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SQSTM1/p62 regulates HTLV-1 tax mediated NF-κB activation

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HTLV-1-mediated cellular transformation relies on Tax-dependent activation of the NF-κB pathway, which has previously been shown to require Tax poly-ubiquitination and interaction with cellular factors, such as Optineurin (OPTN). The recent identification of OPTN as a selective autophagy receptor sharing high sequence similarities with sequestosome-1 (SQSTM-1/p62), a well-described selective autophagy receptor and NF-κB signaling adaptor, led us to hypothesize that Tax could hijack selective autophagy receptors for an efficient NF-κB activation. Using immunoprecipitation and confocal imaging of endogenous SQSTM/p62 in Tax-expressing cells or in HTLV-1 chronically infected T-cell lines, we showed that Tax interacts with SQSTM-1/p62. This interaction was independent of Tax ubiquitination and of the presence of the Tax PDZ-binding motif. Tax-mediated activation of NF-κB in p62-deficient cells was significantly reduced compared to wild type cells, indicating that SQSTM/p62 is necessary for Tax activity. Surprisingly however, over-expression of SQSTM-1/p62 or induction of autophagy led to a dramatic decrease in the amount of soluble Tax, along with a reduced induction of NF-κB. This suggests that Tax could be a substrate of selective autophagy. Altogether, our results reveal the double-edged consequences of Tax / SQSTM/p62 interaction, with the potentiation of Tax activity and the induction of Tax sequestration. They highlight the complex relationships that this viral protein has.

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