

## Commentary

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## Hyperhomocysteinemia and Alcoholism: A Double Hit?

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Homocysteine (HCY) is a non-protein sulfur-containing amino acid. It has received a great deal of attention over the last two decades within the scientific community for its unique role in the induction of several diseases ranging from atherosclerotic cardiovascular disease to neural tube defects (NTD). The hypothesis that hyperhomocysteinemia (HHCY) causes atherosclerosis was proposed by McCully<sup>1</sup> in 1969, when he observed that children with homocysteinuria had atherosclerotic plaques of the peripheral, coronary, and cerebral vasculature. In 1976, the initial epidemiological study of Wilcken and Wilcken<sup>2</sup> supported this hypothesis and provided the first evidence of the pathogenic role of HCY in atherosclerotic cardiovascular disease and alcoholism. HCY strictly associated with alcohol consumption and enhanced the alcohol consumption that leads to alcohol-related disorders such as brain atrophy, epileptic seizures during withdrawal, and mood disorders.<sup>3</sup> Although, HHCY involves both genetic and nutritional causes,<sup>4</sup> the mechanism of HCY toxicity is not completely understood.

In vascular biology and under physiological conditions, the proliferation and apoptosis of cells are balanced as a symphony in which the cell death triggers cell migration and proliferation. However, in the pathogenic conditions, a selective increase in cell proliferation induces hyperplasia and a selective elevation of apoptosis leads to atrophy. As early as 1973, Ross and Glomset<sup>5</sup> proposed that proliferation of smooth muscle cells within the wall of the artery was the key event in the genesis of the lesions of atherosclerosis. Atherosclerosis is a multifactorial process including endothelial dysfunction, and vascular smooth muscle cells (VSMCs) apoptosis, proliferation and migration from the media to the intima, and subsequently, formation of the atherosclerotic plaques.<sup>5-10</sup> Indeed, apoptosis and proliferation of VSMCs are the most prominent hallmarks of atherosclerotic plaque instability. A stable atherosclerotic plaque possesses a thick fibrous cap with excessive numbers of VSMCs, whereas unstable atherosclerotic plaques have a thin fibrous cap with limited numbers of VSMCs. Apoptosis of VSMCs is substantially elevated in unstable plaques which promotes plaque rupture and subsequently led to heart attacks.<sup>9</sup> On the other hand, proliferation of VSMCs is associated with stable plaques.<sup>8</sup>

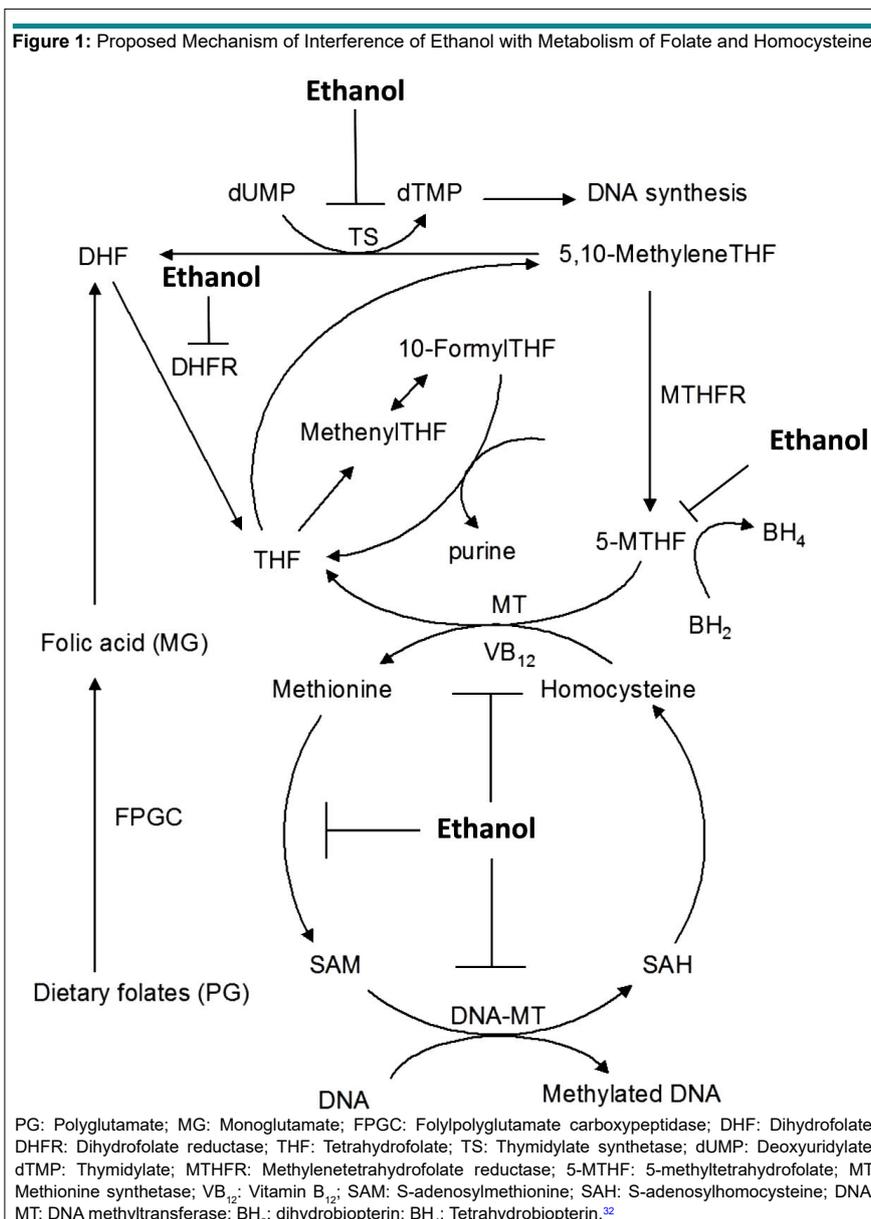
A clinical study by Guang et al<sup>11</sup> reported that HCY might convert a stable plaque into an unstable plaque due to the elevation of oxidative stress and chemokines in patients with acute coronary artery disease. To explain these phenomena, one possibility considered is that HCY initiates monocyte, T-lymphocyte, endothelial cell and VSMCs activities that interact with other inflammatory stimuli (such as C-reactive protein and ox-LDL), sensitize the inflammatory responsiveness leading to an enhanced production of reactive oxygen species (ROS) and a chronic inflammatory condition at the site of atherosclerotic lesions.<sup>11</sup> In this condition, the production of proinflammatory chemokines and ROS are enhanced further by monocyte, T-lymphocyte, endothelial cell and VSMCs.<sup>11</sup> These chemokines increased leukocyte adhesion and transendothelial migration.<sup>11</sup> At the same time, ROS induce further modified LDL into a highly oxidized form, which is taken up by macrophage and results in foam cell formation.<sup>11</sup> Study of Rasmussen et al<sup>12</sup> emphasized that HCY increased VSMC proliferation, whereas there was no change in apoptosis. Similarly, Taha et al<sup>13</sup> reported that HCY enhanced DNA synthesis and proliferation of VSMCs. Although the accumulation of VSMCs is the main cause of intimal thickening of vascular disease, Weissberg and co-workers<sup>14</sup> speculated that VSMC

proliferation might be beneficial. As such long-term treatment to prevent VSMCs proliferation would rupture the atherosclerotic lesions.<sup>15</sup> In our opinion proliferation of VSMCs is not beneficial but it might delay the rupture of the stable plaques. Importantly, a study by Buemi et al showed that HCY elevated both apoptosis and proliferation of VSMCs *in vitro*.<sup>16</sup> Clinically, atherosclerosis appeared to be associated with HCY levels of approximately 250 μM in hyperhomocysteinemic patients.<sup>17-19</sup> In addition, Yan et al<sup>20</sup> denoted that HCY (0.05-1 mM) elevated apoptosis of VSMCs in a dose-dependent manner. Vascular toxicity of HCY seems to be due to the elevation of oxidative stress after auto-oxidation of homocysteine into homocystine.<sup>4</sup> The mechanisms of induction of oxidative stress by HCY have been exclusively studied by Tyagi et al<sup>21,22</sup> and Moshal et al.<sup>23</sup>

More recent studies suggest the deleterious effects of HCY go beyond oxidative stress. For example, Kobus-Bianchini<sup>24</sup> reported that HCY interfered with the proliferation

of neural cells and induced a decrease in neuronal differentiation in the spinal cord. Thus, the molecular networks of homocysteine are multifactorial and also include epigenetic regulation (Figure 1). Alterations in human homocysteine levels can influence DNA-methylation of specific gene sequences that may change the expression and synthesis of proteins important for the genesis and maintenance of alcohol dependence.<sup>25,26</sup>

The metabolism of folates and homocysteine are interrelated (Figure 1). Folic acid catalyzes methylation of homocysteine, leading to a reduction of total plasma homocysteine.<sup>27</sup> Conversion of homocysteine into methionine can occur in a reaction catalyzed by methionine synthetase, which uses 5-methyltetrahydrofolate (5-MTHF) as a methyl donor and cobalamin (vitamin B-12) as an essential co-factor.<sup>28</sup> Consumption of alcohols, negatively, interferes with the physiological and biochemical metabolic pathways of folates and homocysteine (Figure 1) that leads to a double hit. Ethanol



modulated liver methionine/homocysteine metabolism has been reflected by decreased SAM and increased SAH content.<sup>29</sup> Ethanol impaired the renal conservation of 5-methyltetrahydrofolate in the isolated perfused rat kidney.<sup>30</sup> Chronic alcoholism is known to interfere with one-carbon metabolism, for which folate, vitamin B-12, and vitamin B-6 serve as coenzymes.<sup>31</sup> Mean serum HCY was twice as high in chronic alcoholics compared to that of non-drinkers.<sup>31</sup>

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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