Folate Consumption and Alcohol Intake by **Lynn Gretkowski**

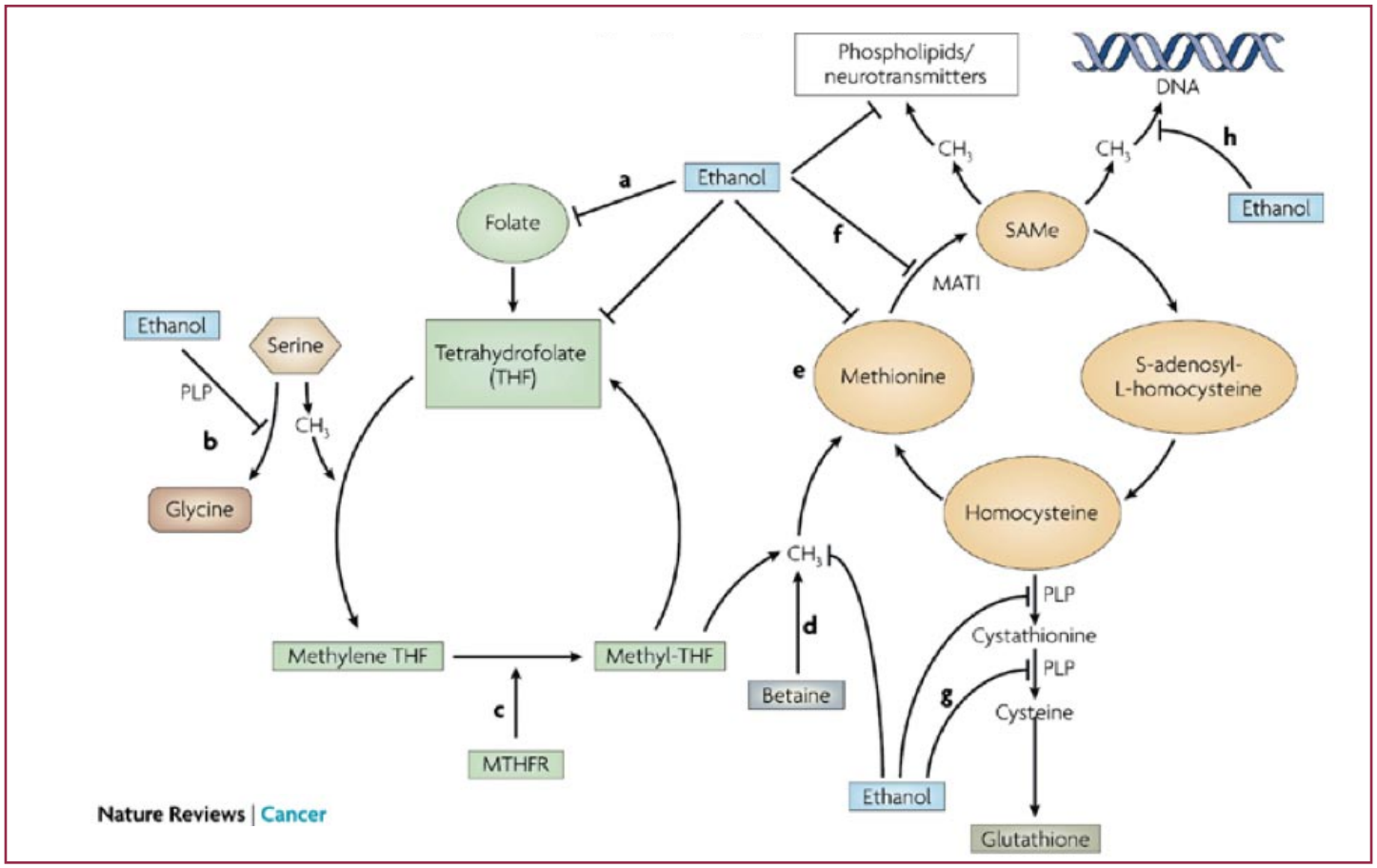
It has been two years since Creina Stockley from the Australian Wine Research Institute visited the subject of whether folate consumption can mitigate the risk of excessive alcohol intake in breast cancer incidence. It is unclear whether we have arrived at the absolute pathways suggestive of embryotoxity, carcinogenesis or neurotoxity which implicate folate deficiency as absolutely causal, but the evidence is mounting.

What is clear and apparent is that folate metabolism can be disrupted in cases of excess alcohol exposure, which can impair the release of folate from hepatocytes (liver cells) and therefore influence its bioavailability for its vital role in methylation.

If impaired when pregnant, this may impact cell division and fetal alcohol syndrome (fetal development, neurotoxity, cranio-facial and neural tube defects). The may also lead to an accumulation of homocysteine (see atherosclerotic cardiovascular risks, miscarriage and placental abruption) or impair the regulation of gene expression (chromosomal strand breaks or inappropriate methylation of protooncogenes like p53). There are many opportunities for alcohol to contribute to cancer risk in the face of nutritional deficiency. (See insert)

Humans do not generate folate, nor are they capable of storing infinite amounts for future use. Intake of 50-100 mcg/day is required. Deficiencies in folic acid (its synthetic form) have been recommended as a supplement in public health policy since 1996. The American College of Obstetrics and Gynecology suggests supplementation in low risk women to be 400 mcg daily at least one month prior to conception. Red blood cell folate levels are a better measure of inherent store than serum levels which reflect recent dietary intake. While studies have correlated a higher relative risk of breast cancer in women who consume alcohol, few studies have correlated red blood cell folate levels and breast cancer incidence prospectively.

The metabolism of folic acid, a B vitamin, contains a glutamate residue which is required to keep it inside cells. It is converted by enzymes in the jejunum of the small intestine to the monoglutamate form from the polyglutamate form and is present in the blood predominantly as 5-methyltetrahydrofolate, entering cells in a variety of methods and potentially losing its methyl group with a Vitamin B-12 dependent conversion. Without B-12, folate could be trapped



and unavailable for use. The active form of folic acid is tetrahydrofolic acid playing a key role in transfer of one carbon methyl units in DNA, RNA and protein synthesis, amino acid synthesis and homocysteine regulation.

In 2008 Stockley referred to studies suggesting adequate or supplemented dietary folate to be associated with lower rates of breast, colon and pancreatic cancers by reducing point mutations and strand breaks in the p53 proto-oncongene or through enhanced cell death via free radical formation through the cytochrome p450 pathway.

The data on folate has been inconsistent, however, and remarkable findings include those correlating high plasma folate levels with an increased incidence of developing premenopausal breast cancer as well as estrogen receptor and progesterone receptor positive cancers. Other studies attempt to look at folate repletion for remission or recurrence of disease.

Questions with regard to folate deficiencies and congenital malformations, neural tube defects continue to go unanswered. Despite a 15 year national campaign in the US with grain fortification and a significant (30%) decline fetal alcohol syndrome (neural tube defects presently occur in .1-.2% of births). Data suggests supplementation has not reached all segments of the world's population. Other data suggests difficulty with compliance with regard to folate supplementation or alcohol restriction in pregnancy. Sorting out nutritional deficiencies versus exposure to alcohol can be very difficult.

Two years later, data with regard to the mitigating effect of folate and breast cancer incidence is varied. Data suggests, however, that the Mediterranean diet, which includes moderate alcohol consumption and is naturally rich in folic acid, is associated with lower rates of cancer, heart disease and birth defects in pregnancy. So, folate appears to be a common thread, linked to alcohol consumption and metabolism which may implicate its deficiency in a variety of human morbidities, but is difficult to study.

It appears that those who have the least risk are likely to be enjoying the Mediterranean diet, high in fruits and vegetables (and therefore folic acid), limited animal fats (and therefore free radicals) and alcohol in moderation.

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