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Category: Postdoc

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Title: SUMO PEPTIDASE ULP-4 REGULATES THE ANTIVIRAL INNATE IMMUNITY BY DESUMOYLATION OF RIG-1 HOMOLOG DRH-1 IN CAENORHABDITIS ELEGANS

Abstract: The COVID-19 pandemic had prioritized the unmet need to understand the basic mechanisms of viral-host interactions, especially in the context of aging, as the elderly are particularly susceptible to severe infection. Orsay virus is a positive strand RNA virus that naturally infects *Caenorhabditis elegans*, and is an emerging model to study virus-host interactions in an intact metazoan animal. To date, infection has only been observed within intestinal cells, which induces an "intracellular pathogen response pathway". We find that the *C. elegans* SUMO isopeptidase *ulp-4*, an enzyme that removes SUMO from proteins, is required for the induction of the intracellular pathogen response upon the Orsay virus infection. In the absence of *ulp-4*, Orsay virus treated animals undergo a progressive disruption of the intestinal lumen, indicating severe viral pathogenesis. We have identified the *C. elegans* RIG-1 homolog DRH-1 as the likely de-SUMOylation target of *ulp-4*. We have discovered that the anti-viral response is declined in old worms, consistently expression of *ulp-4* decreases and increased Sumoylated DRH-1 during normal aging. Collectively, our findings suggest that loss of SUMO regulation may contribute to declining viral innate immunity in older organisms through DRH-1.