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UT MD Anderson Cancer Center
2SCR1.4015 (Conference Room 1 at SCRB1&2)
via Zoom
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Loss of PTDSS1 in Tumor Cells Improves Anti -PD-1 Therapy

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PTDSS1 (Phosphatidylserine synthase 1) encodes an enzyme that facilitates production of phosphatidylserine (PS), which mediates a global immunosuppressive signal. Here, based on in vivo CRISPR screen, we identified PTDSS1 as a target to improve anti-PD-1 therapy. Depletion of PTDSS1 in tumor cells increased expression of IFNγ-regulated genes, including B2m, Cxcl9, Cxcl10, and Stat1. Loss of PTDSS1 in tumor cells also led to increased expression of MHC-I, which was associated with increased expression of cytolytic function related genes in $CD8^+$ T cells and increased frequency of an $iNOS^+$ myeloid subset. A gene signature derived from the $iNOS^+$ myeloid cell subset correlated with clinical benefit in patients treated with anti-PD-1 therapy. Moreover, PTDSS1 knockdown in two different tumor models improved anti-PD-1 therapy. Together, our results provide insights on a new therapeutic strategy for overcoming immunosuppression elicited by PS and provide rationale for development of a combination immunotherapy strategy comprised of PTDSS1 inhibition plus PD-1 blockade.

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