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Molecular Alterations Shed Light on Alteration of Methionine Metabolism in Gastric Intestinal Metaplesia; Insight for Treatment Approach

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Abstract : Gastric carcinogenesis is a lengthy process of histopathological transition from normal to atrophic gastritis (AG) to intestinal metaplasia (GIM), dysplasia toward gastric cancer (GC). The stage of GIM identified as precancerous lesions with resistance to H-pylori eradication and recurrence after endoscopic surgical resection therapies. GIM divided in to two morphologically distinct phenotypes such as complete GIM bearing intestinal type morphology whereas the incomplete type has colonic type morphology. The incomplete type GIM considered to be the greatest risk factor for the development of GC. Studies indicated the expression of the caudal type homeobox 2 (CDX2) gene is responsible for the development of complete GIM but its progressive downregulation from incomplete metaplasia toward advanced GC identified as the risk for IM progression and neoplastic transformation. The downregulation of CDX2 gene have promoted cell growth and proliferation in gastric and colon cancers and ascribed in chemo-treatment inefficacies. CDX2 downregulated through promoter region hypermethylation in which the methylation frequency positively correlated with the dietary history of the patients, suggesting the role of diet as methyl carbon donor sources such as methionine. However, the metabolism of exogenous methionine is yet unclear. Targeting exogenous methionine metabolism has become a promising approach to limits tumor cell growth, proliferation and progression and increase treatment outcome. This review article discusses molecular alterations that could shed light on the potential of exogenous methionine metabolisms, such as gut microbiota alteration as sources of methionine to host cells, metabolic pathway signaling via PI3K/AKt/mTORC1-c-MYC to rewire exogenous methionine and signature of increased gene methylation index, cell growth and proliferation in GIM, with insights to new treatment avenue via targeting methionine metabolism, and the need for future integrated studies on molecular alterations and metabolomics to uncover altered methionine metabolism and characterization of CDX2 methylation in gastric intestinal metaplasia for potential therapeutic exploitation.

Keywords : altered methionine metabolism, Intestinal metaplesia, CDX2 gene, gastric cancer
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