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

MICROBIOME-HOST INTERACTIONS MODULATED BY FLOT CHEMOTHERAPY IN GASTRIC ADENOCARCINOMA SUBTYPES: AN INTEGRATIVE APPROACH

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Introduction: Gastric adenocarcinoma (GA) is one of the most lethal cancers worldwide, exhibiting marked biological heterogeneity between intestinal and diffuse histological subtypes. Although the FLOT regimen (5-fluorouracil, leucovorin, oxaliplatin and docetaxel) has improved survival in resectable cases, its molecular and ecological impacts—particularly on the tumor microbiome and host gene expression—remain poorly understood. **Objectives:** To investigate how neoadjuvant treatment with FLOT affects intestinal and diffuse gastric adenocarcinoma subtypes, as well as the functional interactions between the microbiome and the human transcriptome. **Methods:** This study was approved by the Research Ethics Committee of Hospital Universitário João de Barros Barreto (CAAE: 47580121.9.0000.5634). A total of 23 tumor samples from gastric adenocarcinoma patients undergoing neoadjuvant FLOT chemotherapy were analyzed and classified as diffuse (n = 9) or intestinal (n = 14) according to Lauren's criteria. Human reads were aligned to the GRCh38 reference genome, while non-human reads were taxonomically classified and analyzed for microbial gene expression using Kraken2 and subsequently Salmon. Differential gene expression analysis was performed using DESeq2, followed by functional enrichment analyses and correlation assessments between human and microbial genes. **Results:** The diffuse subtype exhibited a markedly stronger microbial and transcriptomic response to FLOT compared to the intestinal subtype, with 112 positively and 78 negatively regulated microbial genes identified in the diffuse group, versus only 34 in the intestinal group. Microbial species such as *Fusobacterium nucleatum* and *Prevotella intermedia* were more abundant in diffuse tumors, indicating a microbiome more sensitive to chemotherapy. In the human transcriptome, the diffuse subtype showed 205 upregulated genes, including *MMP1*, *MMP9*, *S100A8* and *S100A9*, associated with extracellular matrix degradation and inflammatory processes. Gene enrichment analyses highlighted pathways related to stromal remodeling, leukocyte chemotaxis, angiogenesis and cytokine–integrin interactions. Correlation analyses revealed significant functional links between microbial and human genes, with *F. nucleatum* associated with immunomodulatory and structural genes, while *P. intermedia* correlated with angiogenic regulators such as *VEGFA* and

CXCL12. Additionally, microbial genes such as *cydA*, *nrdA* and *gapdh* demonstrated co-regulation with human stress-response genes, suggesting an integrated host–microbiome response. **Conclusion:** FLOT therapy induces subtype-specific reprogramming of the tumor microenvironment in gastric adenocarcinoma. In diffuse tumors, this reprogramming involves coordinated alterations in both microbial and host gene expression, encompassing inflammatory signaling, angiogenesis, redox regulation and stromal remodeling. These findings emphasize the relevance of integrating microbial and molecular profiling into precision oncology, with potential implications for the development of microbiome-based biomarkers and therapeutic targets in gastric cancer.