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

Liu Y, Shen S, and Wang W

1 Dermatology, Xijing Hospital, Xi'an, Shaanxi, China and 2 Xi'An Jiefang Hospital, Fourth Military Medical University, Shaanxi, Xi'an, China

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 CD7T cells 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. Intraportal injection of THZ1 in mice exhibited an alleviated epidermal hyperplasia and alleviated inflammation caused by imiquimod (IMQ) treatment. THZ1-treated IMQ mice had significantly lower ratio of Th17 cells and higher ratio of Treg cells than the vehicle-treated IMQ mice. Furthermore, we identified IL-23 as an upstream regulator that stimulated CDK7 expression and glycolysis through p-ACK1/H11 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 immuno-modulator for psoriatic therapy in the future.

Development of allergen-specific Foxp3+ROR
t+ Treg cells during allergen-specific immunotherapy

K Zhang, S Kim, S Lee, H Kim, S Kim, S Lee, TS Kappler, C Park, S Yoo, L Liu, H Wang, C Park

1 Department of Dermatology, Yonsei University, Seoul, South Korea, Korea (the Republic of) and 2 Department of Dermatology, Brigham and Women’s Hospital, Boston, Massachusetts, United States

There are two isoforms of BP180 in the mouse brain

Q Chen, L Liu, H Wang, C Park

Yong-Duck Kwon, Ki-Young Park, Shi-Jiun Lee, and Young-Jin Park

Department of Dermatology, Xijing Hospital, Xi'an, Shaanxi, China, 2 Department of Dermatology, Southwest Hospital, Third Military Medical Center, Chongqing, China

Background: The efficacy and autonomy of whole blood injection (AWBI) in treating chronic spontaneous urticaria (CSU) is unclear, which may be explained by seeking appropriate biomarkers to predict the response of the affected patients. Objectives: To explore the possible mechanism of AWBI in treating CSU by investigating the correlation between IgG, D-dimer, anti-FcεRI IgG and basophil FcεRI expression and the clinical symptoms of CSU treated by AWBI 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) and clinical life quality index (QOL) of the patients before and after treatment were compared and analyzed. Levels of plasma total IgG, D-dimer, and anti-FcεRI IgG of 30 AWBI group patients before and after treatment were compared with those of 25 healthy controls. The hapten FcεRI expression in the peripheral venous blood of the patients was also analyzed. Results: A better clinical response was observed in the AWBI treated group than in the control group, while the MrgprB2 knockout mice treated with IMQ had decreased and less imiquimod-induced mouse model of 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 Mrgpr2 knockout mice treated with IMQ 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 Mrgpr2x2 in human mast cell and Mrgprβ2 in mouse mast cell. These results suggested that mast cells participated in the development of psoriasis-like dermatitis via Mrgprβ2 in mice, associated with the IL-23/IL-17 axis, which will help us understand the immunopathogenesis and provide new strategies for the prevention and treatment in psoriasis.

Levels of plasma total IgG and D-dimer and basophil FcεRIexpression and potential predictors of response to autologous whole blood injection in chronic spontaneous urticaria

Wuhu Wang, Wenxia Gao, Xinming Yin, Shuhao Gao, Jianhui Li, Shouguang Li, Hongyan Gao, Feng Zhang, Yajing Zhang, Shuai Liu, Yaping Wang, Zhongwei Tang, Yajia Li, Jialin Wang, Weihua Cao, Ting Zhang, Enhui Lu, Fangyuan Liu, Dandan Li, and Zhihua Huang

1 Department of Dermatology, Wuhan No.1 Hospital, Wuhan, Hubei, China, 2 Department of Dermatology, Southwest Hospital, Third Military Medical Center, Chongqing, China

There are two isoforms of BP180 in the brain that are different in size from BP180 in the skin. The expression level of BP180 mRNA in the skin is about 100 times higher than that in the skin. In the brain, the molecular weight of BP180 in the brain was 160 kD instead of the 180 kD in the skin. The reduced size of BP180 in the brain was produced by alternative splicing, resulting in deletion of exons 1 to 6 and the mRNA translated at the ATG initiate codon in exon 11. Further sequence analysis revealed that BP180 in the brain has two isoforms, isoform 1 lacking exons 1-6 (799 nucleotides) and isoform 2 lacking exons 1-6 and exon 48 (111 nucleotides). By immunoblotting we found that BP180 protein was 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.