The Role of Folate in Brain Cancer

Maternal Folic Acid Supplementation and Risk of Medulloblastoma in Offspring

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Folate Deficiency and Brain Cancer

- Folate deficiency:
  - Most common vitamin deficiency in the U.S [1]
  - Associated with neural tube defects and other developmental abnormalities
  - Recently linked to childhood brain cancer
- Medulloblastoma:
  - Leading form of brain cancer in children [2]
  - Affects tissue in the cerebellum
  - Accounts for approximately 20% of all pediatric brain tumors [2]
  - -Mutations of the *PATCHED1 (PTCH1)* gene reported in significant amount of both sporadic and familial cases [5]

Folate in the Body

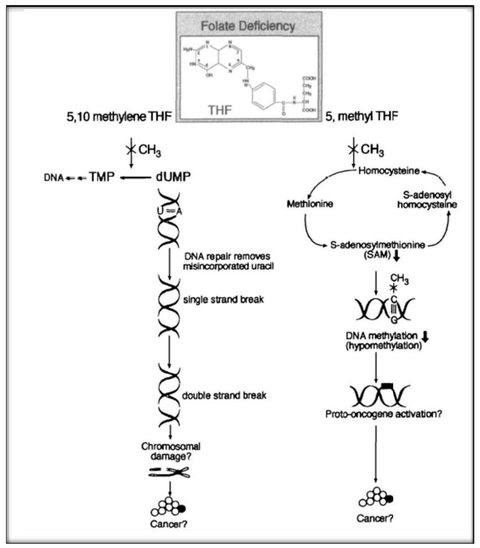

FIGURE 1: The Biochemical Processes of Folate. The adverse health effects of folate deficiency are hypothesized to be attributed to two prominent biochemical processes: 1)DNA repair mechanisms, and 2) DNA methylation. In folate-deficient cells, increased activity of DNA repair mechanisms compromises genome stability by inducing frequent breaks in DNA strands, while lower levels of DNA methylation result in overexpression of specific genes [1].

Research Aim and Hypothesis

- Aim: To examine the effect of maternal dietary folic acid intake on the incidence of medulloblastoma in offspring in a well-defined transgenic mouse model.
- Hypothesis: Low folic acid intake during the peri-gestational period increases the incidence of medulloblastoma in offspring.

Transgenic *Ptch*+/- Mice Were Raised on Three Folic Acid Diets

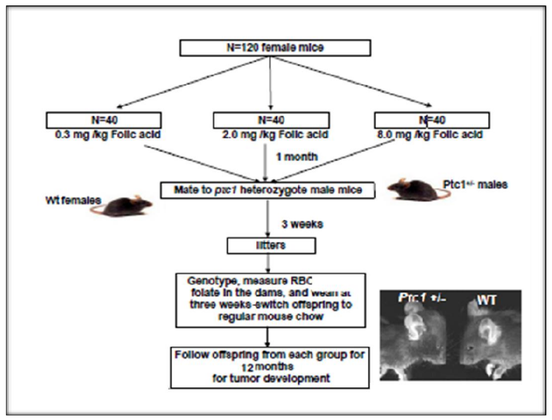

FIGURE 2: Flowchart of Experimental Design. *Ptch+/-* heterozygous mice were raised on one of three different folic acid diets as shown. Mice were aged until they showed signs of morbidity or until nine months. Moribund mice were euthanized and brain necropsies were done to analyze tissues for medulloblastoma tumorigenesis. Tumor findings were confirmed via histological examination. ***

RBC Folate Measurements and Survival Curve

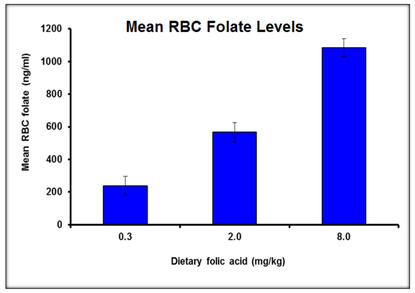

FIGURE 3: RBC Folate Measurements in Dams at Weaning. Red blood cell (RBC) folate levels were measured in the dams of each folic acid cohort. Folate levels were reduced in the low (.3mg/kg) cohort and increased in the high (8.0mg/kg) cohort relative to the control (2.0mg/kg) cohort.

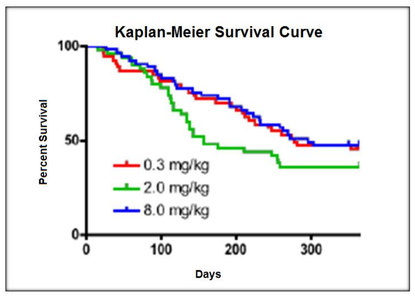

FIGURE 4: Kaplan-Meier Survival Curve of *Ptch+/-* Cohorts. The overall survival of mice of each dietary cohort was observed as shown above. No significant difference was detected n the survival of mice between each cohort. ***

Incidence of Medulloblastoma in Folic Acid Diet Cohorts

Diet (mg/kg)	Number of tumors (%)	Hazard Ratio	95% CI
0.3	18 (34%)	0.55	0.33-0.91
2.0	26 (52%)	1.0	Reference
8.0	24 (45%)	0.70	0.42-1.17

TABLE 1: Risk of MB Development in Offspring by Maternal Folic Acid Group. A summary of the tumor results of each dietary folic acid cohort are shown. Calculation of the 95% confidence interval (95% CI) revealed a significantly reduced tumor incidence of mice fed the low (.3 mg/kg) folic acid diet. ***

Conclusions

- Incidence of medulloblastoma was significantly lower in the low folic acid cohort
- No significant difference in tumor incidence seen in the high folic acid cohort
- These findings do not support the hypothesis that low perigestational intake of folic acid increases the risk of medulloblastoma in offspring

The Role of Folate in Tumorigenesis and Future Studies

- Our findings suggest that folate plays an important role in the survival of cancer cells in addition to that of normal cells
- Folate deficiency may cause cell cycle arrest and apoptosis in the presence of a preexisting *Ptch* mutation
- Further approaches are needed to verify that the mutated *Ptch* allele or similar mutations play a role in determining the effect of folate deficiency in the cell
- Limitations of both human and experimental data should be considered, including biases inherent to epidemiological studies and extrapolation of results from animal models

References & Acknowledgements

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- Supported by NIH grants R03CA141440 and T32CA099936, the Children's Cancer Research Fund and the Brain Tumor Program, Minneapolis, MN

*** Designates experimental protocols and findings that were completed through the funding of the Undergraduate Research Opportunities Program (UROP)