Subtype-Specific Expression and Coexpression Patterns of CFTR in Gastric Cancer

Marcella Vitória Belém Souza[1], Camila Sinimbú Forte[2], Gilderlanio Santana de Araújo[1]

[1]Institute of Biological Sciences, Federal University of Pará
[1]Institute of Technology, Federal University of Pará

Introduction: Gastric cancer is among the most prevalent neoplasms worldwide, predominantly affecting men in developing countries, with incidence rates increasing significantly with age. In individuals with Cystic Fibrosis (CF), gastrointestinal cancers, including gastric cancer, have emerged as notable comorbidities in adulthood. Recent studies have highlighted a potential role for the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene - classically associated with CF - in the pathogenesis of various cancers. CFTR, a key protein responsible for bicarbonate (HCO_3^-) transport and regulation, has been proposed to function as a tumor suppressor gene in the intestinal tract. However, CFTR dysfunction - most notably due to mutations such as ∆F508 - leads to viscous secretions that obstruct ducts and intestinal passages. This obstruction contributes to an inflammatory microenvironment, recurrent infections, and ultimately, tumorigenesis. Despite these associations, the precise biological role of CFTR remains incompletely understood, and its mutation and expression patterns have been scarcely explored in the context of gastric cancer. **Objectives:** This study aimed to investigate the expression profile of CFTR across different gastric cancer subtypes, assess its co-expression networks, gene-gene interactions, and biological pathway associations, and identify possible molecular interactions predictive of specific gastric cancer subtypes. **Methods:** To this end, we conducted a differential gene expression analysis on six molecular subtypes of stomach cancer using data from The Cancer Genome Atlas Stomach Adenocarcinoma (TCGA-STAD). The EdgeR package was used for identifying differentially expressed genes, while CEMiTool was employed for co-expression network analysis, followed by functional pathway over-representation analysis. We further utilized the clusterProfiler R package for functional enrichment analysis to gain deeper biological insights. **Results:** Contrary to initial hypotheses, CFTR was not significantly differentially expressed in any of the 15 pairwise comparisons among the six molecular subtypes of gastric adenocarcinoma in the TCGA-STAD dataset. Nevertheless, our investigation uncovered systemic patterns suggesting a more nuanced role for CFTR in gastric tumor biology. Notably, in the signet ring cell carcinoma subtype, co-expression analysis identified 58 genes interacting with CFTR, pointing to its involvement in broader regulatory networks rather than exhibiting standalone differential

expression. These interactions were also mirrored in Lauren’s histological classification of gastric cancer. **Conclusion:** Our findings suggest that CFTR may exert its influence on gastric cancer progression through modulation of co-expressed genes and pathways, particularly in the signet ring cell subtype. This underscores the importance of considering network-level interactions in understanding CFTR's functional role and its potential as a modulator of tumorigenic pathways, rather than as a direct biomarker of expression change.

Keywords: CFTR; Gastric cancer; Gene expression; Co-expression networks.