
Marine-derived STING inhibitors, Excavatolide B promote wound repair in full-thickness-incision rats

Zhi-Hong Wen^{*1,2}, Chun-Kai Chang¹, Zong-Sheng Wu³, Yi-Hao Lo⁴, and Chun-Sung Sung³

¹National Sun Yat-sen University – Taiwan

²National Museum of Marine Biology Aquarium – Taiwan

³Taipei Veterans General Hospital – Taiwan

⁴Zuoying Armed Forces General Hospital – Taiwan

Abstract

The process of wound healing encompasses both inflammatory and proliferative stages. Excessive inflammation is known to impede the healing of chronic wounds. Activation of the cyclic guanosine monophosphate–adenosine monophosphate synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway causes inflammation during cellular stress and tissue damage. Herein, we examined the anti-inflammatory effects of the marine-derived STING antagonist excavatolide B (EXCB) and its derivatives, EXCB-61 and EXCB-79, in full-thickness-incision rats. Wound area measurements, histopathological observations, and immunohistochemical analyses were performed to evaluate the roles of these compounds in wound healing. These three compounds were found to have low toxicity, with EXCB promoting Hs68 human dermal fibroblast migration and proliferation. EXCB and EXCB61 treatments, but not EXCB79, reduced the wound area. The histopathological results showed a significant decrease in immune cell infiltration and mast cell accumulation in all compound-treated groups. Immunohistochemical analysis revealed that EXCB and its derivatives reduced cGAS-STING pathway factors such as STING, phosphorylated TANK-binding kinase 1, nuclear factor kappa-light-chain-enhancer of activated B cells, and M1 macrophages while increasing the expression of angiogenic factors vascular endothelial growth factor and CD31, as well as M2 macrophages and collagen I/III deposition. We conclude that marine-derived STING antagonists can attenuate inflammatory responses by inhibiting the cGAS-STING pathway and promoting angiogenesis, thereby aiding wound healing.

Keywords: wound healing, cGAS, STING, excavatolide B, antiinflammation

*Speaker