CDK7 inhibitor suppresses psoriasis inflammation via inhibiting glycolysis to modulate Th17/Treg balance

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Psoriasis is a chronic, inflammatory disease characterized by hyper-activated Th17 and suppressive Treg cells, but the mechanism of Th17/Treg cells imbalance is still unclear. Cyclin-dependent kinase 7 (CDK7) which is known as a cell cycle regulator has been reported an anti-inflammatory effect in immune cells. Here we firstly found CDK7-D of psoriasis patients expressed higher levels of CDK7 along with an increased glycolysis levels than those in healthy controls. The chemical inhibitor of CDK7 called THZ1 restricted glycolytic metabolism in CD4+ T cells of psoriasis patients as well as typical glycolysis related genes. More importantly, THZ1 could suppress Th17 cell differentiation and promote Treg cell differentiation even under Th17 polarizing condition in vitro. Immunopotentiation injection of THZ1 in mice exhibited an alleviated epidermal hyperplasia and alleviated inflammation caused by imiquimod (MDM) treatment. THZ1-treated IMQ mice also showed significantly lower ratio of Th17 cells and upregulated the generation of Foxp3+ Treg cells. Furthermore, we identified IL-23 as an upstream regulator that stimulated CDK7 expression and glycolysis through p-akt-Hif-1α signaling pathway. Taken together, our results showed that abnormal CDK7 expression induced by IL-23 in CD4+ T cells in psoriasis patients contributed to the enhanced glycolysis levels which lead to the imbalance of Th17/Treg cells. CDK7 inhibitor THZ1 may serve as an immune-modulator for psoriasis therapy in the future.

Development of allergen-specific Foxp3+RORγt+ Treg cells during allergen-specific immunotherapy

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Allergen-specific immunotherapy (ASIT) is an effective treatment that can induce clinical and immunological tolerances to pathogenic allergens for atopic dermatitis (AD). The main challenge in ASIT is to induce the allergen-specific regulatory T (Treg) cells. Recently, transcriptional and functional analyses of Treg cells have identified three specialized subsets based on RORγt (Rorc) and GATA3 (Gata3) expression along with Foxp3. Although skin Treg cells are composed largely of Foxp3+GATA3+ Treg cells, recent studies have shown that Foxp3+RORγt+ Treg cells have important functions in different pathological and intestinal related organs. In this study, we enrolled AD patients with subcutaneous ASIT against house dust mite (HDM), and allergen-specific Treg cells were analyzed in peripheral blood samples before and after 3, 6, 12 months of ASIT. Treg cells were isolated from peripheral blood mononuclear cells to extract RNA and perform transcriptomic analyses. We observed that Foxp3+RORγt+ Treg cells were increased from 3 months through 12 months of ASIT compared to before ASIT. Foxp3+GATA3+ Treg cells were not significantly increased after ASIT compared to before ASIT. We also found that serum levels of HDM-specific IgG and expression levels of Th1, Th2 and Th17-related genes were significantly decreased after ASIT while serum HDM-specific IgG4 levels were significantly induced after allergen-specific immunotherapy. Taken together, our results suggest that ASIT induces allergen-specific Foxp3+RORγt+ Treg cells to develop immune tolerance in atopic dermatitis.

There are two isoforms of BP180 in the mouse brain

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BP180 is a hemidesmosomal protein in the skin and other epithelial tissues. The extracellular domain NC16A of BP180 is the main target of pathogenic autoantibodies in bullous pemphigoid (BP). Anti-BP180 autoantibodies exist in both the sera and cerebrospinal fluids of patients with dermatitis or stroke, suggesting that BP180 could be a shared autotetigand of the skin and brain. The purpose of this study was to investigate the expression of BP180 in the brain and whether BP180 in the brain is the same as skin in mice. We confirmed that BP180 mRNA and protein exist in the brain. The expression level of BP180 mRNA in the skin is about 1000 times higher than that in the brain. In the molecular weight of BP180 in the brain was 160 kDa instead of the 180 kDa in skin. The reduced size of BP180 in the brain was produced by a signal peptide cleavage. BP180 is expressed in the cerebral cortex, hippocampus, cerebellum and olfactory bulb. In conclusion, this study identified two isoforms of BP180 in the brain that are different in size from BP180 in the skin. Since these isoforms of BP180 have the NC16A domain, they are expected to be targets of anti-BP180 autoantibodies in BP patients with dementia or stroke.

Levels of plasma total IgG and Dimer-dendritic basophil FcεRI expression: potential predictors of response to autologous whole blood injection in chronic spontaneous urticaria

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Background: The efficacy and autologous of whole blood injection (AWBI) in treating chronic spontaneous urticaria (CSU) is unclear, which may be explained by the significant differences in markers that predict the response of the affected patients. Objectives: To explore the possible mechanism of AWBI in treating CSU by investigating the correlation between IgG, Dimer, anti-FcεRI IgG and basophil FcεRI expression and the clinical symptoms of CSU. Methods: Eighty patients with autologous serum skin test (ASST)-positive CSU were enrolled and randomly divided into AWBI treated group (receiving AWBI and antihistamine) and control group (only with antihistamine). Urticaria activity score (UAS-7) and dermatology life quality index (DLQI) of the patients before and after treatment were compared and analyzed. Results: The plasma total IgG, D-dimer, anti-FcεRI IgG and basophil FcεRI expression were different between AWBI responders and non-responders, displaying good diagnostic value in predicting the therapeutic response to AWBI. Basophil FcεRI expression was significantly higher in AWBI responders, with obvious decline during AWBI treatment. Conclusion: This study supported the effectiveness of AWBI in CSU, with the changes of plasma total IgG and D-dimer as potential predictors of treatment response. A possible mechanism of AWBI in treating CSU is through the reduced expression of basophil FcεRI.

Mast Cells participate in an imiquimod-induced mouse model of psoriasis

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Psoriasis is a chronic, inflammatory, polygenic disorder that is associated with both a physical and psychological burden. It is widely accepted that the IL23/IL17/IL17 axis is critical in the development of psoriasis, however, the pathogenesis of psoriasis is still not fully understood. Recent studies reported that mast cells increase and may be the main source of IL-17, IL-22 in psoriatic lesions, while mast cells participate in psoriasis need to be addressed. We used an imiquimod-induced psoriasis-like dermatitis, the phenotype of which closely resembles the one observed in psoriasis patients. We found that wildtype mice treated with imiquimod had significantly increased and activated mast cells in their skin compared to control group, while the MrgprB2 knockout mice treated with imiqimod had decreased and less activated mast cells, with decreased IL-17, IL-22, IL-23 and TNF-α levels. In vitro studies showed that imiquimod could activate MRGPRX2 in human mast cell and MrgprB2 in mouse mast cell. These results suggested that mast cells participated in the development of psoriasis-like dermatitis via MRGPRX2 in mice, associated with the IL23/IL17 axis, which will help us understand the immunopathogenesis and provide new strategies for the prevention and treatment in psoriasis.