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Effect of the dTMP metabolism on the neural tube development in mice

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Nutrient folate deficiency is considered a risk factor for neural tube defects (NTDs), the causal metabolic pathway between them remain obscure. Folate derived one-carbon unit as the sole methyl donor play key roles in 2'-deoxythymidine-5'-monophosphate (dTMP) metabolism. Our aim was to investigate the role of dTMP metabolism via intervention of thymidylate synthase (TYMS) during the process of neural tube development.C57BL/6 pregnant mice were intraperitoneally injected with different doses of 5-fluorouracil (0, 5, 7.5, 10, 11, 12.5, 15 and 30 mg/kg body weight) and embryos were measured, weighed, and examined under a dissecting microscope for external malformations on GD 13.5. Embryonic tissues from control and 5- fluorouracil-treatment group were collected for evaluation of RT-qPCR, western blot analysis, TYMS activity, dTMP and dUMP levels at different time points after 5- fluorouracil treatment. We found that a high incidence of NTDs occurred after inhibited TYMS activity. Decreased dTMP and accumulation of dUMP were observed during the neural tube formation process. The proliferation of neuroepithelial cells were markedly inhibited in NTD embryos compared with non-NTD embryos. Expressions of proliferating cell nuclear antigen (PCNA) and phosphohistone H3 (PH3) were significantly decreased in NTD embryonic neural tube tissues, while P53 and Caspase3 were significantly increased compared with non-NTD embryonic neural tube tissues. The expressions of PCNA, PH3, P53 and Caspase3 were no difference between non-NTDs and control. These results indicated that abnormal dTMP metabolism affected the balance between proliferation and apoptosis in neuroepithelial cells, which might shed some lights on the mechanisms involved in NTDs.

Biography

Xiuwei Wang is currently working at Beijing Municipal Key Laboratory of Child Development and Nutriomics, China. His research interests are pediatric metabolic research, neural tube defects and pediatric nutrition, etc.

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