World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:9, No:09, 2015

Regulation of SHP-2 Activity by Small Molecules for the Treatment of T Cell-Mediated Diseases

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Abstract : The phosphatase SHP-2 is known to exert regulatory activities on cytokine receptor signaling and the dysregulation of SHP-2 has been implicated in the pathogenesis of a variety of diseases. Here we report several small molecule regulators of SHP-2 for the treatment of T cell-mediated diseases. The new cyclodepsipeptide trichomides A, isolated from the fermentation products of Trichothecium roseum, increased the phosphorylation of SHP-2 in activated T cells, and ameliorated contact dermatitis in mice. The trichomides A's effects were significantly reversed by using the SHP-2-specific inhibitor PHPS1 or T cell-conditional SHP-2 knockout mice. Another compound is a cerebroside Fusaruside isolated from the endophytic fungus Fusarium sp. IFB-121. Fusaruside also triggered the tyrosine phosphorylation of SHP-2, which provided a possible mean of selectively targeting STAT1 for the treatment of Th1 cell-mediated inflammation and led to the discovery of the non-phosphatase-like function of SHP-2. Namely, the Fusaruside-activated pY-SHP-2 selectively sequestrated the cytosolic STAT1 to prevent its recruitment to IFN-□R, which contributed to the improvement of experimental colitis in mice. Blocking the pY-SHP-2-STAT1 interaction, with SHP-2 inhibitor NSC-87877 or using T cells from conditional SHP-2 knockout mice, reversed the effects of fusaruside. Furthermore, the fusaruside's effect is independent of the phosphatase activity of SHP-2, demonstrating a novel role for SHP-2 in regulating STAT1 signaling and Th1-type immune responses.

Keywords : SHP-2, small molecules, T cell, T cell-mediated diseases
Conference Title : ICI 2015 : International Conference on Immunology
Conference Location : London, United Kingdom
Conference Dates : September 25-26, 2015

Open Science Index, Medical and Health Sciences Vol:9, No:09, 2015 publications.waset.org/abstracts/29058.pdf