used in this study. Using ELISA and qRT-PCR, the secreted protein and mRNA expression profile for SHH, and its pathway members were respectively determined. Electrical impedance and permeability of MVECs were determined when SHH signaling was activated or inhibited.

#### Results:

ELISA determined that primary DIPG cells secrete SHH compared to astrocytes and hBMVECs. DIPG cells showed a 4-fold increase in SHH secretion when compared to controls. qRT-PCR determined that expression levels of SHH and its pathway members was significantly higher in DIPG cells when compared to astrocytes or endothelial cells. DIPG cells showed >750-fold increase in SHH mRNA levels when compared to other cells. These data suggest that DIPG is highly active in a subset of primary DIPG cells. Next, we determined the electrical impedance/permeability of mBMVECs. mBMVECs cells treated with tumor conditioned media showed significantly increased electrical impedance and decreased permeability to both low (NaFI) and high molecular weight (IR dye PEG 800) compounds. These results were also corroborated by using an SHH agonist, while the antagonist decreased the electrical impedance/permeability suggesting that SHH signaling may play an important role in maintaining the BBB integrity in DIPG tumors.

#### Conclusion:

SHH pathway is integral to BBB integrity in DIPG tumors and may be amenable to modulation for effective therapeutic targeting in these tumors.

**Conclusion:**

Preliminary results suggest that communities with COHI do not have significantly lower rates of dental surgery to treat S-ECC. However, including other known risk factors of S-ECC in further statistical analyses will help to determine whether COHI leads to lower rates of surgery under general anesthesia.