ABSTRACT SUBMISSION FORM

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Exploring the role of sex and gender on health research

CHILD HEALTH RESEARCH DAYS

CHRD 2020: Abstract Submission Form

Submitter Name
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Title
Tumor secreted Sonic Hedgehog promotes blood brain barrier integrity in diffuse intrinsic pontine glioma (DIPG)

Background
DIPG is the leading cause of brain-tumor related mortality in children and is uniformly fatal. Radiation therapy offers transient benefit and is at best palliative. Owing to the inoperable anatomical location, novel therapeutic strategies aimed at targeting DIPG are in dire need. Recent literature suggests that SHH secreted by neurons/astrocytes maintain BBB integrity and that SHH pathway is central to the origin and maintenance of DIPG tumors.

Objective
We hypothesized that DIPG tumor cells secrete SHH and is intrinsic in the strengthening the blood-brain-barrier (BBB) by effecting tight junctions between endothelial cells.

Methods
ELISA was performed to quantify SHH ligand secreted by primary DIPG cells, human brain microvascular endothelial cells (hBMVEC) and astrocytes. Expression of SHH was determined by qRT-PCR and Western blot determined SHH expression. Functional analyses of the secreted SHH In Vitro was determined by trans-endothelial electrical resistance (TEER). Indirect immunofluorescence was employed to visualize tight junction proteins in endothelial cells.

Results
DIPG cells significantly overexpressed and secreted higher amounts of SHH when compared to controls. SHH and its pathway members were confirmed in a cohort of tumor tissue samples by immunohistochemistry. hBMVEC treated with DIPG tumor-conditioned media significantly increased TEER suggesting pro-barrier properties of SHH secreted by DIPG cells. These results were replicated using purified recombinant human SHH (rh-SHH). Inhibition of the secreted SHH ligand using SHH pathway inhibitors (RUSKI-201 and Vismodegib) reversed the TEER to baseline similar to the controls.

Mechanistically, intensity of VE-Cadherin was higher in hBMVEC treated with DIPG tumor-conditioned media and rh-SHH when compared to controls or endothelial cells treated with inhibitors.

Conclusion
Our preliminary results suggest that tumor secreted SHH ligand and pathway is integral to the strengthened BBB in DIPG. Inhibition of SHH and its pathway will modulate the BBB and may help in efficient delivery of effective therapies to treat this universally fatal tumor.

Theme:
Basic Science

Do you have a table/figure to upload?
No

Are you willing to participate in Goodbear's Den?
Yes

Presenter Status:
Non-Trainee

What was your role in the project?
All of the choices mentioned

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