INFLAMMATORY SKIN DISEASES (OTHER THAN ATOPIC DERMATITIS & PSORIASIS)

NLRP3 INFLAMMASOME AGGRAVATES OXIDATIVE STRESS-DRIVEN TH1 IMMUNE RESPONSE IN VITILIGO

S Li [(1)] - P Kang [(1)] - W Zhang [(1)] - Q Zhang [(1)] - X Yi [(1)] - G Wang [(1)] - T Gao [(1)] - C Li [(1)]

Xijing Hospital, Fourth Military Medical University, Department Of Dermatology, Xi'an, China [(1)]

Introduction: The NLR family pyrin domain containing 3 (NLRP3) inflammasome plays a key role in innate immune system and is thought to be involved in oxidative stress-driven autoimmune response in vitiligo. However, the mechanism underlying the activation of NLRP3 inflammasome in vitiligo as well as its exact role in vitiligo pathogenesis is not clear.

Objective: We sought to explicate how oxidative stress activates NLRP3 inflammasome in keratinocytes and its contribution to vitiligo development.

Materials and Methods: Skin and serum samples from vitiligo patients were used to observe the activation of NLRP3 inflammasome in vitiligo. Primary human keratinocytes and HaCaT cells were treated by H2O2, and then the expression of NLRP3 inflammasome components and the intermediated signaling pathway were examined. Vitiligo patient blood-derived CD8+ and CD4+T cells were incubated with the culture supernatants of HaCaT cells with indicated treatments to evaluate the effect of NLRP3 inflammasome on T cell response in vitiligo.

Results: NLRP3 and downstream cytokine interleukin-1β (IL-1β) expressions were increased in serum and perilesions of vitiligo patients, and serum IL-1β was correlated with disease activity and decreased after combined therapy with Diprospan, narrow band-UVB and topical Tacrolimus. Furthermore, H2O2-induced NLRP3 inflammasome activation in keratinocytes was dependent on transient receptor potential cation channel subfamily M member 2 (TRPM2)-mediated intracellular and mitochondrial Ca2+ influx. Moreover, blocking TRPM2-induced NLRP3 inflammasome activation in keratinocytes not only weakened the migration ability of CD8+ T cells from vitiligo patients via repressing CXCL16-CXCR6 and CXCL10- CXCR3 chemotaxis, but also inhibited the activation and effector cytokine production of CD8+ T and CD4+ T cells through suppressing IL-1β/IL-1R signaling.

Conclusions: Our study identifies a critical role of TRPM2-dependent NLRP3 inflammasome activation under oxidative stress in the pathogenesis of vitiligo. Blocking the function of

TRPM2 or NLRP3 can be promising target treatments for the therapy of vitiligo.