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MFG-E8 Selectively Inhibited Aβ-Induced Microglial M1 Polarization via NF-κB and PI3K-Akt Pathways

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Activated microglia are classified into two specificstates: classically activated (M1) and alternatively activated(M2) subtypes. It is believed that the polarization of M1/M2phenotype plays an important role in Alzheimer's disease(AD). However, the mechanisms regulating this process remain unclear. Thus, we addressed this question focusing on milk fat globule epidermal growth factor 8 (MFG-E8). MFGE8is a unique protein which can bind to microglia and regulateits inflammatory responses. It is speculated that it mightplay a role in the balance of microglial polarization. In thecurrent study, we used fibril Aβ42 in vitro to stimulate mouseprimary microglial cultures and found subsequent M1 marker expression, along with retained M2 marker production. Then,we discovered that MFG-E8 pretreatment reversed the increased trend of M1 markers and the decreased expression of M2 markers, which were induced by Aβ42. Moreover, MFG-E8 effects could be effectively blocked by an MFGE8 antibody. Further analysis on the signaling pathways showed that NF-κB upregulation and Akt down regulation inmicroglial cultures were observed after Aβ42 incubation. And the alteration of these pathways could also be reversed by MFG-E8. We then assessed the effects of NF-κB and PI3KAkton M1/M2 alteration using their specific inhibitors. Pyrrolidine dithiocarbamate, a NF-κB inhibitor, inhibited M1 marker expression; moreover, LY294002, an Akt inhibitor,enhanced M1 marker expression. Our study indicated the regulatory role of MFG-E8 on microglia M1/M2 alteration forthe first time, providing a basis for understanding the potential role of microglia activation in AD