

Epigenetics and its role in carcinogenesis

Jibran Sualeh Muhammad*

Department of Basic Medical Sciences, College of Medicine, University of Sharjah, Sharjah, UAE

Epigenetics is a well-known mechanism playing a significant role in cancer development. It is characterized by stable and heritable changes in the function of genes which occur without any alteration to the DNA sequence and includes DNA methylation, histone modification, and RNA interference by microRNAs. These epigenetic modifications can be stable to maintain the specific lineage of cells or dynamic to respond to developmental and environmental signals. Alterations in the epigenetic state of the cell can lead to aberrancies in phenotype which are then passable to daughter cells [1].

DNA methylation in the CpG Islands (CGI) of the gene promoter region is one of the best known and extensively studied epigenetic modification. Methylation of several tumor suppressor gene promoters is responsible for their silencing and thus potentially sustains carcinogenesis. Similarly, histone de-acetylation can lead to oncogene activation. miRNA are small (18-20 nucleotides) non-coding RNA fragments capable of inhibiting other m-RNA, ultimately altering the balance in oncogene and tumor suppressor gene expression. It has been shown that growth of several tumor types can be stimulated by epigenetic changes in various phases of carcinogenesis, and drugs able to interfere with these mechanisms can have a positive impact on tumor progression. As matter of fact, dynamic epigenetic changes can be reversed by epigenetic inhibitors [2].

Recently, we published a study in the International Journal of Cancer which showed that methylation silencing of an autophagy related gene by *Helicobacter pylori* infection leads to carcinogenic transformation in gastric epithelial cells [3]. This study was a collaborative project

between researchers from The Aga Khan University, University of Toyama, and the National Cancer Institute, Tokyo. We showed that *MAP1LC3Av1* was specifically methylation-silenced in *H. pylori*-infected non-cancerous and cancerous gastric mucosae. The inactivation of *map1lc3a*, a rat homolog of the human *MAP1LC3Av1*, disrupts the autophagy pathway, thereby leading to carcinogenesis in gastric epithelial cells. We suggested that, *MAP1LC3Av1* methylation and expression levels could be used as an early indicator of carcinogenic transformation of non-cancerous mucosae in *H. pylori*-infected gastric cancer patients. Chemoprevention may also be achieved against gastric cancer associated with *H. pylori* using by de-methylating agents in future. Although we don't see many cases of *H. pylori*-induced gastric cancer among Pakistani population, however, gastric cancer is amongst the top ten prevalent cancers with gradual rise to a maximum in the 7th decade of life. This study will provide a basis to study the role of DNA methylation in relation to the development of the more prevalent cancers. Similar studies are in pipeline by our research group to investigate the role of epigenetic modifications in association with commonly prevalent diseases and cancers in Pakistani population.

References

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Correspondence to: Dr. Jibran Sualeh Muhammad MBBS, Ph.D., Assistant Professor, Department of Basic Medical Sciences, College of Medicine, University of Sharjah, Sharjah, UAE, E-mail: dr.jibran@live.com

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