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DISSERTATION

“Axl and Mertk receptors cooperate to promote breast cancer progression by combined oncogenic signaling and evasion of host anti-tumor immunity”

by

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Molecular Biology, Genetics & Cancer Track

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ABSTRACT

The TAM receptors (abbreviated Tyro3, Axl, and Mertk), have emerged in recent years as important therapeutic targets in cancer biology. Accumulating evidence indicates that TAMs can act as oncogenic tyrosine kinases dysregulated on tumor cells, as well as immune modulatory receptors expressed on macrophages and other immune cells in the tumor microenvironment (TME) that suppress host immunity. Here, using triple-negative (ER, PR or Her2/neu) Axl-expressing mouse breast cancer 4T1 and EO771 cells, we compared effects of tumor growth, metastasis, and immune cell infiltration in the tumors when Axl was genetically ablated on tumor cells using CRISPR/Cas9 versus when Mertk was genetically ablated or pharmacologically inhibited in the TME using whole body Mertk knockout mice or an anti-Mertk neutralizing mAb respectively. In cell-based assays, Axl KO suppressed cell intrinsic oncogenic properties that include cell proliferation, chemo-resistance, cell migration, cell invasion, induced mesenchymal-to-epithelial transition. When xenografted into syngeneic mice, Axl receptor KO decreased tumor growth and incidence of lung metastasis which showed synergy with anti-PD-1 immunotherapy. When E0771-WT or Axl KO cells were transplanted into WT or Mertk KO mice, mice showed decreased growth, suggesting synergy between TAM receptor signaling on tumor cells and in the TME. To exploit this circuit pharmacologically, we investigated tumor growth in mice treated with anti-Mertk mAb, alone or in combination with anti-PD-1 immunotherapy. Interestingly, while mono-therapeutic administration of anti-Mertk antibody had no anti-tumor activity, however combinatorial treatment with anti-PD-1 significantly decreased tumor growth and incidence of lung metastasis, that could be blocked by pre-treatment with anti-CD8α mAb (T cell depletion), or by transplantation of tumor cells into NOD-SCID mice. Moreover, combinations of anti-Mertk mAb and anti-PD-1 showed decreased secretion of IL-10, and increased infiltration of immune stimulatory T cells versus either monotherapy treatment alone. Finally, using novel small molecule Mertk degraders and PS-targeting immune-biologicals to dissect molecular mechanisms, our data support the idea that Mertk, expressed mainly on macrophages, may act akin to a novel checkpoint inhibitor with applications in immuno-oncology.