Serum metabolomics profiling in patients with Gleason score 7 prostate cancer

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Prostate adenocarcinoma is the second most common cancer in men worldwide. The lack of conclusive diagnostic exams and complex treatment lead to treatment withdrawals of diagnosed patients, increasing mortality rates. Current diagnostic tools include Prostate Specific Antigen levels, digital rectal examination and biopsies graded according to the Gleason Score (GS), a system based on the histological assessment of prostate tissue. Consequently, a GS 7 diagnosis can refer to two different situations: 3+4 and 4+3, which may require different approaches for effective treatment. Therefore, accurately distinguishing between the GS 7 types is essential. An alternative for GS classification is the use of metabolomics, a sensitive omics science that allows the acquisition of metabolic profiles from various samples, and their statistical comparison, facilitating the search for biomarkers of various diseases, including cancer. In this work blood samples were obtained from patients with GS 7 prostate cancer at the Cancer Hospital of Uberlândia, affiliated with the Clinics Hospital of the Federal University of Uberlândia, Brazil. The serum was separated from the blood through centrifugation and stored at -80°C. The samples were thawed, extracted, dried, methoxylated, and sillylated. Analyses were conducted using gas chromatography-mass spectrometry (GC-MS). GC-MS data processing was performed using MS-Dial 5 and Metaboanalyst 6.0 software. The metabolomic findings revealed significant differences in the intensities of 40 metabolites between the GS7 groups, indicating shifts in cellular metabolism associated with disease progression, particularly in the 4+3 group. Among the identified compounds, the increase in sugars such as mannose, tagatose, and glucopyranose, along with butanedioic acid, is attributed to the Warburg effect, where glucose levels suggest a correlation between cellular respiration imbalance and disease aggravation. The increase in lysine also contributes to this effect through the acetylation of the free compound in cytochrome c, leading to a known specificity of prostate cancer escalation. Additionally, increases in linoleic, oleic, and stearic acids can be related to changes in lipid metabolism, a typical behavior of rapidly proliferating cancerous cells. The rise in linoleic acid is linked to its androgen receptor, which controls lipid metabolism by inducing the expression of sterol-regulating proteins and fatty acids, correlating with the higher inflammation observed in prostatectomy. Alternatively, oleic acid stands out as an endometrial cancer promoter due to its positive regulation of Krüppel\'s transcription factor, which is involved in cellular proliferation. Besides the aforementioned compounds, malonic acid, which was also found in higher intensities in the 4+3 group, is known as a biomarker for the lipid signature in the diagnosis of pulmonary cancer and is also a precursor for malonyl-CoA, an important compound in the fatty acid biosynthesis. The increase in specific sugars and fatty acids observed in the 4+3 group suggests a correlation with the Warburg effect and alterations in lipid metabolism, indicating elevated aggressiveness and inflammation potential. These findings contribute to understanding the mechanisms underlying prostate cancer progression and may facilitate the development of biomarkers for faster, less invasive diagnostic exams capable of accurately assessing disease severity.

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