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The Cancer Control Challenge:
Better Understanding It to Better Face It

EXPRESSION PROFILING OF *PD-L1*, *LGALS9*, *TGFB1*, AND *HAVCR2* IN GASTRIC CANCER AND METAPLASIA: IMPLICATIONS FOR TARGETED THERAPIES AND PREVENTION OF MALIGNANT PROGRESSION

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Introduction: Gastric cancer (GC) remains a major global health challenge, with approximately 1 million new cases diagnosed annually, ranking as the fifth most common malignancy and the fourth leading cause of cancer-related mortality worldwide. Early diagnosis through advanced endoscopic techniques and molecular profiling is pivotal for improving patient outcomes. For locally advanced GC, standard treatment encompasses surgical resection, often combined with perioperative chemotherapy or chemoradiotherapy. Minimally invasive techniques, such as laparoscopic and robotic-assisted gastrectomy, have gained traction for resectable disease, offering reduced morbidity. In advanced or metastatic GC, systemic therapies, including immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) and targeted agents against HER2 or VEGF, have improved survival rates. Emerging therapies, such as inhibitors targeting novel immune checkpoints and tumor microenvironment modulators, are under active investigation in clinical trials, showing promise for enhancing therapeutic efficacy and patient quality of life. **Objective:** This study aims to assess the expression profiles of key therapeutic targets and different tissue samples. These targets are currently under investigation for novel pharmacological agents in ongoing clinical trials. **Methods:** A total of 124 GC and 62 ADJ samples (CAAE:47580121.9.0000.5634) from patients who underwent surgical resection, and 20 MP samples obtained via endoscopic biopsy were analyzed. RNA-seq was conducted in a paired-end manner on the NextSeq® platform (Illumina®). The NextSeq® 500 MID Output V2 kit – 150 cycles (Illumina®) was used according to the manufacturer's instructions. Human transcript reads were characterized through alignment and quantification using Salmon v1.5.2, with the coding transcripts from hg v38 (www.ensembl.org) as the reference index and GENCODE v.42 (www.gencodegenes.org) as annotation. The reads were imported from Salmon into RStudio using the Tximport v3.14.0 package (The library used for the differential analysis was DESeq2. Parameters: log2FoldChange and adjusted p-value < 0.05). **Results:** *PD-L1* expression was significantly elevated in MP samples compared to GC and ADJ ($p<0.0001$, Kruskal-Wallis test). *LGALS9, HAVCR2* and *TGFB1* genes showed high expression across all samples, with significantly increased levels in MP ($p<0.01$; $p<0.001$ and $p<0.01$, respectively; Kruskal-Wallis test, adjusted by Benjamini-Hochberg). *LGALS9* overexpression was significantly correlated with decreased survival ($p<0.05$, Kaplan-Meier). **Conclusion:** These findings highlight the importance of targeting these molecules in ongoing clinical trials for novel pharmacological agents, particularly for patients with

metaplasia or advanced GC. The significant correlation between *LGALS9* overexpression and reduced survival underscores its prognostic relevance and potential as a therapeutic target. The pronounced expression of these targets in metaplasia is particularly relevant, as patients with GC frequently exhibit metaplastic lesions in other regions of the stomach. These lesions, often persisting after partial gastrectomy due to incomplete resection of the stomach, are prone to malignant transformation. Targeting *PD-L1*, *LGALS9*, *TGFB1*, and *HAVCR2* with novel pharmacological agents could offer a dual therapeutic benefit: treating residual metaplastic tissue to prevent progression to GC and addressing existing malignancy. This approach holds particular promise for patients undergoing partial gastrectomy, where residual metaplasia may drive recurrent disease. These findings underscore the importance of integrating molecular profiling into clinical management to identify patients who may benefit from targeted therapies, thereby reducing the risk of cancer progression and improving long-term outcomes.

Keywords: Metaplasia; Gastric cancer; Carcinogenesis; Novel targets; Therapy.