Title:
Involvement of mTOR Pathway Modulates Autophagy and Immune Response in Recovery from Spinal Cord Injury

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Spinal cord injury (SCI) consists of primary mechanical injury followed by a secondary inflammatory cascade that hinders recovery. Autophagy is inhibited in SCI, contributing to secondary injury. mTOR pathway inhibition may lead to neuroprotection and functional recovery from SCI by stimulating autophagy and reducing inflammation. Here we studied the effects of Rapamycin (RAPA), an mTORC1 inhibitor, and pp242, a dual-inhibitor of both mTORC1 and mTORC2 on autophagy, immune response, and recovery from SCI. In a balloon-compression model of SCI, rats (n=52) were randomized into four treatment groups: RAPA, pp242, vehicle-treated controls, and no-lesion no-treatment controls. Treatments were administered intraperitoneally daily, starting from the second day and repeated until the sixth day after the SCI. Rats were sacrificed on day 7 post-SCI. Behavioral testing (BBB) was performed to assess recovery status. IHC, Western Blot, and ELISA were used to analyze the effects of mTOR pathway inhibition on inflammatory and autophagic markers. Downstream target of mTORC1, pS6, was downregulated by RAPA or pp242. Another target of mTORC1, 4EBP1 was hyperphosphorylated following treatment with RAPA or pp242. Expression of autophagic marker, LC3B, was elevated after SCI and potentiated by RAPA or pp242 treatment. RAPA or pp242 treatment altered cytokine production in SCI. Pro-inflammatory cytokines were increased by pp242 treatment and reduced by RAPA treatment. Both RAPA and pp242 induced downregulation of cytokines IL-1β, MIP-1α, and IL-10. Lastly, mTOR inhibition led to increased functional recovery as shown by higher BBB scores. Our results demonstrated that mTOR inhibition via mTORC1 may suppress inflammation and upregulate autophagy leading to improved functional recovery in a rat model of SCI.