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5529/19: “Proteomic Profiling of FFPE Tumor Samples from Melanoma Subjects Treated with Anti-PD-1 Immunotherapy Identifies Proteins Associated with Response to Treatment”

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Background

Immune checkpoint inhibitors (ICI) have greatly improved the treatment options for patients with advanced stage melanoma, with improved clinical responses and overall survival compared to standard systemic therapies. However, a large percentage of melanoma patients do not respond to ICIs, highlighting the need for a greater understanding of the tumor environment and host immune response. Here, we apply unbiased discovery proteomics, based on label-free data independent acquisition (DIA) mass spectrometry, to deeply characterize global tumor proteomes to identify proteins and pathways that are associated with pre-treatment response to anti-PD-1 immunotherapy.

Methods

Unbiased, data-independent acquisition (DIA) mass spectrometry was used to analyze formalin fixed paraffin imbedded (FFPE) tumor tissue samples from subjects with Stage III-IV melanoma which were resected prior to initiation of first-line anti-PD-1 ICI therapy. The selected samples represent two distinct clinical subgroups; those who received clinical benefit, with a stable disease or better (SD, PR and CR, n = 13), and those with no clinical benefit (PD, n = 9). Samples were prepared for mass spectrometry using standard procedures. All samples were analyzed using 4-hour gradients on a LC-MS/MS setup operated in DIA mode. Data was extracted using Spectronaut (Biognosys) with a sample specific spectral library which was combined with a large human tissue resource library. Statistical analysis was conducted to identify proteins that are up- or down-regulated with respect to benefit group. Pathway analysis was also conducted to highlight dysregulated biological functions and pathways.

Results

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In analysis with 2-hour gradients, >7,500 proteins were quantified across all samples. Univariate statistical testing between groups identified 254 proteins are dysregulated (120 up- and 134 down-regulated) in subjects who received clinical benefit, of which a subset of 25 proteins was identified that describe the variance between the two sample groups. When annotated to their sub-cellular location, all up-regulated species are identified as mitochondrial proteins, indicating an enhanced metabolic environment in the responder subgroup. Additionally, GM2A and PLEKHA5 were strong diagnostic predictors of responder status. This updated analysis, conducted with a deeper level of characterization, will focus on additional metabolic pathways as well as known proteins associated with metabolic resistance (e.g. CD39 and CD73) to more fully characterize the tumor metabolic environment.

Conclusions

Global profiling of the tumor proteome provides a unique characterization of melanoma tumor biology. A pathway level analysis shows increased metabolic processes may underly some of the differences in benefit related to ICI therapy.

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