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Acute lung injury: Study of pathogenesis and therapeutic interventions

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Acute lung injury: Study of pathogenesis and therapeutic interventions

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Acute lung injury (ALI), denominated acute respiratory distress syndrome (ARDS) in its most severe form, is characterized by lung inflammation, hypoxia, non-cardiogenic pulmonary edema and decreased lung compliance. Despite numerous experimental and clinical studies, the mortality of ARDS remains between 30-70%, and its pathogenesis is still largely unknown.

The overall aim of the present thesis was to use experimental mouse models of ALI/ARDS to identify cells and mediators involved in the pathogenesis of the syndrome. Moreover, we have used these models to evaluate the therapeutic effects of the corticosteroid dexamethasone as well as the antioxidants N-acetylcysteine (NAC) and Vitamin E (α -tocopherol: α -toc).

In the first study, we investigated the inflammatory response in lung tissue and bronchoalveolar lavage (BAL) after inhalation of bacterial endotoxin (Lipopolysaccharide: LPS), a commonly used experimental animal model of ALI. Our results demonstrated that exposure to LPS induced a dose-dependent increase of neutrophils in BAL fluid (BALF) reaching a maximum after 12h at a low dose and after 24h at a high dose. Furthermore, a low dose induced an early (2h) and transient onset of cytokine and chemokine gene expression in lung tissue, while a high dose caused more delayed and sustained (6-12h) activation. In addition, expression of T-cell derived IFN- γ , IL-2, IL-17 and Rantes was only recorded when mice were exposed to a high dose, indicating a dose-dependent activation of T-cells after LPS inhalation.

In the second and third study, we investigated therapeutic interventions in the LPS inhalation model. Significant reduction of neutrophils in BALF was obtained through a single i.p injection of dexamethasone (10mg/kg), whereas treatment with NAC only resulted in reduction of neutrophils when administrated at a high dose (500mg/kg). Measurement of cytokine and chemokine expression in lung tissue revealed marked down-modulation with dexamethasone, while NAC demonstrated poor anti-inflammatory effect. In the third study, we demonstrated that Vitamin E protect against lung tissue damage and exerts anti-inflammatory properties as shown by the decreased number of neutrophils in airspaces when administrated at a dose of 50mg/kg body weight. This effect was due to a reduced transendothelial migration of neutrophils, but without a profound effect on the early pro-inflammatory response.

The fourth study was conducted to investigate if a generalized Shwartzman reaction (GSR) can display similar pathophysiology in mice as observed in clinical ARDS. Our results demonstrated that the generalized Shwartzman reaction induced rapid decline in lung function and 80% mortality. Furthermore, characteristic hallmarks of ARDS, such as lung tissue neutrophilia and edema formation, were observed. However, the lung neutrophilia was not closely associated with the mortality observed in the generalized Shwartzman reaction. Therapeutic effects of 50mg/kg Vitamin E and dexamethasone (10mg/kg) were also evaluated in this model, demonstrating that both drugs improved lung function and exerted anti-inflammatory properties measured as decreased levels of cytokines in serum.

In conclusion, the results in this thesis indicated that lymphocytes may be involved in the extensive inflammatory responses observed in ALI/ARDS. Furthermore, we have shown that neutrophils are not solely responsible for the rapid decline in lung function during the progress of experimental ARDS. Therapeutic interventions demonstrated that Vitamin E, alone or in combination with corticosteroids, might be effective for treatment of ALI and ARDS.

Key words: Acute lung injury, ALI, Acute Respiratory Distress Syndrome, ARDS, endotoxin, lipopolysaccharide, generalized Shwartzman reaction, dexamethasone, N-acetylcysteine