ABSTRACT

Mechanisms of CD4 T Lymphocytes Differentiation in Different Sensitizing and Exposure Doses of Der p1 Allergen Through Changes in Heat Shock Protein 70 and Notch Ligands Expression by Dendritic Cells

Experimental Study in Balb/c Mice

Objective: To elucidate the mechanisms of differential $CD4^+$ T lymphocyte response after stimulation (sensitization and exposure) to differential (high vs. low) doses of allergen, we stimulate (sensitize and expose) groups of male Balb/c mice with high or low doses of Der p1 allergen.

Methods: The mice were randomly allocated to 9 different groups of intervention, i.e. sham, or low dose (10 μg), or high dose (1000 μg) intraperitoneal Der p1 allergen sensitization, and subsequent 7 days of sham, or low dose (15 μg), or high dose (1500 μg) Der p1 allergen inhalation. Levels of Hsp70 expression, IL-12 secretion, Notch ligands (Jagged1/Jagged2 and Delta1/Delta4) expression by lung dendritic cells, Notch receptors (Notch1, Notch2, Notch3), and transcription factors (GATA-3, T-bet) expression by mediastinal lymph nodes $CD4^+$ T lymphocytes, cytokines secretion in bronchoalveolar lavage fluid (IL-12, IL-4, IFN-γ) and in serum (IL-4, IFN-γ) were measured and analyzed.

Results: Low dose Der p1 allergen stimulation (sensitization and exposure) caused low level of Hsp70 expression, low level of IL-12 secretion, and low levels of Notch ligands (Jagged1/Jagged2 and Delta1/Delta4) expression by lung dendritic cells, which in turn induce GATA-3 transcription factor expression in mediastinal lymph nodes $CD4^+$ T lymphocytes and lead to the secretion of Th2 specific cytokines (IL-4). On the contrary, high dose Der p1 allergen stimulation (sensitization and exposure) caused high level of Hsp70 expression, high level of IL-12 secretion, and high level of Notch ligands (Jagged1/Jagged2 and Delta1/Delta4) expression by lung dendritic cells, which in turn induce T-bet transcription factor expression in mediastinal lymph nodes $CD4^+$ T lymphocytes and lead to the secretion of Th1 specific cytokines (IFN-γ). Allergen sensitization doses turn out to have more significant influence compared to allergen exposure dose. Hsp70 expression play a central role in driving the behavior of lung dendritic cells as an antigen presenting cells in such a way that enable them to change the polarization of CD4 T lymphocyte from Th2 to Th1 type of immune response.

Conclusion: The mechanisms of $CD4^+$ T lymphocytes differentiation after different doses of Der p1 allergen stimulation (sensitization and exposure) occured through changes in levels of: Hsp70 expression, IL-12 secretion, Notch ligands (Jagged1/Jagged2 and Delta1/Delta4) expression by lung dendritic cells, which in turn induce differential expression of transcription factors (GATA-3 or T-bet) in mediastinal lymph nodes $CD4^+$ T lymphocytes, and lead to differential cytokines synthesis and secretion of Th2 (IL-4) or Th1 (IFN-γ) specific cytokines.

Keywords: *Der p1, Hsp70, Notch ligand, Notch receptors, Dendritic cells, $CD4^+$ T lymphocytes, GATA-3, T-bet, animal asthma model*