Form 2-4-2

Japan-U.S. Brain Research Cooperation Program
Group Joint Study Project Program FY2017 - FY2019: Report

Field: ① cellular/molecular

1. Principal Researcher
Name Yukihiko Fujii
Title Professor
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2. Project Title: Elucidating the role of Gli3 in medulloblastoma as a target for treatment

3. Japanese Group
Names, Titles and Affiliations of Principal Researcher and Collaborating Research Members
Principal Researcher
Name: Yukihiko Fujii
Title and Affiliation: Professor, Department of Neurosurgery,
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Collaborating Researchers
Name (Title and Affiliations):
Manabu Natsumeda (Assistant Professor, Dept Neurosurgery, Niigata University)
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Akiyoshi Kakita (Professor, Department of Pathology, Brain Research Institute, Niigata University)
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4. U.S. Group
Names, Titles and Affiliations of Principal Researcher and Collaborating Research Members
Principal Researcher
Charles G. Eberhart
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Collaborating Researcher
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Mario Suva
Associate Professor, Department of Pathology, Massachusetts General Hospital

5. Research Period, from/to (mm/dd/yyyy) and total number of years.
From April 1, 2017 to March 31, 2020 (3 years)

6. Abstract, Results, and Research Significance (300 words):

Medulloblastoma is one of the most common malignant brain tumors observed in the pediatric population. Recent advances in treatment has improved outcome, however, these tumors remain resistant to treatment at relapse. In this project, we focused on the function of Gli3, a downstream factor of the Hedgehog pathway, in medulloblastoma. The main function of Gli3 in medulloblastoma formation is to repress the Gli1/2 complex, leading to cell differentiation. The Japanese group has previously shown that Gli3 induces neuronal differentiation in the nodules of desmoplastic/nodular (D/N) type medulloblastoma and is associated with good survival (Miyahara et al., *Neuropathol*, 2013). The US group has shown that Gli1/2, which cause increased proliferation and decreased apoptosis, is expressed in the desmoplastic areas of these tumors (Bar et al., *Am J Pathol*, 2007).

In the present study, we aimed to see which molecular subgroups were associated with increased Gli3 expression, and if there were differences in Gli1/2/3 distribution among different molecular subtypes. Nanostring and R2 public database analyses were performed, and we found that Gli3 was upregulated in WNT-activated and SHH-activated medulloblastoma. Next, in collaboration with Dr. Mario Suva of Massachusetts General Hospital, single cell RNA sequence data in WNT-activated and SHH- activated medulloblastoma was analyzed, and we found that Gli3 was upregulated in cells expressing neuronal differentiation, and Gli1/2 were upregulated in cells not expressing neuronal differentiation in the SHH-activated group. On the other hand, Gli3 was diffusely expressed and Gli1 diffusely repressed in WNT-activated medulloblastoma. These results suggest that Gli3 may be a master regulator of morphology, neural differentiation and favorable prognosis in medulloblastoma.

7. Other (Research-related concerns, particular points of note):

* Furthermore, in collaboration with Advance Animal Model Support (AdAMS), a Gli3-inducible SHH-mouse model was to be generated, but this project has been delayed because of the COVID-19 situation.

* The data from this project has been submitted to Brain Pathology and is presently under review.

* During the research period, the following medulloblastoma paper was accepted to Neuropathology.

Natsumeda M, Liu Y, **Nakata S**, Miyahara H, Hanaford A, Ahsan S, Stearns D, Skuli N, **Raabe EH**, Rodriguez FJ, **Eberhart CG**. Inhibition of enhancer of zest homologue 2 is a potential therapeutic target for high-MYC medulloblastoma. ***Neuropathology***, 39(2):71-77, 2019.

*Please attach any reference materials as necessary.