ku0063794, a dual mtorc1 and mtorc2 inhibitor, reduces neural tissue damage and locomotor impairment after spinal cord injury in mice

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Autophagy is an intracellular catabolic mechanism for the degradation of cytoplasmic constituents in the autophagosomal–lysosomal pathway. This mechanism plays an important role in homeostasis and it is defective in certain diseases. However, whether enhanced autophagy will reveal a possible cause of cell death or whether it serves as part of the induction of an endogenous protective response are still controversial. The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that plays a key role in the regulation of cell metabolism, cell proliferation, cell death and is involved in physiological processes. Moreover, mTOR is involved in the regulation/inhibition of autophagy. Spinal cord injury (SCI) is a serious and debilitating health problem that usually causes lifelong disability and leads to neurological dysfunction at and/or below the level of the injury. Previous studies have shown that autophagy is emerging as an important mediator of pathological responses associated to SCI and plays a key role in secondary injury causing progressive degeneration of the spinal cord. Thus, based on this evidence in the present study we used different selective inhibitors of mTOR activity to better investigate the functional role of autophagy in an *in vivo* model of SCI and to better determine whether the autophagic process is involved in spinal cord tissue damage. We treated animals with a new synthetic inhibitor Temsirolums and with a dual mTORC1 and mTORC2 inhibitor KU0063794 compared all with the well know inhibitor of mTOR the Rapamycin. Our results demonstrated that the administration of Rapamycin and Temsirolums significantly decreased the phosphorylation of the p70S6K and pAKT protein and control the expression levels of LC3 and Beclin 1 in the injured spinal cord but KU0063794 is able to modulate the autophagy process better than Rapamycin and Temsirolimus.

Moreover, we investigated if the mTOR inhibitors could modulate the neuroinflammation associated to SCI and the results that we obtained clearly demonstrated that Rapamycin and Temsirolimus significantly decreased the expression of iNOS, COX2,GFAP and restored nNOS levels; but the administration of KU0063794 is able to blunt the neuroinflammation better than Rapamycin and Temsirolimus. In addition, neuronal loss and cell death in the injured spinal cord were significantly reduced in the KU0063794 treated mice.

Thus, taken together our results indicate that the administration of KU0063794 produced a neuroprotective function at the lesion site following SCI, representing a novel therapeutic strategy after SCI.