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TLR3 is a key component of rabies virus induced Negri bodies

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Human neurons express the innate immune response receptor, Toll-like receptor-3 (TLR-3) as it has been shown in human post mitotic neurons and in Purkinje neurons of cerebellar cortex in postmortem human rabies cases. Here, we investigated further the expression and cellular localization of neuronal TLR3 in the time course of rabies virus (RABV) infection in human neuronal cells. In the absence of infection, TLR3 molecules are located in endosomes. Following RABV infection, TLR3 is not only present in endosomes but also in detergent resistant inclusions bodies located at the nucleus vicinity. Besides TLR3, these inclusions bodies contain rabies virus proteins (N and P but no G). The size of these cytosolic structures (2–4 μm), their composition and the absence of surrounding membrane, as shown by electron microscopy, suggest they correspond to the previously described Negri bodies (NB). NB are associated to the microtubule network and cellular components involved in protein chaperoning. In the absence of TLR3, RABV-infected cells do not exhibit viral NB anymore, establishing a role of TLR3 in their formation. Moreover, viral genome is detected within the RABV NB, suggesting that TLR3 might associate to the viral proteins via its binding with the RNA genome. Finally, confocal analysis and 3D modelling indicate that NB structure is strictly organized with a TLR3-containing core surrounded by a halo of viral N and P proteins. The central localization of TLR3 within RABV NB correlates with its crucial role in the full formation of these structures. Further experiments will allow understanding the mechanism by which TLR3 is sequestered by viral NC proteins and the impact of an absence of TLR3 on viral life cycle.