Folate Pharmacology and Metabolism with Focus on MTHFR and RFC-1 in Orofacial Clefts

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Objectives

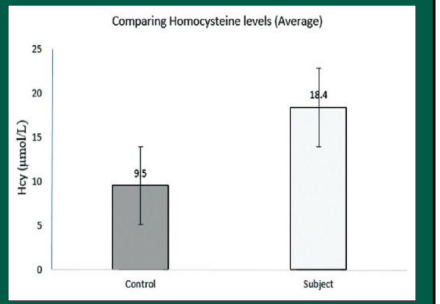
Orofacial clefts (OFC) constitute a significant portion of global birth defects, encompassing various manifestations such as cleft lip only, isolated cleft palate, or cleft lip and palate. The multifactorial etiology of non-syndromic OFC underscores the importance of understanding the interplay between molecular genetics and environmental factors. We conducted a review of the literature to investigate folate metabolism in the context of OFC, with a particular focus on Methylenetetrahydrofolate reductase (MTHFR) and Reduced folate carrier-1 (RFC-1). The review aims to explore the role of folate metabolism, specifically examining the involvement of MTHFR and RFC-1, to elucidate mechanisms and identify potential prevention strategies for OFC.

Methods

A comprehensive literature search was conducted across databases PubMed and Google Scholar with restriction to articles published in English from 1990 to 2024. Keywords folate metabolism, orofacial clefts, MTHFR, RFC-1, were used to retrieve studies investigating the relationship between folate metabolism and OFC.

Results

The search produced 184 articles. After excluding duplicities and applying other restrictions 17 articles were selected that highlighted the complex interplay between genetic and environmental factors in OFC etiology. Folate (Vitamin B-9) is primarily found in dark green leafy vegetables, beans, peas, and nuts. Folic acid, the synthetic form of folate, is essential and is commonly included in prenatal vitamins as well as many fortified foods like cereals and pastas[3]. Folate plays a critical role in DNA synthesis, methylation processes, and subsequent cell division, with supplementation significantly reducing the risk of orofacial clefts. Folate deficiency leads to elevated homocysteine levels, which are associated with orofacial clefts [4]. Mutations in RFC-1 and MTHFR have been implicated in increasing the risk of orofacial clefts due to their roles in the absorption (RFC-1) and processing of folate (MTHFR) in the body [5,6]. However, data providing support for a direct role of polymorphisms in genes involved in folate metabolism in OFC pathogenesis are limited [7].



Subjects: NSCL ± P

(Fig 1. Abdulla et al. J Oral Maxillofac Pathol. 2016 Sep-Dec; 20(3): 390–394. doi:10.4103/0973-029X.190910)

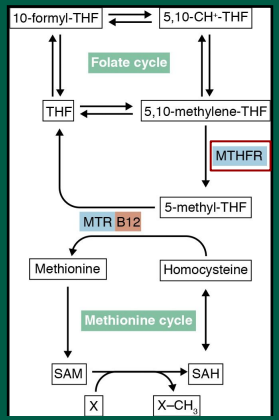


Fig 1 (Zheng J Exp Med. 2019 Feb 4; 216(2): 253–266. Doi: 10.1084/jem.20181965)

Conclusion

Folate plays a critical role in DNA synthesis, methylation processes, and cell division, with deficiency linked to elevated homocysteine levels associated with OFC. Further research is needed to elucidate precise mechanisms underlying the association between genetic polymorphisms related to folate metabolism and OFC. This understanding could pave the way for personalized prevention approaches.

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OKU Sutro Excellence Day Project Cover Sheet

Project Title

Folate Pharmacology and Metabolism with Focus on MTHFR and RFC-1 in Orofacial Clefts

Full name(s) and class year(s) of all project collaborators

Example: Jane Smith, DDS 2022; John Smith, DDS 2022

Tyler Starley, DDS 2024; Marie M. Tolarova; Miroslav Tolar

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Results: The search produced 184 articles. After excluding duplicities and applying other restrictions 17 articles were selected that highlighted the complex interplay between genetic and environmental factors in OFC etiology. Mutations in RFC-1 and MTHFR have been implicated in increasing OFC risk due to their roles in folate absorption and processing. However, data providing support for a direct role of polymorphisms in genes involved in folate metabolism in OFC pathogenesis are limited.

Conclusion: Folate plays a critical role in DNA synthesis, methylation processes, and cell division, with deficiency linked to elevated homocysteine levels associated with OFC. Further research is needed to elucidate precise mechanisms underlying the association between genetic polymorphisms related to folate metabolism and OFC. This understanding could pave the way for personalized prevention approaches.

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