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INVITED COMMENTARY

SALL4 Expression in Epithelial Gastric Cancer: Epigenetic or Epiphenomenon?

Trinath Jamma[1]

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The incidence of gastrointestinal cancer is increasing at an alarming rate of 7.1 per 100,000 per year [1, 2]. With a corresponding mortality rate of 2.8 per 100,000 annually, there is a pressing need to identify diagnostic markers that can predict the presence of disease in its early stages with sensitivity and specificity. Considering that the cancer cell shares several properties such as rapid proliferation and lack of differentiation with healthy stem cells, identifying markers that are specific to cancer cells is under intense investigation. Some of the reported markers include carcinoembryonic antigens CEA, CA19-9, and CA72-4, that are widely used for detecting gastric cancer in clinical practice [3].

Recent advances in cancer genomics and transcriptomics have identified the Spalt-like (SALL) family of 4 C_2H_2 zinc finger transcription factors that are important for embryonic development, helping regulate cell proliferation, survival, migration, and stemness [4]. These factors were later found to be upregulated in numerous human genetic disorders and cancers. Of the four isoforms, SALL4 is the most extensively studied in the context of tumor development, cancer progression, and therapy. At the molecular level, the regulation of SALL isoform expression, predominantly SALL4, is under intensive investigation for its increased expression across tumor tissues, including breast, lung, liver, endometrial, germ cell, and gastric cancer [5, 6]. SALL4 has also been considered as a biomarker that identifies tumors of germ cells and trophoblast origin [7]. Interestingly, several downstream signaling events activated by SALL4 have been identified, including the Wnt-β-catenin pathway implicated in tumor progression.

In this issue of *Digestive Diseases and Sciences*, Liu et al. [8] identified epigenetic regulation of SALL4 gene expression in cancer tissues and cancer cell lines of gastric origin. In this context, the expression of two epigenetic modifiers correlated with overall survival (OS) as well as a local invasion (T stage), lymph node metastasis (N stage), and distant metastasis (M stages) of gastric cancer. Reduced expression of the histone methyl transferases EZH2 that promotes H3K27 methylation on the SALL4 promoter was identified in advanced stages of gastric cancer. In contrast, KDM6A, a histone demethylase, was significantly upregulated in several stages of gastric cancer in patient-derived samples. The transient knockdown of these epigenetic modifiers and SALL4 in gastric cancer cell lines vs. control confirmed the importance of epigenetic modification of SALL4 gene expression and its implications in gastric cancer.

Even though it is widely reported that overexpression of SALL4 is associated with multiple cell signaling pathways, including Wnt, the precise mechanisms associated with SALL4 and Wnt pathway activation remain unexplored [9]. Importantly, differential expression of SALL isoforms was noticed in tissue samples. The opposing effects of methylases and demethylases on SALL4 and other isoforms may potentially inform the development of novel therapeutics in isolation or in combination with the existing gastric cancer treatment regimens. Moreover, given the impact of this disease on health and quality of life, with overall survival still < 5 years from the time of diagnosis, understanding the intricate molecular mechanisms associated with the development of this disease at the cellular level holds promise towards improving gastrointestinal health outcomes.

Declarations

Conflict of interest The author declares no potential conflict of interest.

✉ Trinath Jamma
trinath@hyderabad.bits-pilani.ac.in;
karunya.friend@gmail.com

[1] Department of Biological Sciences, Birla Institute of Technology and Science-Pilani, Hyderabad, Telangana 500078, India

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