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

MMP FAMILY GENES AND PROTEIN INTERACTION NETWORKS IN GASTRIC CANCER: INSIGHTS FROM A BRAZILIAN COHORT

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Introduction: Gastric cancer (GC) is a multifactorial disease characterized by various alterations that can differ among patients, contributing to tumor heterogeneity. The matrix metalloproteinase (MMP) family includes genes that are modulated during the carcinogenesis. These genes primarily regulate the extracellular matrix (ECM) and are involved in the development and progression of GC. **Objectives:** This study aims to evaluate the correlations between altered genes from the MMP family and genes across the entire transcriptome, as well as to investigate the protein-protein interactions (PPI) associated with these genes. **Methods:** For this purpose, samples from patients treated at a reference oncology center in the state of Pará were used. A total of 88 samples were analyzed: 34 paired samples of tumor and adjacent tissue, 15 tumor-only samples, and 5 non-tumor adjacent tissues (CAAE: 10272913.8.0000.0017). Total RNA was extracted using TRIzol® and RNA sequencing was conducted on the Illumina NextSeq platform. Sequencing reads were converted to FASTQ format using Reporter software and subsequently mapped to the hg38 reference genome (GENCODE) using the Salmon tool v.1.5.2. Differential gene expression analysis was performed with the DESeq2 package v.3.14 from RStudio v.4.1.0, comparing tumor vs. adjacent samples and considering genes with a |Log2(Fold-Change)| greater than two and a p-value < 0.05 as differentially expressed (DE). Correlations were assessed using Pearson's correlation test, via RStudio v.4.1.0, with a threshold of $r \geq 0.6$ considered to be relevant when comparing DE MMPs and other DE genes from tumor samples. The PPI analysis was conducted from the genes selected based on their correlation with the DE MMPs and the hierarchical network was generated in Cytoscape v.3.10.2 using the STRING database. **Results:** Among the 24 genes of the MMP family, six genes (MMP2, MMP7, MMP9, MMP10, MMP12, and MMP14) were overexpressed in the analyzed samples. Through an extensive analysis, the correlation of the six MMP family genes, with altered expression relative to the control, with other genes across the entire genome was demonstrated. It was shown that MMP2 correlated with the genes CTSK (r=0.6418),

GJA1 (r=0.6007), GREM1 (r=0.8117); MMP7 correlated with the genes CTSL (r=0.6049), CTSK (r=0.5467); MMP9 correlated with the genes CTSL (r=0.6661), MMP12 (r=0.6659); and MMP12 correlated with the genes CTSL (r=0.6346), GJA1 (r=0.6007), CSF2 (r=0.6197). Furthermore, the PPI network revealed 20 interactions including 8 proteins: MMP2, MMP7, MMP9, MMP12, CTSK, GJA1, CTSK, and SCF2, showing association mainly with ECM modulation pathways. **Conclusion:** Altered MMP family is correlated with several genes involved in the modulation of GC, playing an important role in the patient's biological processes. Therefore, we suggest that this set of genes is associated with proteolysis, particularly in the catabolism of collagen and elastin, as well as in the ECM disassembly, processes modulated by MMPs in GC. However, further assays are required to validate our hypothesis.

Keywords: Gastric Cancer; MMP; Extracellular Matrix.