IMMUNOLOGICAL MECHANISMS OF RESISTANCE TO CDK4/CDK6 INHIBITORS IN BREAST CANCER

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Background Hormone receptor+ (HR+) breast cancer (BC) is the most frequent cause of BC-related deaths. CDK4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) emerged as an effective approach for metastatic HR+ BC. However, >60% women with HR+ BC receiving CDK4/6i + ET ultimately relapse, potentially due to activation of poorly characterized immunosuppressive pathways in the tumor microenvironment (TME). Thus, strategies breaking resistance to CDK4/6i+ET in women with HR+ BC are urgently awaited. Radiation therapy (RT) mediates immunostimulatory effects that only partially overlap with those of CDK4/6i+ET, standing out as a promising therapeutic partner. Consistent with this notion, we recently demonstrated that RT followed by the CDK4/6i palbociclib + ET (RT-P+ET) enables superior tumor control in various immunocompetent mouse models of HR+ BC. These findings have inspired the design of a randomized phase II clinical trial testing P+ET vs. RT-P+ET in patients with oligometastatic HR+ BC (CIMER, NCT04563507). In this context, we set out to dissect the immunological mechanisms underlying sensitivity vs. resistance to treatment in HR+ BC exposed to P+ET vs. RT-P+ET.

Methods To dissect the impact of these treatments on immune contexture in HR+ BC, we performed single-cell RNAseq on CD45+ cells infiltrating MPA/DMBA (M/D)-driven carcinomas established in immunocompetent mice (a unique model of luminal B BC), coupled to bulk RNAseq, bioinformatic analysis on public patient datasets, functional studies on ex vivo immune cells and efficacy studies.

Results We observed that (1) RT and P+ET alone mediate partial efficacy correlating with accumulation of immunosuppressive TREG and IL17A-producing γδ T cells, respectively, (2) γδ T cell depletion improves the efficacy of P+ET, (3) RT-P+ET mediates superior (but incomplete) tumor control, which is partially offset by CD4+/CD8+ T cell co-depletion and correlates with limited infiltration by γδ T cells and TREGS, but accumulation of PD-L1 expressing myeloid cells and M2-polarized TREM2+ macrophages, which have been ascribed robust immunosuppressive effects in multiple settings; and (4) that PD-1 blockage does not ameliorate the therapeutic effects of RT-P+ET (not shown), pointing to TREM2+ macrophages as to the main culprits for resistance in this setting.

Conclusions Our observations suggest that γδ T cells and TREM2+ macrophages support the resistance of HR+ BC to CDK4/6i and RT-CDK4/6i, and hence constitute potential targets to delay disease progression.

REFERENCES

Ethics Approval Animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of Weill Cornell Medical College (n° 2019–2022).

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