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Review

Folate: Metabolism, genes, polymorphisms and the associated diseases

Fakhira Hassan Nazki [a,1], Aga Syed Sameer [b,*,2], Bashir Ahmad Ganaie [a,3]

[a] Department of Biochemistry, University of Kashmir, Hazratbal, Srinagar, Kashmir 190006, India
[b] Department of Biochemistry, Sher-I-Kashmir Institute of Medical Sciences Associated Medical College, Bemina, Srinagar, Kashmir 190018, India

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ABSTRACT

Folate being an important vitamin of B Complex group in our diet plays an important role not only in the synthesis of DNA but also in the maintenance of methylation reactions in the cells. Folate metabolism is influenced by several processes especially its dietary intake and the polymorphisms of the associated genes involved. Aberrant folate metabolism, therefore, affects both methylation as well as the DNA synthesis processes, both of which have been implicated in the development of various diseases. This paper reviews the current knowledge of the processes involved in folate metabolism and consequences of deviant folate metabolism, particular emphasis is given to the polymorphic genes which have been implicated in the development of various diseases in humans, like vascular diseases, Down's syndrome, neural tube defects, psychiatric disorders and cancers.

Contents

Abbreviations: THF, tetra-hydro folate; DHF, di-hydro folate; MTHFR, methylene tetra-hydro folate reductase; DHFR, di-hydro folate reductase; TS, thymidylate synthetase; MTR, methionine synthase; CBS, cystathionine β-synthase; CTH, cystathionine γ-lyase; dUMP, deoxyuridylate monophosphate; dTMP, deoxythymidylate monophosphate; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; DNMTs, DNA methyltransferases; NTD, neural tube defects; DS, Down's syndrome.

* Corresponding author. Tel.: +91 9906727948 (mobile).
E-mail addresses: faakhra.nazki@gmail.com (F.H. Nazki), mousvi786@gmail.com (A.S. Sameer), agsysa@gmail.com (B.A. Ganaie).

[1] Did the literature survey, analyzed the results of various studies and wrote the manuscript.
[2] Designed the review, did the literature survey and edited and structured the draft copy to make it in final form.
[3] Helped in the literature survey.

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1. Introduction

The folates include the family of B-group vitamins composed of an aromatic pteridine ring attached through a methylene group to p-aminobenzoic acid and a glutamate residue (Shane, 1995). Folate metabolism plays a vital role in nucleic acid synthesis, methionine regeneration, shuttling and redox reactions of one carbon units required for normal metabolism and regulation (Bailey and Gregory, 1999). Folates mediate the transfer of one carbon units required in various biochemical reactions. It plays a critical role in the synthesis of S-adenosylmethionine (SAM) which serves as the methyl group donor in several methylation reactions; like DNA, RNA and protein methylation. DNA methylation in turn is an important epigenetic determinant in gene expression, DNA stability, DNA integrity and mutagenesis. Folate also plays an essential role in the de novo synthesis of purines and thymidylate, which is required in DNA replication and repair (Kim, 2000). Thus, deviant distribution of methyl groups due to abnormal folate metabolism affects both methylation and DNA synthesis-processes which play an essential role in the development of cancers (Hubner and Houlston, 2009). Abnormal folate status has also been implicated in the development of diseases like; cardiovascular diseases, neural tube defects, cleft lip and palate, late pregnancy

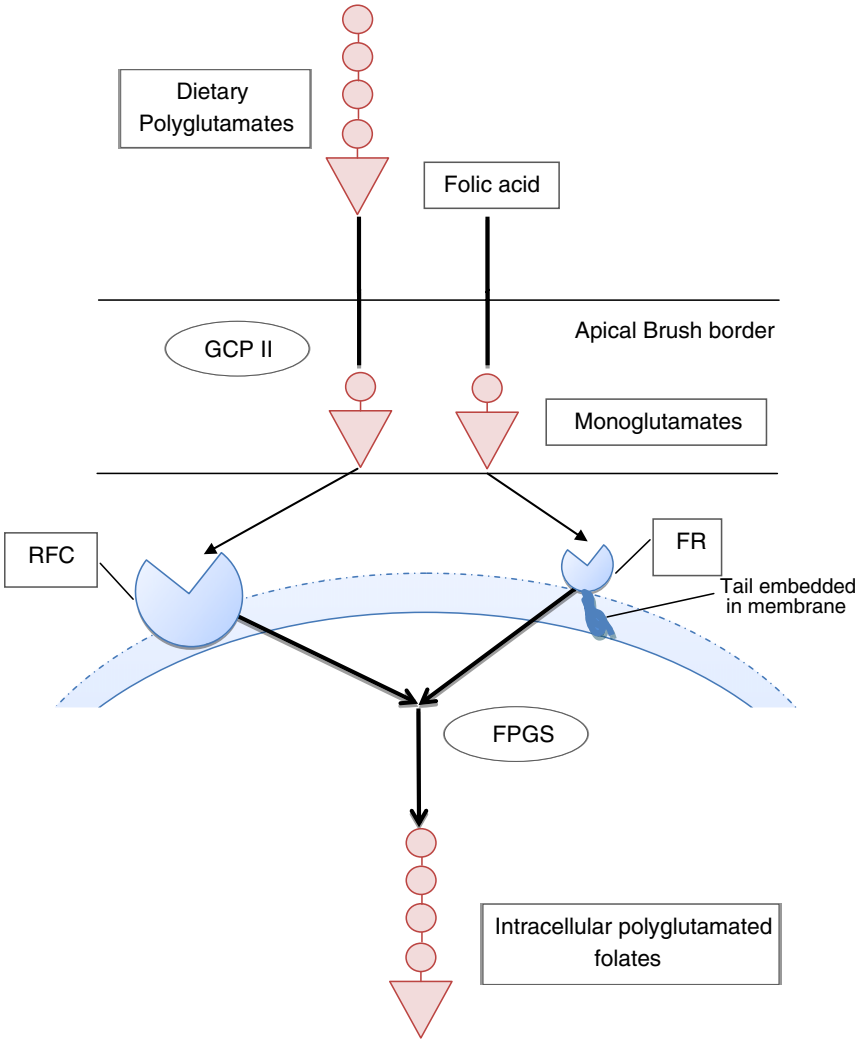

Fig. 1. Summary of folate transport. The polyglutamates are converted into monoglutamated folates by gamma-glutamylcarboxypeptidase activity in the intestinal juice. Folate is then absorbed into the blood through a pH dependent carrier mediated process in the jejunum brush border. The monoglutamates in the blood are then transported inside the cell via different processes involving membrane embedded folate receptors or reduced folate carrier. Folate is retained in tissues by polyglutamation. Abbreviations: FR, folate receptor; RFC, reduced folate carrier; FPGS, foly-poly-glutamate-synthase; GCP II, glutamate carboxypeptidase II.