

A Peripheral Innate Immune Cell Recruitment Blocker (Tx) Alters Immune Response In Brains Of Amyloid Depositing APP/PS1 Mice.

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INTRODUCTION

- A defining feature of Alzheimer's disease (AD) is the accumulation of β -amyloid aggregates in brain parenchyma. β -amyloid also aggregates around cerebral vasculature, indicative of Cerebral Amyloid Angiopathy (CAA), which is highly co-morbid with AD. The monoclonal antibody therapeutics Leqembi and Kisunla reduce amyloid deposition to slow progression of AD, but exacerbate vascular damage resulting in edema and microhemorrhage, which are observed as Amyloid-Related Imaging Abnormalities (ARIA).
- AD, CAA, and ARIA are all associated with a maladaptive inflammatory response. Parenchymal amyloid deposits are surrounded by CD11c+ innate immune cells. We have shown in APP/PS1 and 5XFAD mouse models that blocking their recruitment into the brain with systemic delivery of an anti-CD11c antibody reduces synaptic damage underlying AD.
- Here, we investigated in ARTE10 mice whether CD11c+ immune cells are recruited to vascular amyloid deposits and whether eliminating this recruitment impacts the microhemorrhage induced by an amyloid-lowering antibody treatment, 3D6, and which is associated with vascular amyloid deposits.

METHODS

- Female APP/PS1 ARTE10 mice were purchased from Taconic (#16347) and aged in-house. Mice aged 2yr 2mo were dosed with either a non-depleting anti-CD11c antibody (Tx; n=11) or isotype control antibody (n=10) on D1 of each week + 3D6 (anti-amyloid antibody) on D3 of each week. Mice were dosed weekly for 8 weeks. Brains were processed for immunofluorescence and Prussian Blue staining.

RESULTS

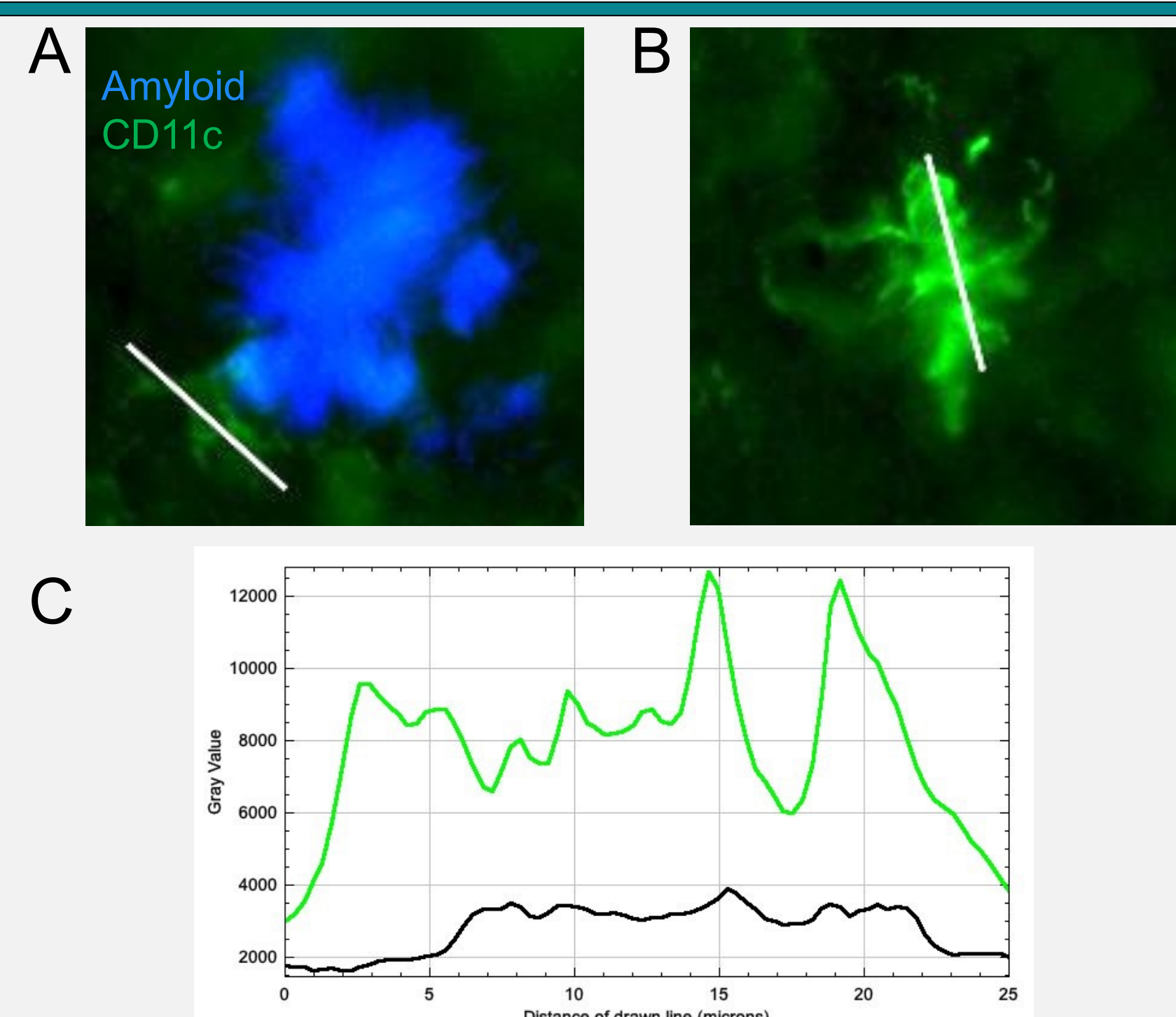


FIGURE 1: Intensity analysis of CD11c+ cells. (A) CD11c+ cell (green) next to an amyloid plaque (blue). (B) CD11c+ cell not associated with a plaque. (C) Line profile depicting the intensity (gray value) of pixels along the lines drawn in A (black line) and B (green line).

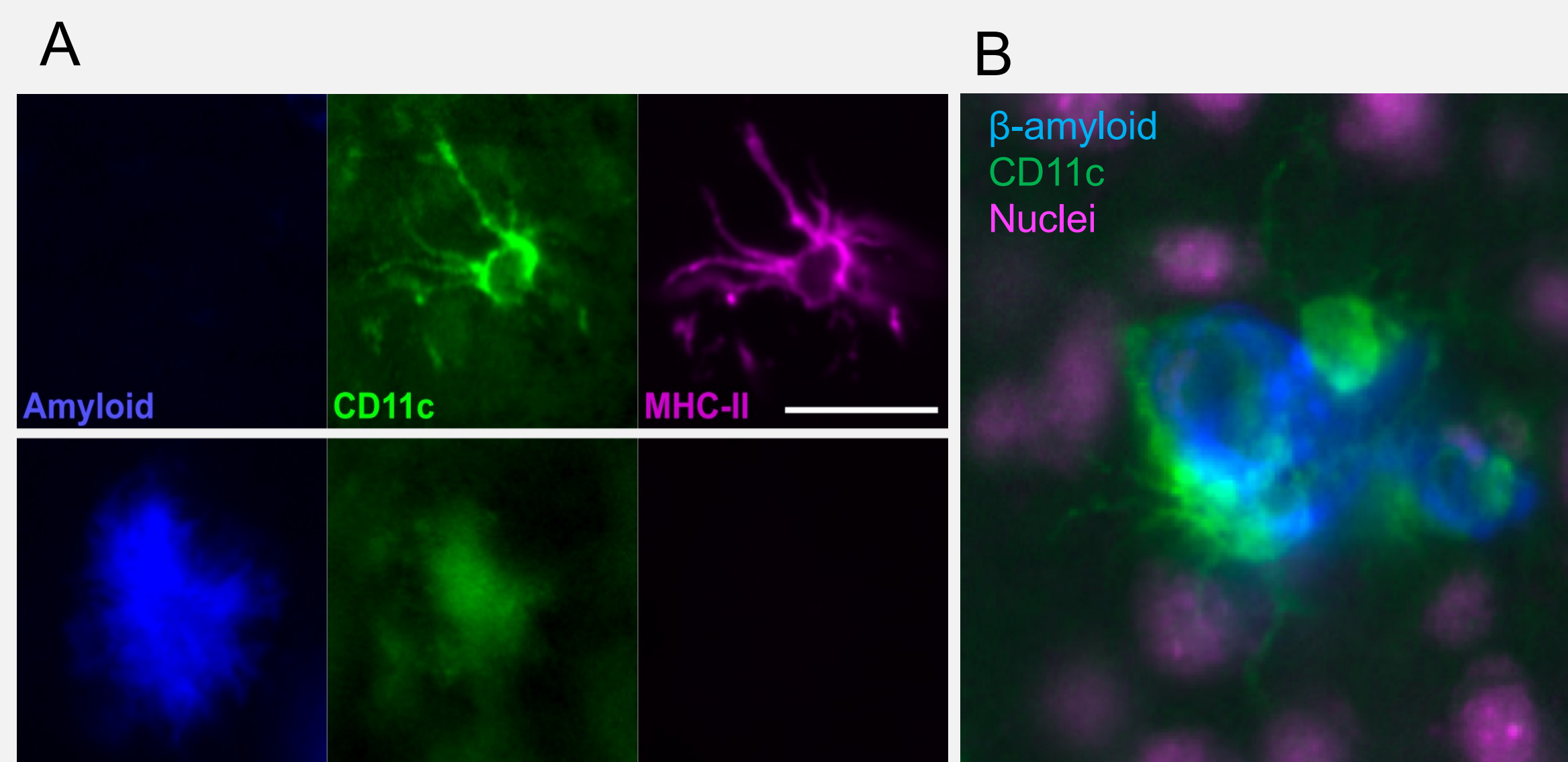


FIGURE 2: CD11c/MHCII cells tend to localize away from plaques and instead surround vascular amyloid. (A, top) CD11c MHCII cell not near a plaque. (A, bottom) Near a plaque, there is no CD11c or MHC-II signal. (B) CD11c+ cell in close association with a blood vessel containing amyloid.

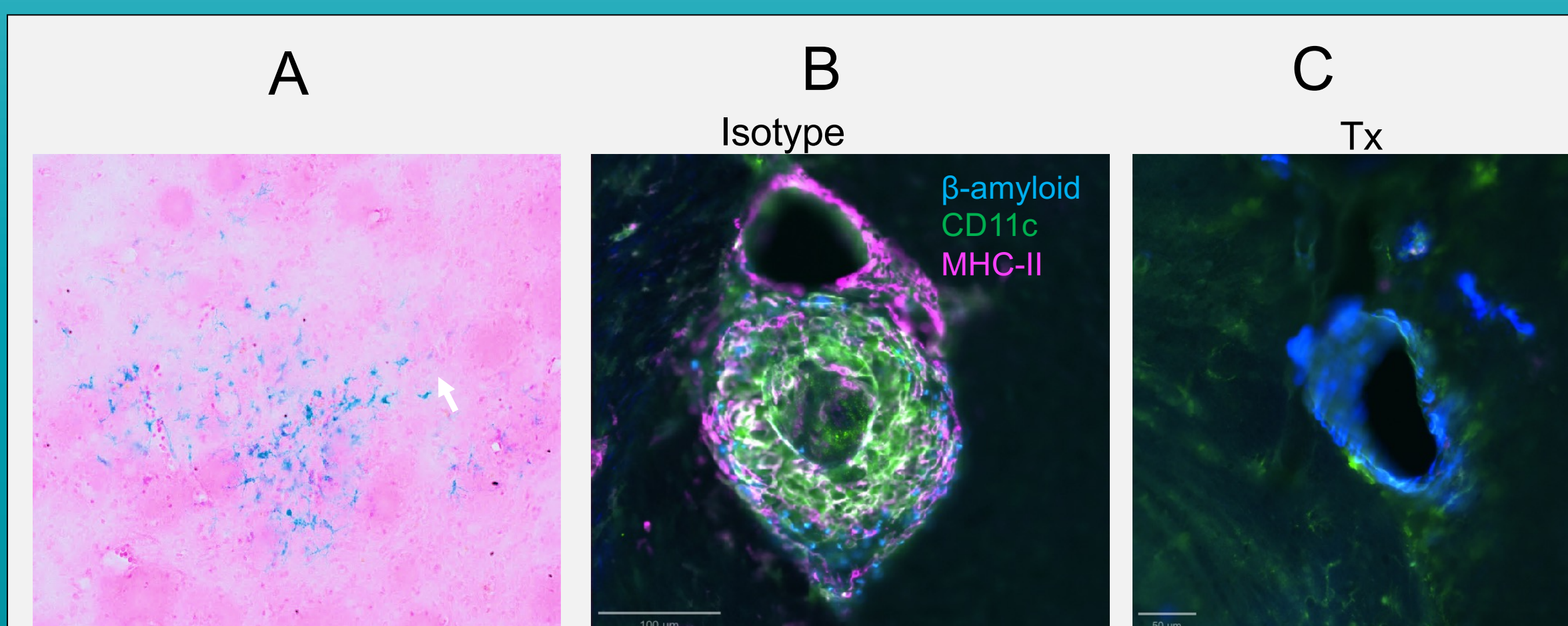


FIGURE 3: 3D6 treatment increases brain microbleed frequency and is accompanied by an inflammatory response around affected blood vessels in 2-year-old APP/PS1 mice. (A) Microbleed frequency is increased with 3D6 treatment revealed by Prussian Blue stain. (B) An inflammatory response is seen around vessels in isotype + 3D6 animals and is greatly reduced in (C) Tx + 3D6.

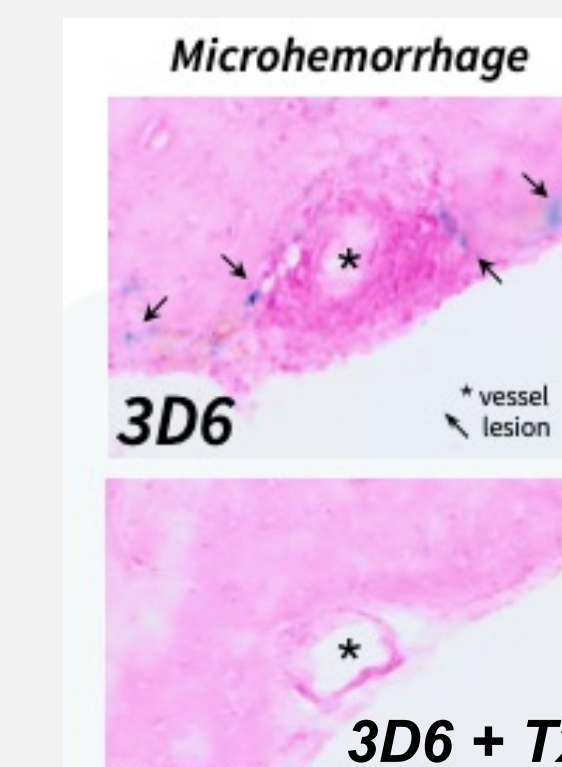


FIGURE 4: 3D6 treatment increased an inflammatory response around affected blood vessels in 2-year-old APP/PS1 mice is reduced by Tx. (A) Prussian Blue stain (arrows) reveals microbleeds in brain and an inflammatory response is seen around vessels in isotype + 3D6 animals and are greatly reduced in Tx + 3D6 treated mice

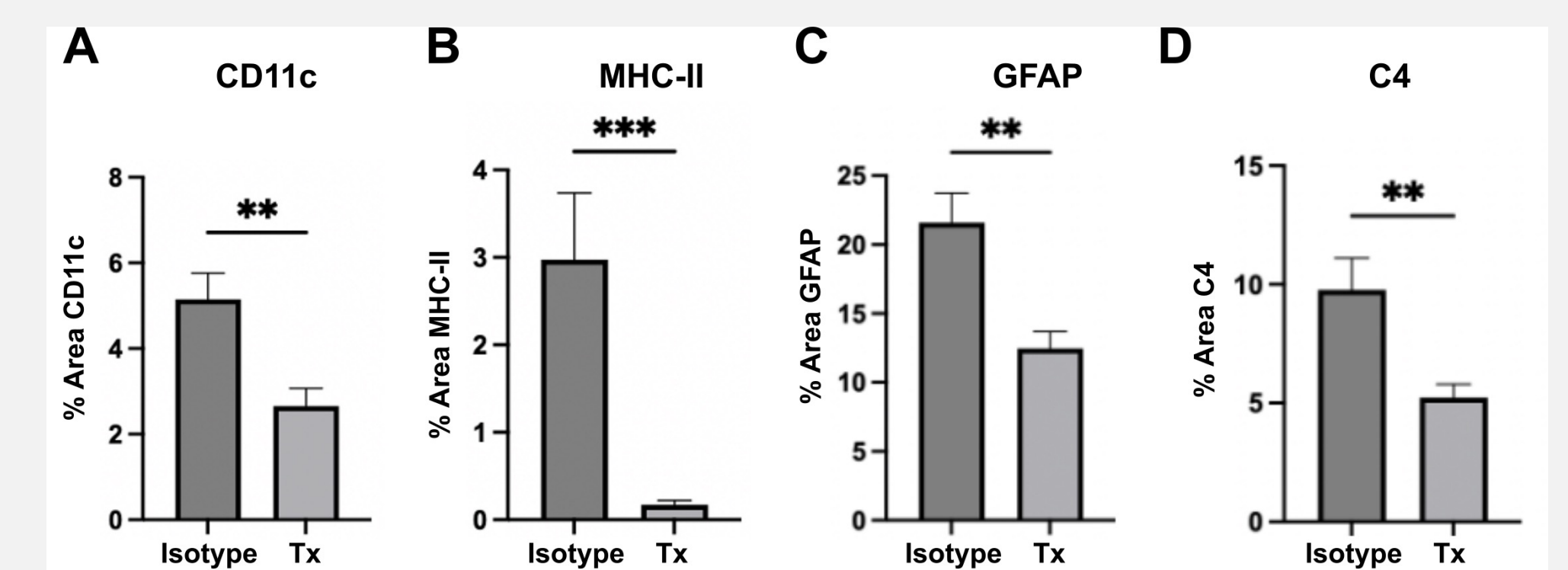


FIGURE 5: The inflammatory response around blood vessels is greatly reduced with Tx. Signature DAM markers CD11c (A) and MHC-II (B) are reduced in 3D6 + Tx compared to 3D6 + isotype. N=20. Astrogliosis (C) and complement response (D) are also significantly reduced. N=21.

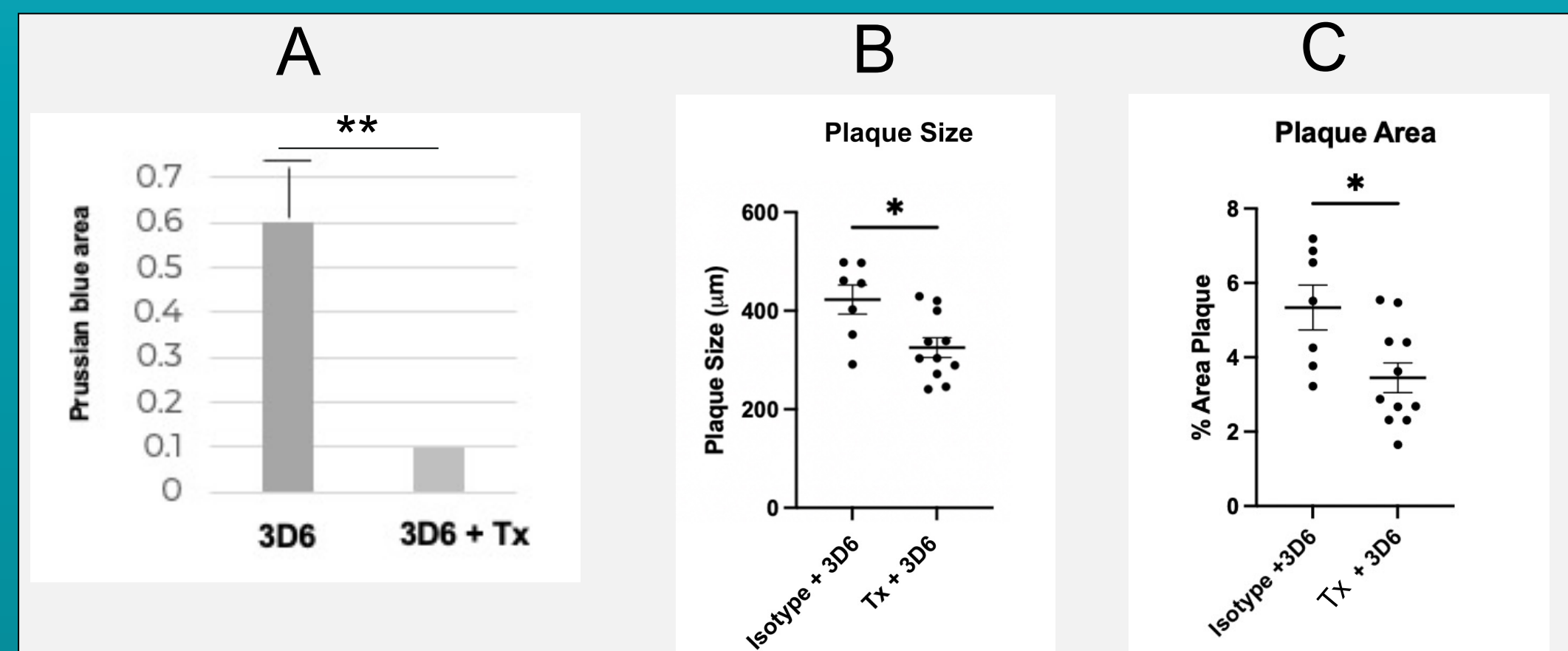


FIGURE 6: Microbleeds, plaque size and plaque area are reduced with co-treatment of Tx plus 3D6. (A) Prussian Blue area is reduced in brains of Tx + 3D6 mice compared to isotype + 3D6. N=20 (B) Plaque size and (C) area significantly decreases with Tx + 3D6 treatment, N=18

CONCLUSIONS

- In ARTE10 APP/PS1 mice, we observed amyloid deposits in the form of parenchymal plaques and surrounding cerebral blood vessels.
- Treatment of ARTE10 mice with the anti-amyloid antibody 3D6 increases the number of microbleeds, modeling ARIA.
- CD11c and MHCII immune cells were detected, which are not present in brains of WT mice, and these cells preferentially localize around amyloid deposits associated with blood vessels rather than parenchymal plaques.
- Systemic CD11c blockade (Tx) significantly reduced CD11c and MHCII immune cells. The effect of Tx is interpreted as a block of recruitment of these cells into brain, based on other data from our lab.
- Tx blocked the increase in microbleeds induced by 3D6 treatment. Astrogliosis and complement activation were also reduced, and plaque size and area were reduced. Tx alone had no effect on plaques (not shown).
- Our results suggest that CD11c+ cells, recruited from periphery into brain, drive inflammation caused by vascular amyloid deposits (CAA) and exacerbated by anti-amyloid therapy (ARIA). Blocking recruitment of these cells into brain ameliorates this deleterious inflammatory response and reduces microbleeds.*