Estradiol represses IRF3-7 signaling pathways in ER+ astrocytes to suppress immune surveillance during early brain metastatic colonization

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ABSTRACT

While estrogen (E2) is the main permissive ovarian hormone, in breast cancer, we have shown that non-ovarian estrogen biosynthesis (ER) promotes brain metastases of ER-negative breast cancer (M1), in part through effects on the tumor microenvironment (TME) that promote microglial activation. E2 promotes brain metastasis in part by repressing immune surveillance by microglia through the transcription factor IRF3 (IRF3). Here we show that E2 suppresses IRF3, and that this repression is mediated by the transcription factor TGFβ, which in turn suppresses IRF3 expression. Therefore, E2 and TGFβ repress IRF3 and promote M1 microglial activation. Our data suggest that E2 promotes brain metastasis by repressing immune surveillance by microglia and that these processes are mediated by TGFβ, which acts in the tumor microenvironment to suppress IRF3 expression.

RESULTS

A. Astrocytes become reactive and express ER and estrogen since early stages of metastatic colonization

- Spontaneous metastases model: early dissemination
- Reactive gliosis + Freely disseminated tumor cells
- Primary tumor size

B. Aromatase inhibitors block E2 synthesis in vitro

- Activity of aromatase (the enzyme that synthesizes estrogens) in astrocytes is increased in the presence of estradiol (E2)

C. Aromatase inhibitors upregulate IRF7 signaling in astrocytes in vitro

- Mouse astrocytes treated with letrozole (ARO) show increased expression of IRF7 compared to untreated astrocytes

D. Conclusions

- E2 represses early microglial/CNS macrophage activation in the brain TME
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