

The different perspectives of calcineurin inhibitor (FK-506) use during sepsis

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Objective: our aim was to investigate FK-506 (a calcineurin inhibitor classified as immunosuppressive) effects in the innate immunity and cardiovascular sepsis related dysfunctions as well in the immunosuppression after sepsis.

Methods: wild type C57/BL6 mice were treated with FK-506 and submitted to cecal ligation and puncture (CLP) sepsis model. Besides the survival curves, other sepsis parameters were obtained, such as cell migration, bacteremia, cytokines levels and injury biochemical markers, neutrophil expressing CXCR2 receptors percentage, mean arterial pressure and heart rate. Macrophages previously treated with FK-506 were stimulated with lipopolysaccharide (LPS) and the levels of chemokines were measured. Immunosuppression after sepsis assays are being performed.

Results: we used 3 different FK-506 (2mg/kg) treatments. First, we started the treatment 1 hour after CLP and these animals presented lower survival to CLP. To simulate the transplanted patients, we treated the animals 15 days before CLP and divided them in two groups. In the first one, we interrupted the FK-506 treatment, while in the second one, we continued. We observed that the interruption is sufficient to prevent the mortality increasing, indicating that FK-506 exerts an innate immunity acute effect. With the higher mortality associated with FK-506 treatment 1 hour after CLP, we also saw reduced neutrophils migration to the peritoneal cavity; increased bacteria number in the blood; more pronounced reduction of CXCR2 chemotactic receptor expression in circulating neutrophils; elevated inflammatory response; higher injury markers and bradycardia. The FK-506-treated macrophages LPS-stimulated presented higher CXCL-1 and CXCL-2 production.

Conclusion: the calcineurin activity in the innate immunity is important to neutrophil migration and infection control during sepsis. These data together with the understanding of the calcineurin role in the immunosuppression after sepsis, can help us to answer the question: is the immunosuppressive classification adequate to calcineurin inhibitors?