NK cell cytotoxicity and protein microarrays predict efficacy of melanoma immunotherapies

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Notwithstanding the impressive advances in melanoma-directed immunotherapies, resistance is common and many patients still succumb to the metastatic disease. In this context, natural killer (NK)-cells, although side-lined in the recent development of melanoma immunotherapy, could provide therapeutic benefits in the future. To identify molecular determinants of NK-cell-mediated melanoma killing (*NKmK*), we quantified NK-cell cytotoxicity against a panel of genetically-diverse melanoma cell lines and observed a highly heterogeneous susceptibility. Melanoma cell protein microarrays revealed a correlation between protein abundance/activation and *NKmK*. A "protein-killing-signature", identified metabolic factors as essential regulators of *NKmK.* Using 2D and 3D killing assays and melanoma xenografts, we demonstrated that the PI_3K/Akt/mTOR signaling-axis controls *NKmK* via expressional regulation of NK cell-relevant surface proteins. Moreover, we developed algorithms to predict *NKmK* of additional melanoma cell lines and the response of melanoma patients to anti-PD-1 checkpoint therapy. Our findings identify novel NK-cell-related prognostic biomarkers and might thus contribute to improved and personalized melanoma-directed immunotherapies.