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High collagen density augments mTOR-dependent cancer stem cells in ER α + mammary carcinomas, and increases mTOR-independent lung metastases

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Abstract

Metastatic estrogen receptor alpha positive (ER α +) cancers account for most breast cancer mortality. Cancer stem cells (CSCs) and dense/stiff extracellular matrices are implicated in aggression and therapy resistance. We examined this interplay and response to mTOR inhibition using ER α + adenocarcinomas from NRL-PRL females in combination with *Col1a1*^{tmJae/+} (mCol1a1) mice, which accumulate collagen-I around growing tumors. Orthotopic transplantation of tumor cells to mCol1a1 but not wildtype hosts resulted in striking desmoplasia. Mammary tumors in mCol1a1 recipients displayed higher CSC activity and enhanced AKT-mTOR and YAP activation, and these animals developed more and larger lung metastases. Treatment with the mTOR inhibitor, rapamycin, with or without the anti-estrogen, ICI182780, rapidly diminished mammary tumors, which rapidly reversed when treatment ceased. In contrast, lung metastases, which exhibited lower proliferation and pS6RP, indicating lower mTOR activity, were unresponsive, and mCol1a1 hosts continued to sustain greater metastatic burdens. These findings shed light on the influence of desmoplastic tumor microenvironments on the CSC niche and metastatic behavior in ER α + breast cancer. The differential mTOR dependence of local mammary tumors and pulmonary lesions has implications for success of mTOR inhibitors in advanced ER α + disease.

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