Oncomodulin is required for the conditioning lesion response in dorsal root ganglion neurons in vivo

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Regeneration can occur in the peripheral nervous system after injury, but the mechanisms that underlie this process have not been fully determined. We have previously demonstrated the involvement of macrophages acting in peripheral ganglia in the enhanced regeneration that occurs in sensory and sympathetic neurons after a conditioning lesion (CL). Oncomodulin (Ocm) has been proposed as a macrophage and neutrophil secreted pro-regenerative molecule that stimulates optic nerve regeneration following inflammation in the eye. We have utilized an Ocm knockout (KO) mouse strain to investigate whether Ocm plays a role in the CL response in sensory neurons after sciatic nerve injury. First, we measured neurite outgrowth in cells maintained in dissociated culture after a CL. A robust increase in neurite outgrowth was seen in neurons from both wild type (WT) and Ocm KO mice after a CL. Next, we examined the CL response in explanted ganglia. Increased neurite outgrowth following a CL was seen in explants from both WT and KO mice; however, the magnitude of the effect was significantly smaller in the explants from KO animals. Finally, we examined the CL effect in vivo measured in response to a sciatic nerve crush. A CL response was seen in WT animals but not in KO animals. Flow cytometry studies measuring macrophage number in dissociated culture, explant culture, and DRG in vivo, demonstrated that the Ocm-dependent deficit in regeneration is seen only under experimental conditions in which a significant number of macrophages are present. To begin to determine how Ocm influences regeneration, Il-6 mRNA was measured in axotomized DRG from WT and Ocm KO animals where increased levels were significantly higher in ganglia from WT animals. Thus, our data shows that Ocm is necessary for the conditioning lesion response in vivo and may act to support regeneration through IL-6.