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Accumulation of CD38 in hybrid epithelial/Mesenchymal cells promotes immune remodeling and metastasis in breast cancer

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Background : Triple negative breast cancer (TNBC) is an aggressive subtype with high metastatic potential and limited treatment options. A key mechanism in metastasis is the epithelial-to mesenchymal transition (EMT), which occurs in a nonbinary fashion and gives rise to hybrid epithelial/mesenchymal (EM) cells. Recent studies highlight the enhanced metastatic potential of hybrid EM phenotype. However, molecular insights and targetable vulnerabilities within hybrid EM remain elusive. We discovered that hybrid EM murine tumors are enriched in CD38, an immunesuppressive molecule associated with worse clinical outcomes in liquid malignancies. Hence, we sought to investigate role of CD38 in hybrid EM-driven metastasis. We hypothesize that hybrid EM tumors drive metastasis via intratumoral accumulation of CD38, promoting an immunosuppressive tumor microenvironment (TME).

Methods: Reverse Phase Protein Array, cell migration/invasion assays, flowcytometry and immunohistochemistry were used to evaluate phenotype, immune cell populations and molecular mechanisms upon CD38 knockdown (KD) and overexpression (OE) in vivo. Results- CD38 KD weakened EMT, reducing cell migration and invasion. Such tumors showed increased infiltration of CD8+ T cells and M1-like (anti-tumor) macrophages coupled with a decrease in immunosuppressive regulatory T cells (Tregs) and M2-like (pro-tumor) macrophages. Most strikingly, hybrid EM tumors that no longer express CD38 show reduction in lung metastases and circulating tumor cell colonies. In contrast, cancer cells with CD38 OE maintained a hybrid EM phenotype and showed significant increase in cell migration and invasion. Such tumors displayed a significant increase in Tregs. TNBC patient samples harbored CD38 tumoral expression that correlated with PD-L1 expression. Consequently, co-targeting CD38 and PD-L1 in hybrid EM murine models delayed tumor growth and augmented an anti-tumor immune response. Taken together, these findings suggest that CD38 is important for the metastatic and immune evasive potential of hybrid EM breast cancers.

Conclusion : Our research establishes CD38 as a specific survival strategy utilized by hybrid EM tumors to suppress immune cells and sustain metastasis. Co-targeting CD38 and PD-L1 is a first in-class therapeutic approach in TNBC with strong implications in other cancers enriched in hybrid EM properties.