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Dr. Partha Majumder
Biomedical Scientist, Former Head of Department of Applied Biotechnology & Bioinformatics, Sikkim Manipal University, CC: 1637, Kolkata, India.

Dr. Sufal Halder
Senior Consultant Physician, Acharya Pranavananda Sevashram, Po: Purba Nischintapur, Budge Budge, Kolkata, India.

Correspondence
Partha Majumder
Biomedical Scientist, Former Head of Department of Applied Biotechnology & Bioinformatics, Sikkim Manipal University, CC: 1637, Kolkata, India.

Folate biosynthesis, *E. coli* mutants and pregnant women – An approach in favour of conservation of biodiversity

Dr. Partha Majumder, Dr. Sufal Halder

Abstract
The human microflora comprises a complex ecological system maintaining an executive homeostasis that plays important role in human health, such as, by stimulating the immune response, aiding digestion of food materials and helping to prevent pathogens from colonizing on epithelial surfaces. Folic acid, also called folate or folacin, is a vital raw material for production of Red Blood Cells (RBC), as well as norepinephrine and serotonin (important components of nervous systems). In human, non-pathogenic strains ofintestinal flora bacteria- Escherichia Coli (*E. Coli*), impart vital role in favour of synthesizing folate from simpler compounds and focuses a significant insight paying regards to conservation of biodiversity especially in case of pregnant women. We have analyzed the consequences and the capability of synthesizing folate by *E. Coli*, present in human intestine as a beneficial microbial flora, by utilizing different software, widely used in Bioinformatics andour review suggest that, conservation of different features of *E. Coli* appears to be very important in case of pregnant women to prevent the offspring from several vulnerable stages.

Keywords: Folate biosynthesis, pregnant women, homeostasis, *E. Coli mutants*

1. Introduction
Folates are required in a variety of reactions (known as one-carbon metabolism) in both bacterial and mammalian tissues, where they act as carriers of one-carbon units in various oxidation states. Folic acid also helps to synthesize genetic material in every cell of the body and normalize brain function. In humans, folate deficiency contributes to problems [1-3] in neural tube development in the fetus resulting in spinal cord defects in newborns, and is implicated in cardiovascular disease. Folates are required for the normal growth and proliferation of all cells and when they are not available cells ultimately die. A better understanding of the biosynthesis of folates and the consequences of disturbing folate biosynthesis in microorganisms will contribute to our understanding of this important biochemical pathway as well as assist us to devise appropriate drug that are not subject to jeopardize any event associated with various defects in newborns. Non-pathogenic laboratory strains of the human intestinal bacteria *Escherichia coli (which are beneficial for humans)* may be an excellent model system for the study of biosynthesis of folates. First, like many other pathogens, *E. col*i synthesizes folates from simpler compounds [4] and thereby permitted us to study the entire biosynthetic pathway. Secondly, there is a wealth of genetic, biochemical and molecular data available for *E. coli*, helped us in favour of rapid dissection of novel phenotypes. Many of folate's healthful properties help women specifically. It's particularly important for pregnant women to get enough folate to keep the fetus healthy. It also seems to prevent cancer of the cervix.

Methods of Analysis
It has already been reported that, *E. coli* mutants that lack dihydrofolate reductase (DHFR) grow on minimal media containing combinations of the folate end products but do not grow on media supplemented with other combinations. We have analyzed the enzyme dihydrofolate reductase present in *E. Coli* utilizing different software widely used in Bioinformatics study like BLAST2.0, Pfam search tools and KEGG (Kyoto Encyclopedia of Genes and Genomes).

Results

We found that Dihydrofolate reductase (DHFR) catalyses the NADPH-dependent reduction of dihydrofolate to tetrahydrofolate, an essential step in de novo synthesis both of glycine and of purines and deoxythymidine phosphate (the precursors of DNA synthesis) PUBMED: 2830673, and important also in the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate. Although DHFR is found ubiquitously in prokaryotes and eukaryotes, and is found in all dividing cells, maintaining levels of fully reduced folate coenzymes, the catabolic steps are still not well understood (PUBMED:3383852).

Bacterial species possesses distinct DHFR enzymes (based on their pattern of binding diamine heterocyclic molecules), but mammalian DHFRs are highly similar (PUBMED: 500653). The active site is situated in the N-terminal half of the sequence, which includes a conserved Pro-Trp dipeptide; the tryptophan has been shown (PUBMED: 6815178) to be involved in the binding of substrate by the enzyme. Its central role in DNA precursor synthesis, coupled with its inhibition by antagonists such as trimethoprim and methotrexate, which are used as anti-bacterial or anti-cancer agents, has made DHFR a target of anticancer chemotherapy. However, resistance has developed against some drugs, as a result of changes in DHFR itself (PUBMED: 2601715).

Discussion

Since the 1960s, folate has been linked to neural tube defects. But it wasn't until 1992 that the U.S. Public Health Service acknowledged the link and recommended that women of childbearing age consume 400 micrograms (mcg) of the vitamin per day. This simple measure has significantly reduced the number of babies born with neural tube defects. Folate early in pregnancy also reduces the risk of other health problems in the fetus, such as brain tumors, cardiovascular problems, poor nerve development, and limb deformities [5-8]. It was also reported that, high homocysteine levels are a risk for heart disease and stroke. Folate helps clear the body of excess homocysteine, but it does the job even better when teamed up with vitamins B6 and B12. High homocysteine levels may also be linked to osteoporosis in postmenopausal women. Homocysteine can interfere with collagen production, which makes up the matrix, or base, of bone tissue. Folate protects cell DNA in a woman's cervix. In more than one study, women who had abnormal cells in their cervix or who had cancer of the cervix, had lower levels of folate than women with a healthy cervix.Even a slight deficiency of this vitamin might make the cells of the cervix more susceptible to viral attack, which seems to be a predecessor of cancer in some women. If abnormal cells are identified early, huge doses of folate, 10 mg per day, are often able to stop the progression to cancer in many women [11].

Like many of the other B vitamins, folate affects mental function. It helps serotonin production, elevating mood and acting as a mild antidepressant. However, it takes extremely large doses -- up to 50 mg -- to get results. Other nutrients help alleviate depression at much lower levels. It might be a better idea to just get plenty of all the B vitamins and look to other substances for help in alleviating depression.

The RDA for folate is 400 micrograms (mcg) for all adults. Pregnant women require 600 mcg because so many new cells are being made. The average American diet provides about 200 to 250 mcg of the vitamin. Most prenatal supplements contain 800 mcg [11].

Foods contain folate both in free form and bound to amino acids. To absorb folate, however, it must be freed. Vitamin B12 helps to free the folate for absorption. The discovery of folate was closely tied to the discovery of vitamin B12. These two vitamins work together in several important biological reactions. A deficiency of either vitamin results in a condition known as megaloblastic, or macrocytic (large-cell), anemia. In 1930, researcher Lucy Wills and her colleagues reported that yeast contained a substance that could cure macrocytic anemia in pregnant women. But it wasn't until the early 1940s that folate was finally isolated and identified.

Folate functions as a coenzyme during many reactions in the body. It has an important role in making new cells, because it helps form the genetic material DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). DNA carries and RNA transmits the genetic information that acts as the blueprint for cell production [12-15].

Conclusion

When there is any sort of mutation takes place in the enzyme dihydrofolate reductase resulting loss of proper catalytic activity, it appears not only non-functional paying regards to folate metabolism, but also appears as a harmful event as antibodies against human placental folate receptors are found to be blocked for binding of folic acid to folate receptors on placental membranes [16]. This reflects the importance of taking care in order to maintain homeostasis in pregnant women from maladministration of any resourse, even antibiotics [1, 4] from any sort vulnerable effects in offsprings.

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Author's Contribution

Partha Majumder is Gold Medalist in Human Physiology, having expertise in the area of cultivation in recent Biomedical research and former Head of the Department of Applied Biotechnology and Bioinformatics, Sikkim Manipal University, CC:1637, Kolkata, India.

Dr. Sufal Halder is Senior Consultant Physician of Acharya Pranavananda Sevashram, located at Po: Purba Nischintapur, Budge Budge, Kolkata- 700138, India.

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