

Mesenchymal Stem Cells Regulate Microglial Polarization via Inhibition of the HMGB1/TLR4 Signaling Pathway in Diabetic Retinopathy

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Abstract

Diabetic retinopathy (DR) is recognized as the most prevalent retinal degenerative disorder. Inflammatory response particularly precedes microvascular alteration, considered the primary factor of diabetic retinopathy. Activated microglia express many pro-inflammatory cytokines exacerbates retina inflammation and disruption. In the present study, we investigated that MSCs alleviated blood–retina barrier (BRB) breakdown in diabetic rats, as evidenced by reduced retinal edema, decreased vascular leakage, and increased occludin expression. The MSCs-treated retinal microglia in the diabetic rats exhibited reduced expression of M1-phenotype markers, including inducible nitric oxide synthase (iNOS), CD16, and pro-inflammatory cytokines. Meanwhile, MSCs increased the expression of M2-phenotype markers, such as arginase-1 (Arg-1), CD206, and anti-inflammatory cytokines. HMGB1/TLR4 signaling pathway is activated in DR and inhibited after MSCs treatment. Consistent with in vivo evidence, MSCs drove BV2 microglia toward M2 phenotype in vitro. Knocking down HMGB1 or TLR4 in microglia had comparable effects as with MSCs treatment, suggesting HMGB1/TLR4 pathway is necessary for MSCs' regulatory effects on microglia polarization. Collectively, MSCs exert a beneficial effect on DR by polarizing microglia from M1 toward M2 phenotype via inhibiting the HMGB1/TLR4 signaling pathway.

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Figure 1

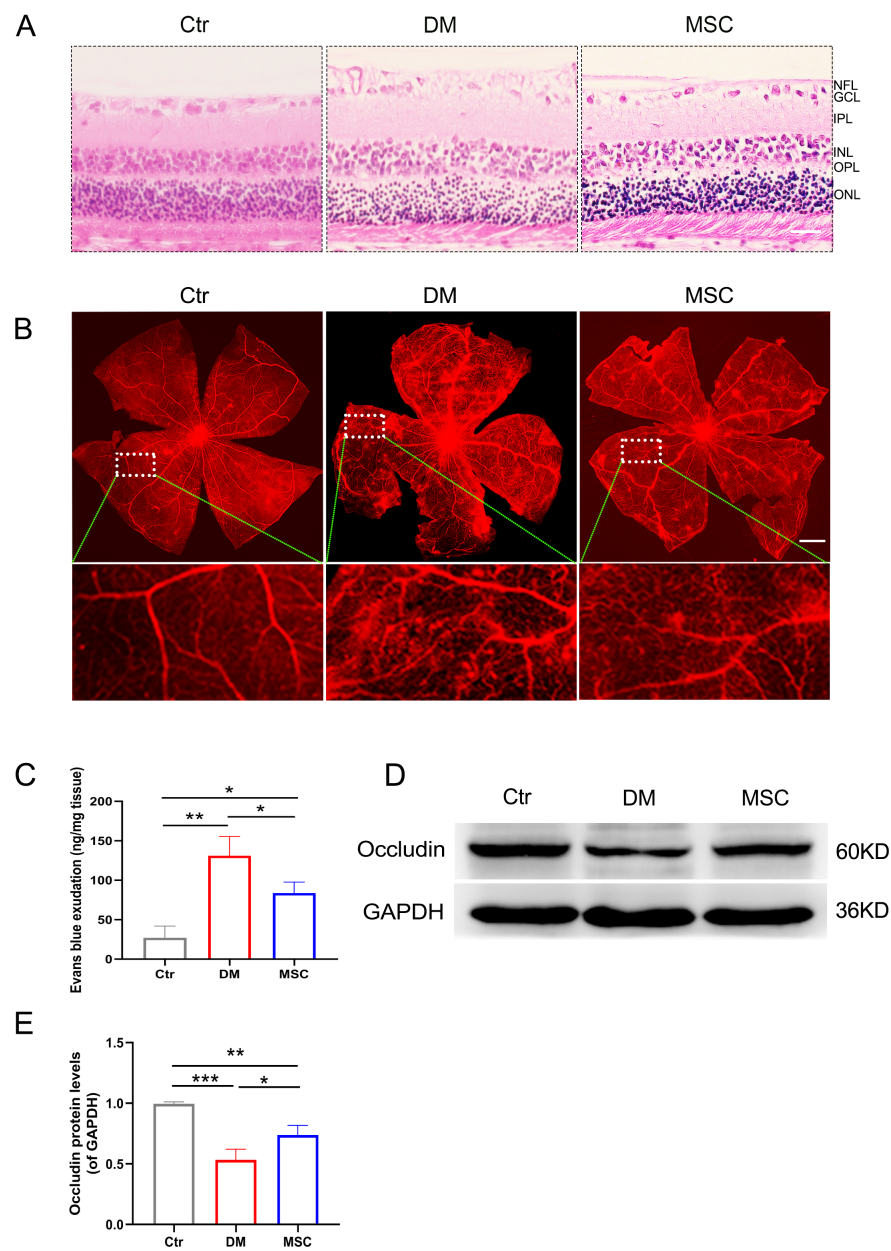


Figure 2

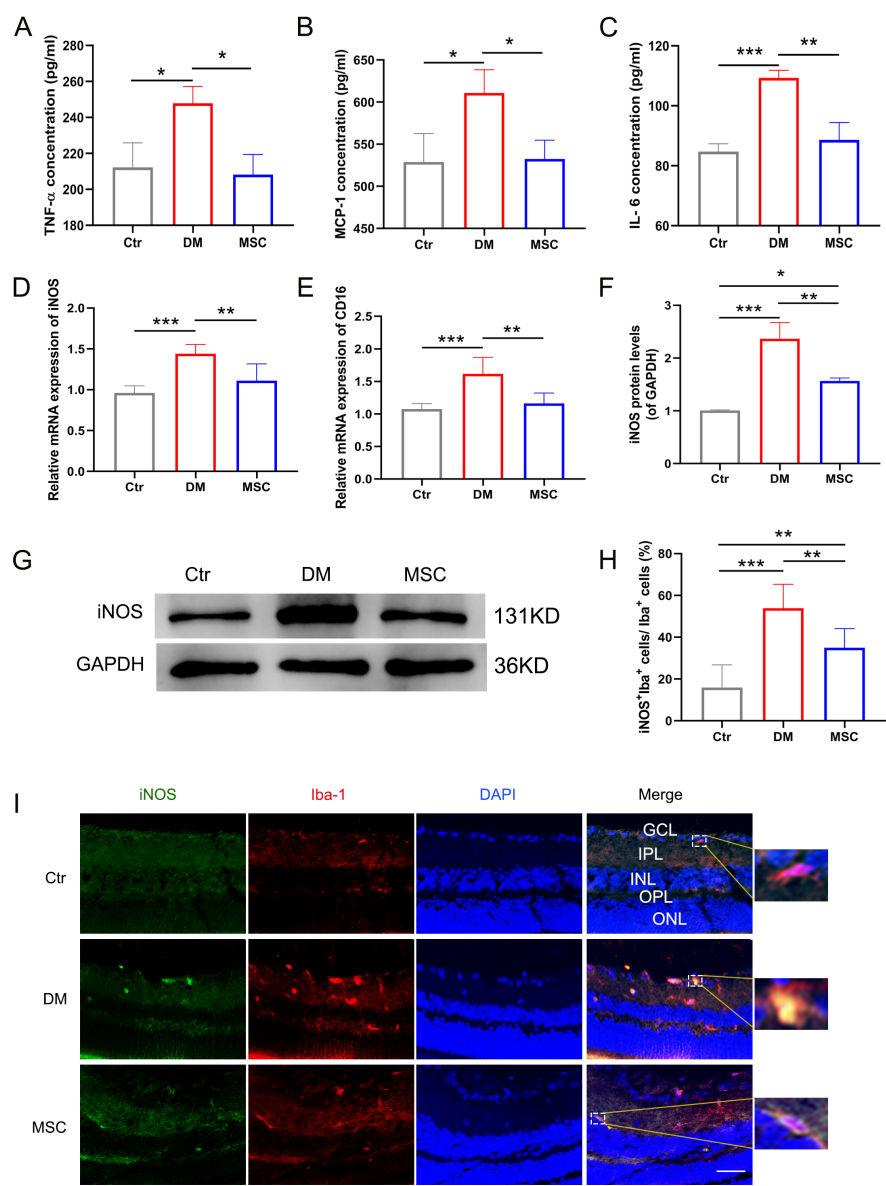


Figure 3

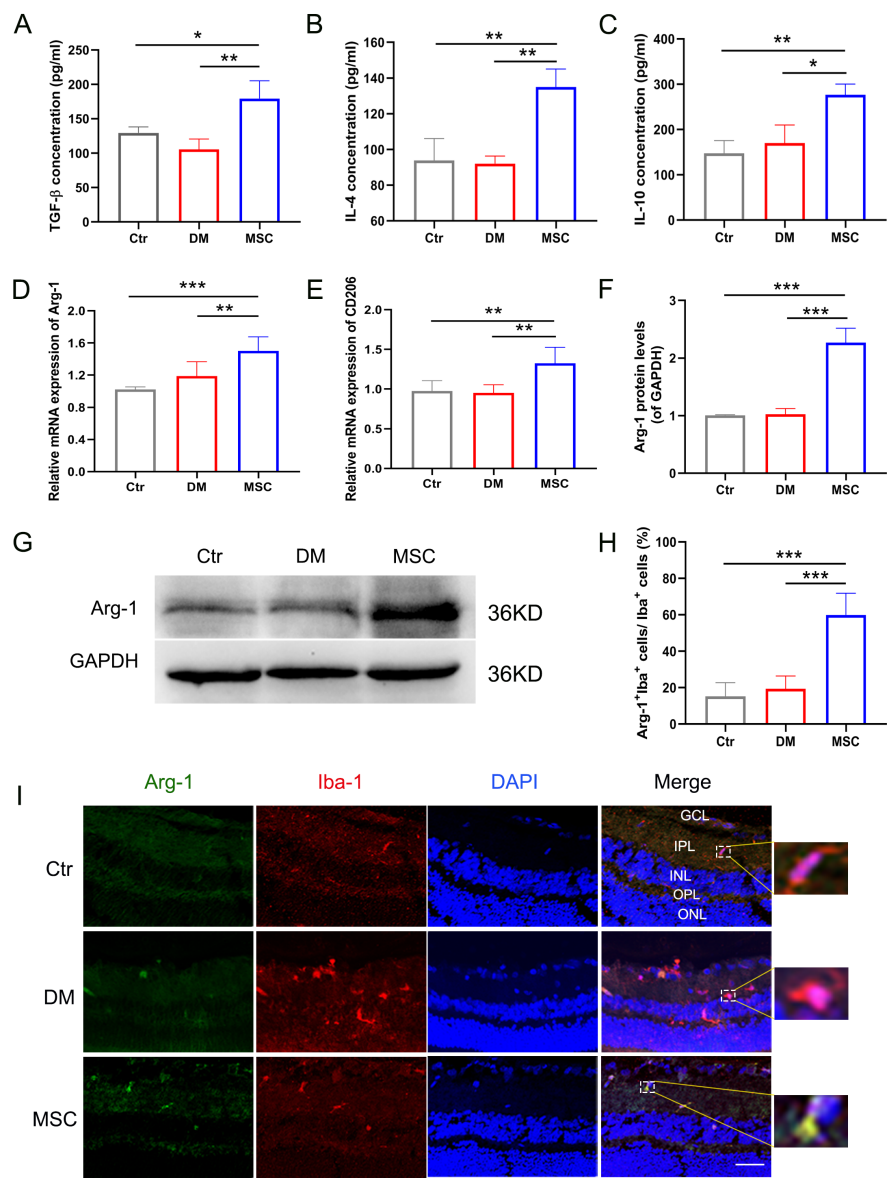


Figure 4

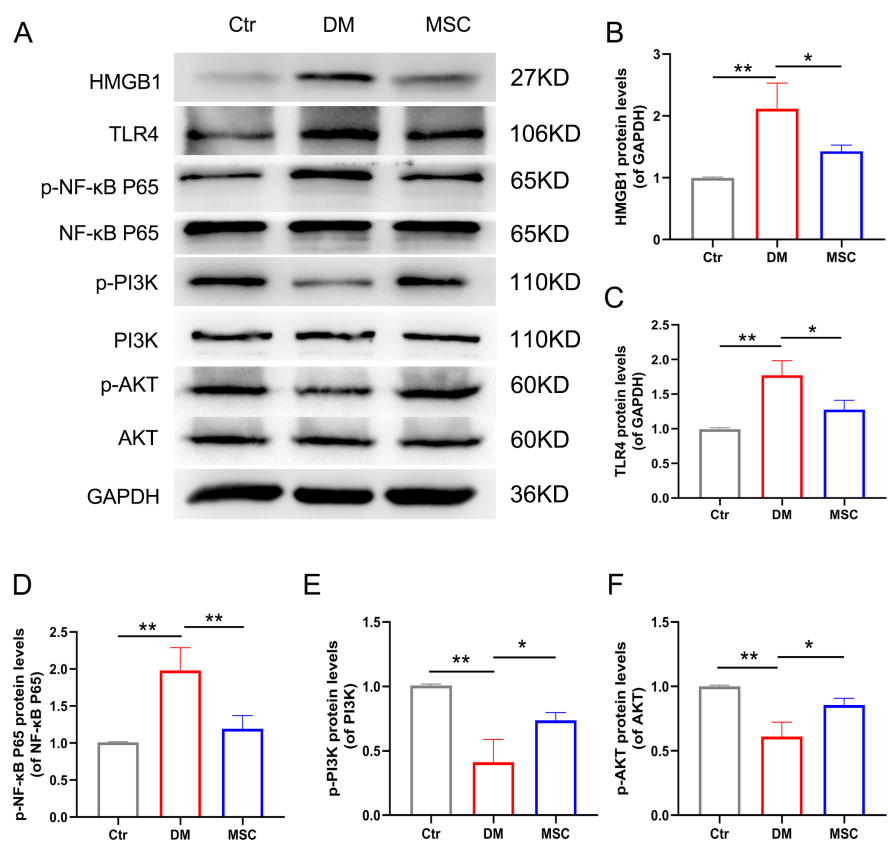


Figure 5

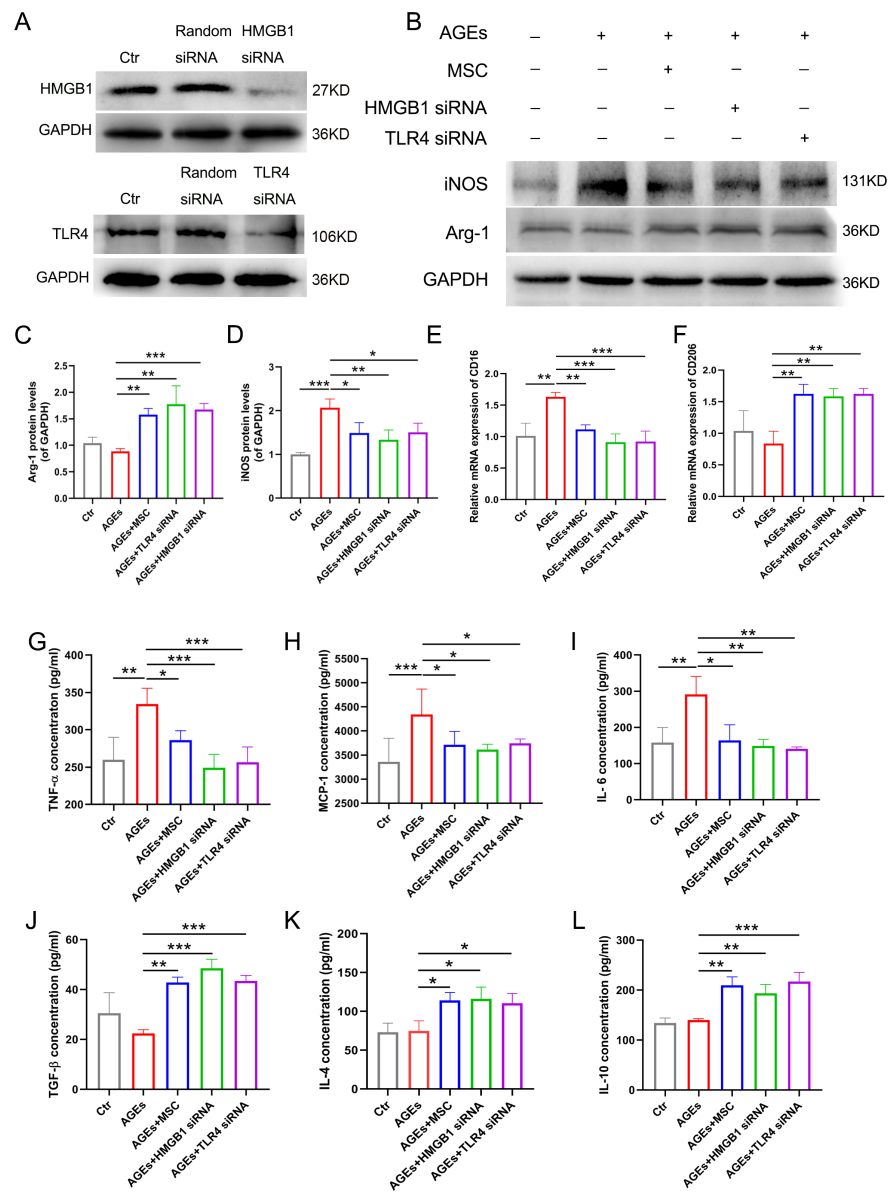


Figure 6

