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Differential Expression of GLUT-1 and FASN Across Histological Grades of Pancreatic Neuroendocrine Neoplasms

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BACKGROUND

Pancreatic neuroendocrine tumors (PanNETs) are a heterogeneous group of tumors that exhibit variable clinical behavior. Understanding metabolic alterations across tumor grades may reveal diagnostic and therapeutic opportunities. In this study, we examined the expression of two critical metabolic proteins, glucose transporter 1 (GLUT-1) and fatty acid synthase (FASN), in various histological grades of PanNETs and metastatic lesions.

METHODS

Seventeen formalin-fixed, paraffin-embedded PanNET samples were selected retrospectively from the Huntsman Cancer Institute (University of Utah) and classified using the current World Health Organization (WHO) grading criteria. The samples were classified as follows: grade 1 (n = 7), grade 2 (n = 8), grade 3 (n = 1), and metastatic (n = 1). Immunohistochemistry for GLUT-1 and FASN was performed using an automated Leica Bond platform. Staining quantification was carried out using QuPath software with a compartment-specific analysis. GLUT-1 staining was defined as both cytoplasmic and membranous, while FASN staining was defined as exclusively cytoplasmic. Five representative regions per tumor were analyzed, and data were subjected to statistical comparison using the Kruskal-Wallis and Dwass-Steel-Critchlow-Fligner post-hoc tests (Jamovi v2.3.28.0), with $p < 0.05$ considered significant.

RESULTS

GLUT-1 expression was limited to the islets of adjacent normal pancreatic tissue, whereas the neoplastic areas exhibited diffuse cytoplasmic and membranous staining. Grade 3 tumors showed markedly lower GLUT-1 expression (8.5%) and lower staining intensity (0.11) than grades 1 (56.1%, intensity 0.30) and 2 (61.3%, intensity 0.26). Significantly, higher GLUT-1 expression was observed in grades 1 and 2 compared to grade 3 ($p < 0.05$ for both comparisons). A similar pattern was observed for staining intensity, however, a statistically significant difference was found only between grades 1 and 2 ($p < 0.05$). FASN exhibited strong, diffuse cytoplasmic staining in both normal pancreatic tissue and

neoplastic tissue, with relatively lower expression in normal islets. In neoplastic cells, FASN expression remained high across most groups, with over 93% of cells staining positive in grades 1 and 2 and metastatic tumors, but staining positivity decreased to 65.6% in grade 3 tumors. The mean staining intensity was highest in grade 1 tumors (0.65), followed by metastatic tumors (0.60) and grade 2 tumors (0.51). It was lowest in grade 3 tumors (0.33). While the percentage of FASN-positive cells did not differ significantly among the groups, staining intensity was significantly higher in grades 1 and 2 than in grade 3 ($p < 0.05$ for both comparisons).

CONCLUSIONS

GLUT-1 expression is markedly reduced in well-differentiated (grade 3) PanNETs, suggesting impaired or altered glucose uptake pathways in high-grade tumors. In contrast, FASN remains highly expressed across tumor grades, although staining intensity progressively decreases in grade 2 and 3 well-differentiated tumors, but increases in the metastasis. These findings underscore the distinct metabolic profiles across PanNET grades and suggest that GLUT-1 downregulation may be a marker of aggressive behavior. Further studies in larger cohorts are necessary to validate these biomarkers for clinical application.

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