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Chloride Ion Channels Play a Role in Mediating Immune Response during Pseudomonas aeruginosa Infection

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Abstract : Cystic fibrosis (CF) is a disease that affects respiratory function and in EU it affects about 1 in 2,500 live births with an average 40-year life expectancy. This disease caused by mutations within the gene encoding the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) chloride channel leading to dysregulation of epithelial fluid transport and chronic lung inflammation, suggesting functional alterations of immune cells. In airways, CFTR been found to form a functional complex with S100A10 and AnxA2 in a cAMP/PKA dependent manner. The multiprotein complex of AnxA2-S100A10 and CFTR is also regulated by calcineurin. The aim of this study was i) to investigate whether chloride ion (Cl−) channels are activated by Pseudomonas aeruginosa lipopolysaccharide (LPS from PA), ii) if this activation is regulated by cAMP/PKA/calcineurin pathway and iii) to investigate the role of LPS-activated Cl− channels in the release of pro-inflammatory cytokines by immune cells. Human peripheral blood monocytes were used in the study. Whole-cell patch records showed that LPS from PA can activate Cl− channels, including CFTR and outwardly-rectifying Cl− channel (ORCC). This activation appears to require an intact PKA/calcineurin signalling pathway. The Gout in the presence of LPS was significantly inhibited by diisothiocyanatostilbene-disulfonic acid (DIDS), an ORCC blocker ($p<0.001$). The Gout was further suppressed by CFTR(inh)-172, a specific inhibitor for CFTR channels ($p<0.001$). Monocytes pre-incubated with PKA inhibitor or calcineurin inhibitor before stimulated with LPS from PA that were resulted in DIDS and CFTR(inh)-172 insensitive currents. Activation of both ORCC and CFTR was however, observed in response to monocytes exposure to LPS. Additionally, ELISA showed that the CFTR and ORCC play a role in mediating the release of pro-inflammatory cytokines such as IL-1β upon exposure of monocytes to LPS. However, this secretion was significantly inhibited due to CFTR and ORCC inhibition. However, Cl− may play a role in IL-1β release independent of cAMP/PKA/calcineurin signalling due to the enhancement of IL-1β secretion even when cAMP/PKA/calcineurin pathway was inhibited. In conclusion, our data confirmed that LPS from PA activates Cl− channels in human peripheral blood monocytes. Our data also confirmed that Cl− channels were involved in IL-1β release in monocytes upon exposure to LPS. However, it has been found that PKA and calcineurin does not seem to influence the Cl− dependent cytokine release.

Keywords : cystic fibrosis, CFTR, Annexin A2, S100A10, PP2B, PKA, outwardly-rectifying Cl− channel, Pseudomonas aeruginosa
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