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FGFR1 PROMOTES ER+ BREAST CANCER BRAIN METASTASIS AND MODULATES INTERACTIONS WITH NEURONS

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While triple-negative and HER2+ breast cancer (BC) have higher rates of brain metastasis (BM), BM affect 16% of metastatic ER+ BC patients, and often occur in older or post-menopausal women. Preclinical models of ER+ BCBM require exogenous estrogen (E2) supplementation and are often performed in young mice. Hence, lack of clinically relevant models mimicking the progression of BM in the E2-deprived or aged microenvironment has hindered a better understanding of the mechanisms underlying ER+ BM. FGFR1-amplification is the only genomic alteration shown to predict increased risk of late metastatic recurrence in anti-estrogen-treated ER+ BC, paracrine activation of FGFR1 has been shown to promote tumor progression of ER+ BC in postmenopausal mouse models, and canonical FGF2/FGFR1 signaling decreases in the brain with aging. Thus, we hypothesize that FGFR1 plays non-canonical functions in the brain TME that support ER+ BCBM in the aged/E2-depleted brain TME. To define the dependency on E2 and aging, UCD65 (ER+ PDX, FGFR1-amp-14x) cells were intracardially injected into young-OVX mice (<14weeks), young-OVX mice +E2, and aged-naïve mice (52+weeks), and metastases quantified via IVIS. In young mice, E2 promoted BM in 61% mice compared to 0% in OVX mice. By contrast, 38% of aged-naïve mice presented BM, suggesting increased promotion of BM in aged mice. BMs in aged-naïve mice did not result from low E2 levels, as independent studies showed similar incidence of BM in aged-naïve vs aged-OVX mice. FGFR1 knockdown in UCD12 (ER+ PDX, FGFR1-amp-12x) and UCD65 did not alter proliferation alone in vitro, but reduced growth in organotypic coculture and decreased BM colonization and outgrowth in vivo in aged mice. Mechanistically, FGFR1 KD decreased density of synapses (punctate colocalization PSD95 and Synapsin) in UCD65 spheres plated with organotypic brain slices. Ongoing studies are defining the role of neuronal activity to promote FGFR1-dependent colonization of ER+ BCBM.