LUNG TARGETED DELIVERY OF EVEROLIMUS AS A NEW TREATMENT OF SCLERODERMA-RELATED INTERSTITIAL LUNG DISEASE (SSC-ILD) DEVELOPED BY PSGL-1 KO MICE

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Background: Intestinal lung disease (ILD), the main cause of mortality in scleroderma (SSc) patients (1), has no treatment (2). P-selectin glycoprotein ligand 1 (PSGL-1), the main ligand for P-Selectin, is expressed on leukocytes and responsible for the initial steps of extravasation (3). The absence of PSGL-1 in mice spontaneously develops an autoimmune syndrome similar to human SSc with fibrosis, vascular damage, autoantibodies and pulmonary arterial hypertension in females, and almost 60% of animals older than 12 months develop ILD with aging (4). In this work, the therapeutic action of everolimus-loaded nanomedicine given by local administration as a treatment for ILD was evaluated. The intratracheal administration of everolimus loaded into liposomes decorated with hyaluronic acid (HA) is studied as an administration strategy to reach the inflammatory area of the lung, targeting these cells and avoiding systemic effects and possible toxicity on epithelial cells

Objectives: 1) To study the effect of everolimus on bronchoalveolar lavage (BAL) cell populations and in lung pathology in SSC-ILD PSGL-1 KO mice
2) To analyze the intratracheal application of everolimus included in empty liposomes (Lip+Ev) vs. liposomes decorated with hyaluronic acid (Lip-HA+Ev) as an administration strategy to decrease drug toxicity and increase drug efficacy

Methods: In an observational study, PSGL-1-/- C57BL/6 males older than 12 months (n=4) were treated intratracheally with 4 doses of Lip or Lip-HA (with or without everolimus included), once a week (Lip+Ev 295.67µg/mL; Lip-HA+Ev 82.73µg/mL; Lip-HA+Ev 82.73µg/mL). The activity of these, were measured and evaluated for interstitial inflammation and fibrosis degree. Lip-HA was selected as the treatment of choice for a second experiment (n=8) following the same experimental design (68.22µg/mL)

Results: The observational study showed an increase in CD45+, alveolar macrophages (AM), eosinophils (Eos), granulocytes (Gr1+) and T cells in the BAL of untreated PSGL-1-/- compared with WT mice. Everolimus reduced these populations to WT levels in all cases.

Lip-HA+Ev administration was chosen for further experiments because a lower dose of the drug gave a better result than the high dose in undecorated liposomes. Reduction of CD45+, AM, eosinophils, and CD45+ cell populations by Lip-HA+Ev was confirmed. Lip-HA treatment increased the number of neutrophils and T cells, but this effect is controlled by the everolimus administration strategy to decrease drug toxicity and increase drug effectivity.

Histological lung analysis showed an increase in interstitial inflammation and fibrosis in untreated PSGL-1-/- and empty Lip-HA experimental groups. Treatment with everolimus included in Lip-HA reduced the fibrotic and inflammatory interstitial lung lesions, reaching values similar to those observed in WT mice.

Conclusion: PSGL-1 KO mice present ILD associated with scleroderma (SSC-ILD) with an increase of CD45+, Gr1+, Eos, T cells and AM populations in the BAL. Intratracheal treatment with everolimus included in liposomes decorated with hyaluronic acid reduces immune cell infiltration and fibrosis once SSC-ILD is established

REFERENCES: