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In depth proteomic characterization of the response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer using data independent acquisition mass spectrometry (DIA-MS)

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Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is the standard of care in patients with locally advanced rectal cancer (LARC) which increases local control and survival rates. Patients' responses to treatment differ, and it's yet unclear who will benefit the most from nCRT and is eligible for the watch and wait approach. The purpose of this study was to identify specific tissue molecular features that might influence the response to therapy and patient outcomes. Samples from 20 patients with confirmed LARC were retrospectively evaluated in this study. Patients were treated with concomitant RT/5FU+Leucovorine and divided into responders (R) and non-responders (NR) based on the tumor regression grade (TRG) (TRG1/2 vs. TRG 3-5, according to the Mandard scale). Liquid chromatography/Data independent acquisition mass spectrometry (DIA-MS) was performed on digested proteins isolated from FFPE pretreatment biopsy samples, while DIA-NN, MaxQuant Perseus and Metascape were used for data processing. The analysis revealed 915 differential expressed proteins (DEPs) between responders (215 DEPs overexpressed in R/NR) and non-responders (700 DEPs overexpressed in NR/R) (Welch t-test p0.05; S0=0.1). To clarify differences in treatment response, further enrichment analysis was performed. An evident difference in signaling pathways depending on the response to therapy was observed. Ten DEPs overexpressed in responders compared to non-responders included HAS1, DERL1, CPS1, PTX4, SH2D3C, SERPINB12, CASP14, EME2, ZBTB33, GP1BB, while top 10 DEPs overexpressed in non-responder group compared to responder group included QPRT, RBP3, SPTB, MOCS2, NHLRC3, SMPDL3A, SPTA1, CLCA4, COPS7A, SYNJ2. Listed proteins have promising predictive potential and further validation of our findings in a prospective patient cohort is currently ongoing. Based on obtained results the DIA-MS approach offered unprecedented proteome coverage for FFPE samples. The detected pretreatment differentially expressed proteins and biological processes constitute interesting findings that hold the potential for improving LARC patient management.

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