PROGESTERONE IMPACTS THE GROWTH AND IMMUNE CELL INFILTRATION OF MURINE MAMMARY GLAND TUMORS

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Background Clinical studies have linked usage of progestins (synthetic progesterone) to breast cancer risk. However, little is understood regarding the role of native progesterone (P4), signaling through the progesterone receptor (PR), in breast tumor formation. Recently, we demonstrated that P4 treatment or PR overexpression can drive changes in immune cell populations in the murine mammary gland and that PR overexpression leads to increased development of mammary gland tumors in mice. Given these findings, we sought to investigate whether P4 impacts tumor growth and immune cell infiltration of mammary gland tumors.

Methods To evaluate the effect of P4 on PR+ mammary gland tumor growth, orthotopic syngeneic mammary gland tumors were utilized. Briefly, mice were implanted with P4 (30mg) or placebo pellets and were injected with mammary gland tumor cells. After 28 days, tumors were excised and immunophenotyping was performed via flow cytometry. To determine the effect of anti-progestin treatment on mammary gland tumor growth and immune cell infiltration, two syngeneic mammary gland tumor models were used, in which mice were implanted with onapristone (30mg) or placebo pellets followed by mammary gland tumors. After 28 days, tumors were excised and immunophenotyping was performed via flow cytometry. The experiment was repeated in SCID mice to determine if effects of onapristone were immunologically mediated.

Results In syngeneic mammary gland tumor models, P4 promoted tumor growth and impacted immune cell infiltration of PR+ mammary gland tumors. Numbers of tumor-infiltrating dendritic cells were decreased and exhausted T cells and regulatory T cells were increased with P4 treatment in PR+ tumors. Onapristone treatment led to significantly decreased tumor volumes in two syngeneic mammary gland tumor models and reversed the effect that P4 had on tumor-infiltrating regulatory T cells. To determine if inhibition of tumor growth by onapristone was immunologically mediated, SCID mice bearing PR+ mammary gland tumors were treated with onapristone. Results revealed a decreased ability of onapristone to inhibit tumor growth in SCID mice compared to immunocompetent mice, suggesting that inhibition of tumor growth is, in part, immunologically mediated.

Conclusions These findings offer a novel mechanism of P4-driven mammary gland tumor development and provide rationale in investigating the usage of anti-progestin therapies to promote immune-mediated elimination of mammary gland tumors.