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).¹ 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,² 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.³ 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 $\gamma\delta$ T cells, respectively, (2) $\gamma\delta$ 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 $\gamma\delta$ 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 settings⁴; 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 $\gamma\delta$ 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.

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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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