Staphylococcal enterotoxin B (SEB) is a potent activator of the Vβ8+T-cells leading to the proliferation of nearly 30% of the T-cell pool. As a consequence, excessive amounts of cytokine mediators are released leading to extensive tissue damage and sometimes toxic shock and death. Due to the ease with which SEB can be aerosolized and disseminated, it is considered a biological weapon. In the current study, we investigated the pro-inflammatory effects of SEB in two mouse models of acute inflammatory lung injury. Specifically, while inflammatory cues are known to elicit changes in key transcriptional factors and gene expression, we explored for the first time, the role of microRNA following SEB exposure. We found that C57BL/6 mice exposed to a single dose (50 μg/mouse) of SEB demonstrated symptoms of pulmonary inflammation characterized by cellular infiltration, histopathological damage and the release of copious amounts of IFN-γ. Upon conducting microRNA microarray analysis and applying cutting-edge bioinformatics analysis, we identified the overexpression of miR-155 and the subsequent repression of its target gene Soes1 following SEB exposure. Further, through the use of miR-155−/− mice, we demonstrated the critical role for SEB-induced miR-155 in mediating damage. In a more severe model of acute inflammatory lung injury, C3H/HeJ mice were exposed to two smaller quantities (2 μg and 5μg/ mouse) of SEB given two hours apart. As a result, mice succumb to vascular leak, excessive cellular infiltration and exaggerated cytokine and chemokine release. Pulmonary damage is associated with the dysregulation of several miRNA. Those miRNA that were overexpressed were found to target key regulators of inflammation and those
that were underexpressed allowed for the expression of pro-inflammatory genes demonstrating that several SEB-inducing miRNA act in concert to orchestrate inflammation. Therapeutic strategies to combat inhalation exposure to SEB are either lacking in their efficacy or with regards to acute inflammatory lung injury, limited to supportive care. As a result, we investigated the role of the marijuana cannabinoid- Delta-9-Tetrahydrocannabinol (THC), a known anti-inflammatory agent in the treatment of SEB-triggered inflammation. Interestingly, C3H/HeJ that succumbed to SEB toxicity, were completely protected by THC treatment. Upon investigation of the anti-inflammatory nature of THC, we demonstrated for the first time the ability of THC to modulate a prominent inflammatory miRNA cluster (miR-17-92) involved in activation of the PI3K/AKT signaling pathway. THC, by acting as an inhibitor of this pathway, via the downregulation of the cluster, induces T-regulatory cells, reduces cellular proliferation and decreases IFN-γ production. Taken together, our studies highlight the importance of miRNA in SEB-induced inflammatory damage. Moreover, we provide further insight into the anti-inflammatory properties of THC and emphasize its potential as a powerful therapeutic agent.