BREAKING THROUGH THE RESISTANCE OF BREAST CANCER TO IMMUNE CHECKPOINT BLOCKERS IN A UNIQUE MOUSE MODEL OF HR+ DISEASE

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Background Hormone receptor (HR)+ breast cancer (BC) causes most BC-related deaths in the US. Standard treatment for non-metastatic disease involves surgery plus adjuvant hormone therapy. However, approximately 50% of patients ultimately relapse and require additional lines of treatment including chemotherapy, which is unfortunately associated with limited clinical benefits and severe toxicity. In HR+ BC patients, the efficacy of immunotherapy has also been disappointing so far. Indeed, objective responses to PD-1 blockade with pembrolizumab in women with HR+ BC have been in the range of 5–10%, with no clear advantage on survival. Thus, resistance to PD-1 blockers constitutes a major obstacle towards the implementation of immunotherapy in HR+ BC patients.

Methods To obtain insights into the immunological alterations accompanying disease relapse in HR+ BC exposed to PD-1 blockade, we harnessed a unique endogenous model of BC driven in immunocompetent mice by progesterone and a carcinogen. This model recapitulates key aspects of human luminal B BC, including a relatively ‘cold’ microenvironment, hence limited sensitivity to PD-1 blockage. To overcome PD-1 resistance we treated mice with Flt3-L to stimulate the maturation of cross-presenting dendritic cells, and radiation therapy that can act as an adjuvant to inflame tumor microenvironment. In parallel, we tried to achieve complete control of the primary tumor by identifying ablative doses of fractionated radiation therapy (RT).

Results Immunotherapy (PD-1 + Flt3L), despite slowing down the tumor growth, failed to improve the overall survival (OS) of mice elicited by RT alone in a unique mouse model of HR+ BC, potentially linked to an accrued systemic immunosuppression (T cells exhaustion, and increase of Tregs). The addition of CTLA-4, even though providing an initial response, failed to improve the tumor growth and OS, due to immunoresistance (immature macrophages, and decrease in T cells and NK cells at the systemic level). Partially ablative RT doses were able to improve the OS and will be combined with PD-1 + Flt3L in the near future.

Conclusions Breaking through resistance of HR+ tumors to PD-1 blockers can direct strategies to overcome resistance in HR+ BC patients, the majority of BC patients. If successful, this can inform therapeutic approaches to enable superior therapeutic responses in patients with HR+ BC, hence significantly reducing BC-related deaths.

REFERENCES

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