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Title: The SUMO peptidase ULP-4 Is Essential for Orsay Virus Infection 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 and proteostasis, 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. Through a targeted feeding-based RNAi screen, we have identified the transcription factor DVE-1 as the possible de-SUMOylation target of ulp-4. DVE-1 is a critical component of the mitochondrial unfolded protein response, and a transcriptional regulator that influences C. elegans longevity. We have discovered that the anti-viral response is declined in old worms, and consistently expression of ulp-4 decreases during normal aging. Collectively, our findings suggest that loss of SUMO regulation may contribute to declining viral innate immunity in older organisms through DVE-1 and possibly through alterations in mitochondrial proteostasis.