

Amyloid β 40-Stimulated Endothelial Exosomes Induce Lysosomal Failure in Disease-Associated Microglia to Exacerbate CAA

#4044

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Endothelial exosomes link vascular A β 40 to disease-associated microglial lysosomal failure in CAA

INTRODUCTION

Endosomal-lysosomal dysfunction in disease-associated microglia (DAM) contributes to impaired A β 40 clearance and vascular pathology in cerebral amyloid angiopathy (CAA). Endothelial injury is an early event in CAA, but how it drives microglial dysfunction remains unclear. We investigated whether endothelial exosomes mediate endothelial-microglial communication during CAA progression.

METHODS

Primary brain microvascular endothelial cells (BMECs), primary microglia, and tg-SwDI mice were used. BMEC-derived exosomes (BMEC-Exo) were isolated following A β 40 stimulation and characterized. BMEC-Exo uptake by DAM was assessed in vivo and in vitro. Lysosomal integrity, acidification, and phagocytic function were evaluated using molecular, biochemical, and imaging approaches.

RESULTS

1. A β 40-stimulated BMEC-Exo were efficiently internalized by DAM in vivo. At early stages (8m) of CAA, these BMEC-Exo induced lysosomal dysfunction in DAM, accompanied by aggravated A β 40 accumulation.

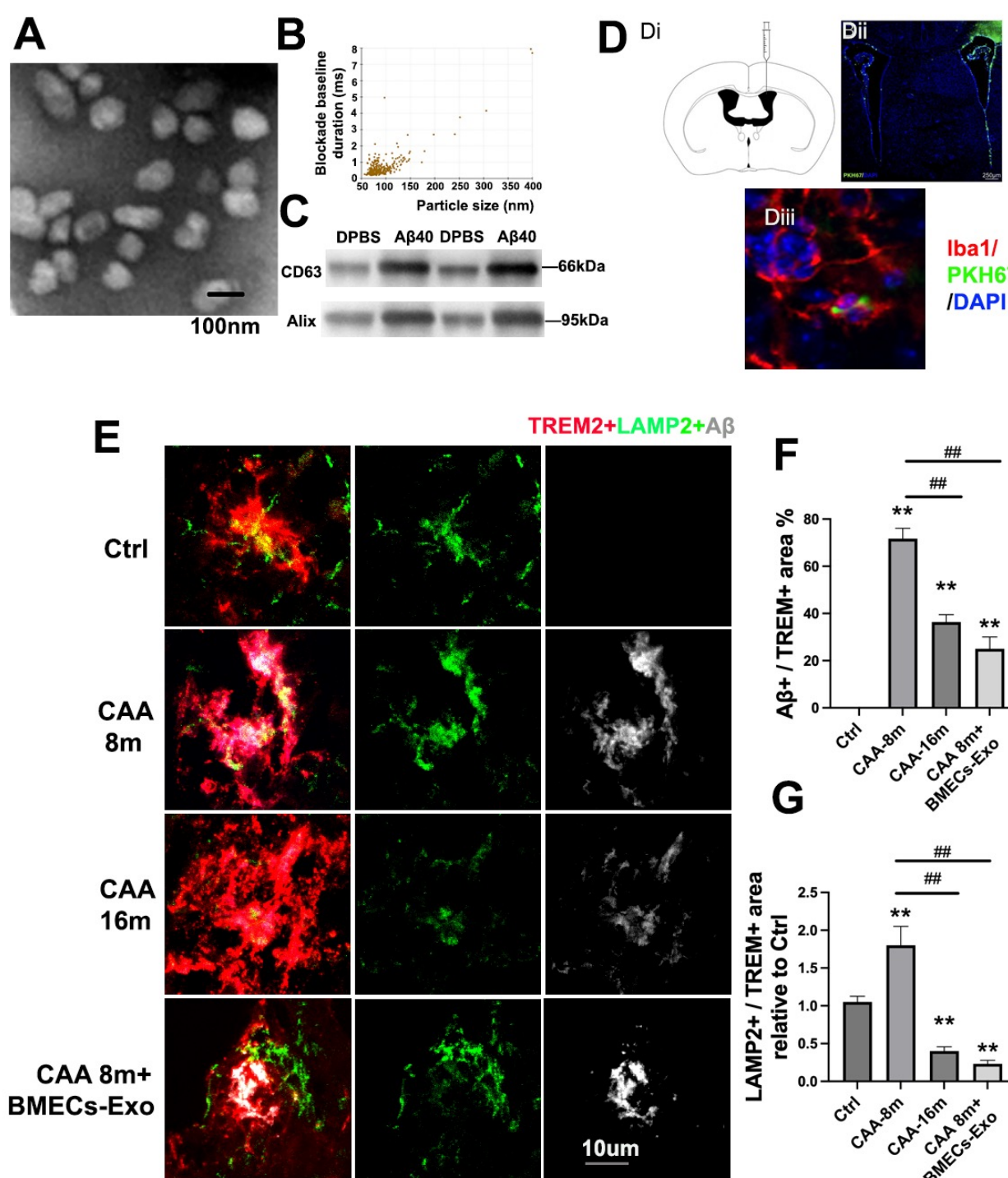


Figure 1: A β 40-stimulated BMEC-Exo induces lysosome dysfunction and A β deposition in DAM
(A–D) A β 40-treated BMECs released increased EVs (BMECs-Exo) that were efficiently taken up by microglia in vivo. PKH67: Exosome labeling (E–G) BMECs-Exo stereotactic injection induced lysosomal abnormalities and increased A β accumulation in DAM. TREM2, DAM marker; LAMP2, lysosomal marker. **p < 0.01 vs. Ctrl; ##p < 0.01 vs. CAA-8m.

2. BMEC-Exo increased lysosomal membrane permeability, disrupted lysosomal acidification, and impaired V-ATPase V1–V0 assembly. Together, these structural and functional lysosomal defects reduced the degradative function of DAM.

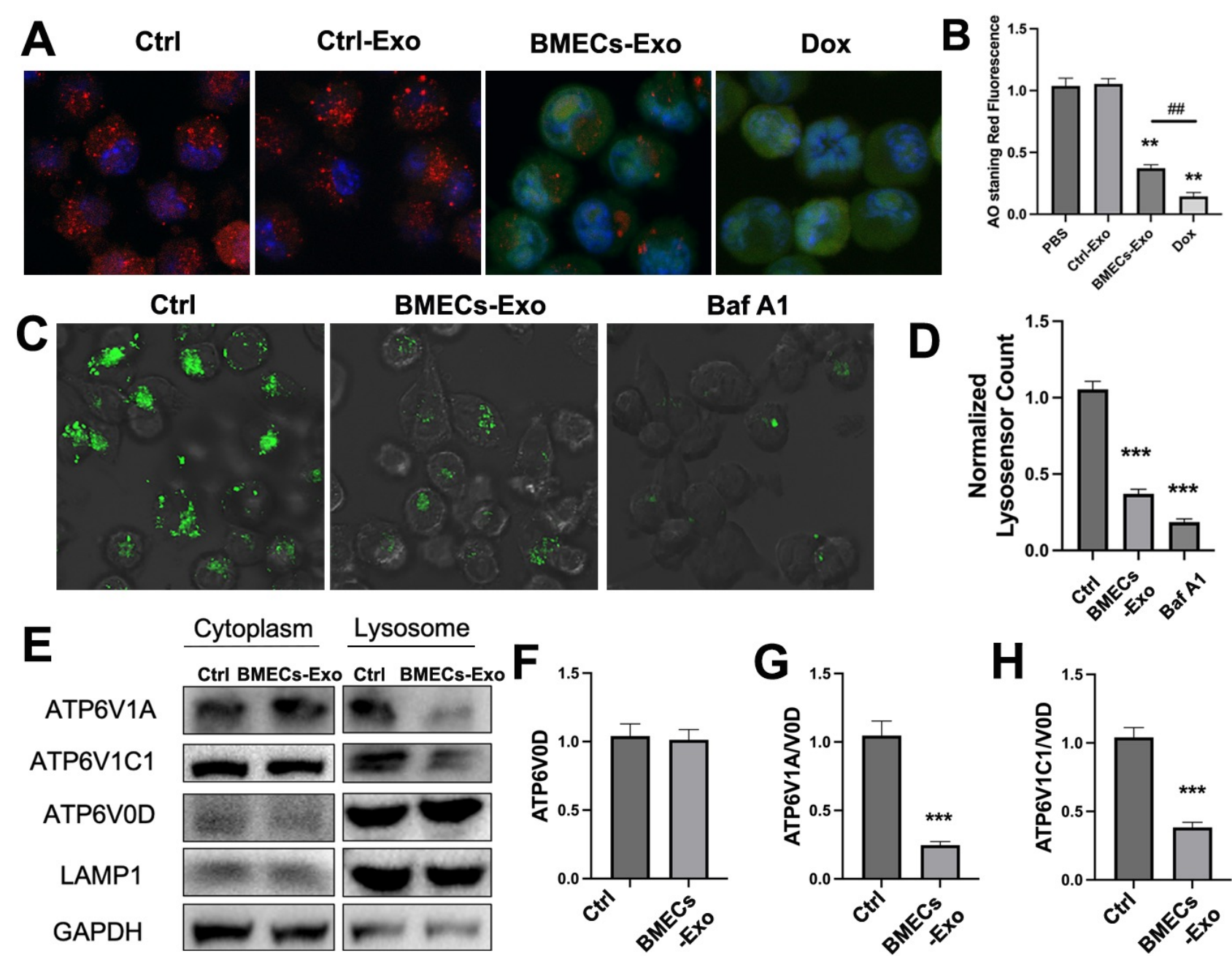


Figure 2: A β 40-stimulated BMEC-Exo induces lysosome dysfunction in DAM
(A, B) BMEC-Exo increased lysosomal membrane permeability in DAM. DOX (1 μ M, 24 h) was used as a positive control. (C, D) LysoSensor analysis showed impaired lysosomal acidification following treatment with BMEC-Exo. Baf A1 served as a positive control. (E, F) Western blot analysis of lysosomal fractions revealed reduced recruitment of V-ATPase V1 subunits to lysosomal membranes, suggesting defective V1–V0 assembly of V-ATPase. **P<0.05, ***P<0.01 vs Ctrl group.

CONCLUSION

A β 40-stimulated BMEC-Exo links early endothelial injury to lysosomal failure in DAM. This endothelial-microglial crosstalk promotes vascular pathology and CAA progression and may represent a potential therapeutic target.

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