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Small molecule inhibitors of STOML3 promise to treat neuropathic pain

Keywords: neuropathic pain, diabetic neuropathy, STOML3 inhibitor, sensory mechanotransduction, Piezo ion channels

INVENTION NOVELTY

Small molecule inhibitors of STOML3 (stomatin-like protein-3), a protein controlling the sensitivity of Piezo mechanically gated ion channels, were found to reverse mechanical hypersensitivity in pathophysiological conditions following nerve injury or diabetic neuropathy upon local application to mouse skin.

VALUE PROPOSITION

These are the first pharmacological agents to modulate the first step in the transformation of light touch stimuli into an electrical signal, a process otherwise known as sensory mechanotransduction.
Moreover, mechanosensitive ion channels like Piezo1 and Piezo2 may be difficult targets to exploit for pharmacological intervention, as their gene deletion is lethal. The compounds described here circumvent these shortcomings by not directly affecting essential functions of Piezo proteins and rather targeting their modulator STOML3. This approach allows for a selective and powerful inhibition of sensory mechanotransduction in pathophysiological conditions.

TECHNOLOGY DESCRIPTION

STOML3 regulates the sensitivity of Piezo ion channels through its self-association. A high-throughput cellular screen using bimolecular fluorescence complementation (BiFC) led to the identification of OB-1 (Oligomerization Blocker-1), an effective inhibitor of STOML3 oligomerization. OB-1 was found to reversibly reduce the sensitivity of mechanically gated currents in acutely cultured mouse sensory neurons and to silence mechanoreceptors in vivo. Its application to the skin has shown remarkable efficacy in reducing touch-evoked pain behavior in a mouse model of painful diabetic neuropathy as well as in a CCI (chronic constriction injury) model of neuropathic pain.

COMMERCIAL OPPORTUNITY

We are currently looking for a licensing and/or co-development partner.

DEVELOPMENTAL STATUS

A high-throughput small molecule screen led to the identification of hit compounds OB-1 and OB-2 from a library containing 35.000 compounds. Both compounds have been further profiled in vitro and might represent new modalities for topical treatment. Additional derivatives with improved parameters for systemic administration are being developed in parallel.

PATENT SITUATION

Patent applications (priority date: 7.12.2016) in EP (EP3551183) and US (US2019382386) are pending.

FURTHER READING

Small-molecule inhibition of STOML3 oligomerization reverses pathological mechanical hypersensitivity. Nature Neuroscience (2017) 20 (2), 209-221.

MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT

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