**Background** Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer characterized by a lack of specific targets and a 35% incidence of brain metastasis. There is no targeted treatment for managing brain metastasis associated with TNBC; therefore, new strategies are urgently needed to overcome disease mortality. The CD47/SIRPα signaling pathway is implicated in tumor progression due to bypassing innate and adaptive immune surveillance. Most strategies targeting this pathway focus on targeting the receptor CD47; however, targeting SIRPα as a potential strategy to mitigate metastatic tumor burden remains understudied.

**Methods** Breast cancer patient biopsies were stained with antibodies against SIRPα. A Real-Time Cell Analysis (RTCA) impedance assay was used to determine migration, proliferation, and microglia-mediated cancer cell clearance changes. Female BALB/C mice were used in a TNBC brain metastasis model by intracardiac injection of the 4T1-Br3-Luc cell line. Brain metastatic burden was measured by the in vivo imaging system (IVIS) and quantified by luciferase luminescence. Differences in protein expression were measured by proteomic digital spatial profiling (DSP) of brain lesions and immune infiltrated regions of interest (ROIs).

**Results** Immunohistochemical staining of patient biopsies revealed a 3.5-fold increase in SIRPα expression in metastatic lesions compared to the primary tumor (n=19; p ≤ 0.0001). Additionally, there was an 84% increase in SIRPα in brain-trophic 4T1-Br3 TNBC cells compared to 4T1 parental cells (n=3; p ≤ 0.05). RTCA impedance assay revealed that SIRPα blockade inhibits brain-trophic 4T1-br3 cell migration (24h; n=3; p ≤ 0.05) and proliferation (48h; n=3; p ≤ 0.05) and promotes microglia-mediated cancer cell clearance (n=3; p ≤ 0.05). Furthermore, SIRPα blockade reduced metastatic brain lesion formation in vivo by approximately 90%, determined by IVIS imaging (n=4-7; p ≤ 0.05). DSP of the brain lesions revealed that immune checkpoints cluster of differentiation 152 (CTLA4), programmed cell death protein 1 (PD-1), programmed death ligand-1 (PD-L1), and cluster of Differentiation 276 (CD276 or B7-H3) were significantly reduced in anti-SIRPα treated brain lesions (n=3-6; p ≤ 0.05). Furthermore, spatial profiling revealed that SIRPα blockade promotes pro-inflammatory microglia polarization in brain lesions (n=3-6; p ≤ 0.01). Additionally, the extracellular matrix protein fibronectin, which contributes to invasion, metastasis, and immune evasion, was reduced by 70% in anti-SIRPα-treated brain lesions (n=3-6; p ≤ 0.05).

**Conclusions** These data suggest that SIRPα blockade modulates immune and TNBC cells to limit metastatic spread. Therefore, targeting SIRPα may be a new immunotherapeutic strategy to treat TNBC brain metastasis.