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

EXPRESSION PROFILING OF NOVEL THERAPEUTIC TARGETS IN GASTRIC CANCER

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Introduction: Gastric cancer (GC), a significant global health burden, records approximately 1 million annual incident cases. Early detection through comprehensive diagnostic modalities is critical for optimizing therapeutic outcomes. Standard management of locally advanced GC involves surgical resection combined with systemic therapies. Minimally invasive surgical approaches are increasingly adopted for resectable disease, while advanced stages benefit from immune checkpoint inhibitors and molecularly targeted therapies. Emerging therapeutic strategies, including novel targeted agents and next-generation immunotherapies, demonstrate potential for enhancing survival and quality of life. **Objective:** This study evaluates the expression of therapeutic targets for advanced GC—*HER2*, *TROP2*, *VEGF*, *CLDN18.2*, *FGFR2*, *PD-1*, *PD-L1*, *VEGFR2*, *CTLA-4* and *TIGIT*—in gastric tissue samples with and without cancer. These targets are currently under investigation for novel pharmacological agents in ongoing clinical trials. **Methods:** A total of 124 GC and 62 adjacent to tumor (ADJ) samples from patients who underwent surgical resection, and 20 metaplasia (MP) samples obtained via endoscopic biopsy were analyzed. RNA-seq was conducted in a paired-end manner on the NextSeq® platform (Illumina®), using the NextSeq® 500 MID Output V2 kit – 150 cycles (Illumina®), according to the manufacturer's instructions. Human transcript reads were characterized through alignment and quantification using Salmon v1.5.2, with coding transcripts from hg v38 as the reference index and GENCODE v.42 as annotation. Reads were imported into RStudio using the Tximport v3.14.0 package. **Results:** Expression of *HER2*, *FGFR2*, *VEGFR2*, *CLDN18.2* ($p < 0.0001$), *TROP2* and *VEGF* ($p < 0.001$, Kruskal-Wallis test adjusted by Benjamini-Hochberg) was significantly elevated in GC and ADJ compared to MP. Notably, patients with high *FGFR2* expression showed greater survival ($p < 0.05$, Kaplan-Meier). *PD-L1* expression was significantly higher in MP compared to GC and ADJ, while no statistical differences were observed for *CTLA-4*, *TIGIT* and *PD-1* gene expression among the samples. **Conclusion:** Elevated *HER2*, *FGFR2*, *VEGFR2*, *CLDN18.2*, *TROP2* and *VEGF* levels in GC and ADJ reflect their established roles in tumor proliferation, angiogenesis and metastasis, currently explored as therapeutic vulnerabilities. The association between high *FGFR2* expression and improved survival contrasts with most published studies linking *FGFR2* overexpression to poor prognosis; however, evidence suggests *FGFR2* activation may upregulate immune-modulating molecules such as *PD-L1* via MAPK, PI3K and JAK/STAT3 pathways, potentially enhancing anti-tumor immunity through increased immune cell infiltration. This immune-modulating effect offers a plausible explanation for the observed findings and highlights the complex role of *FGFR2* in cancer biology. The higher *PD-L1* expression in MP compared to GC and ADJ may indicate an early immune evasion mechanism or a distinct local immune microenvironment, warranting further investigation. The lack of differential expression of

CTLA-4, *TIGIT* and *PD-1* suggests these immune checkpoints may act predominantly in early gastric tumorigenesis, potentially explaining the heterogeneous clinical responses to checkpoint blockade therapies. Collectively, these results underscore the importance of molecular stratification in guiding personalized therapeutic strategies for GC, with ongoing trials expected to further refine these approaches.

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