2-YIA-45 YIA

Caveolin-1 regulates P2X7-mediated ATP signaling in pro-inflammatory macrophages.

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[Background] Macrophage (Mϕ) plays crucial roles in innate immunity and its dysfunction is involved in the pathogenesis of chronic inflammatory diseases such as arteriosclerosis and diabetes. Cytokine secretion and phagocytosis are main functions of Mϕ and modulated by the activity of ion channel, ionotropic purinergic P2X7 receptor.

Caveolin-1 (Cav-1) enables effective intracellular Ca^{2+} signaling by accumulating Ca^{2+} channels and their associated proteins within caveolae structure. In this study, the functional coupling between Cav-1 and P2X7 receptor was analyzed using Cav-1 knockout (Cav-1 KO) mice.

[Methods] In murine bone marrow-derived Mϕ (BMDM), expression of Cav-1 was analyzed by real-time PCR and Western Blotting. Localization of Cav-1 and P2X7 receptor was analyzed with total internal reflection fluorescence microscope (TIRFM). Ca^{2+} influx and K^+ efflux through P2X7 receptor were measured with Fluo-4 AM and APG-2, respectively. Furthermore, activation of P2X7 receptor was measured by nuclear dye (TOPRO-3) uptake.

[Results] The expression of Cav-1 was increased by LPS (lipopolysaccharide, 1 μg/mL)-induced inflammatory stimulation in BMDM. Thereafter, Cav-1 was co-localized with P2X7 receptor on the cell membrane. ATP (1 mM)-evoked TOPRO-3 uptake was increased in BMDM derived from Cav-1 KO mice compared to WT. Furthermore, Ca^{2+} influx and K^+ efflux following ATP stimulation were increased in Cav-1 KO compared to WT. These results suggest that the activity of P2X7 receptor is enhanced and thus Ca^{2+} influx and K^+ efflux are facilitated in BMDM derived from Cav-1 KO mice.

[Conclusion] Cav-1 negatively regulates the activation of P2X7 receptor and modulates immune responses in Mϕ. This study may contribute to the development of novel drugs for chronic inflammatory diseases.