ABSTRACT

Stalled replication forks are processed by multiple enzymes to promote fork restart. The MRE11 nuclease plays a central role in this process by degrading newly replicated DNA, in a manner that is tightly controlled by the homologous recombination factors BRCA2 and RAD51. We have identified SAMHD1 as a novel factor that acts with MRE11 to resect nascent DNA at stalled forks. SAMHD1 is a HIV restriction factor that protects quiescent cells from viral infections by depleting dNTP pools. We have found that the function of SAMHD1 at stalled forks is distinct from the regulation of dNTP pools and is mediated by phosphorylation by S-phase CDKs. This resection activity is required to activate the ATR pathway and to promote fork recovery. Mutations in SAMHD1 are implicated in a severe inflammatory disease called Aicardi-Goutières syndrome. The mechanism by which SAMHD1 protects cells from chronic inflammation is currently unknown. Remarkably, we have found that SAMHD1 prevents the release of ssDNA fragments from stalled replication forks. In SAMHD1-deficient cells, these fragments accumulate in the cytosol and activate type I interferons in a STING-dependent manner. In conclusion, our data indicate that SAMHD1 is a novel player in the replication stress response that prevents inflammation by limiting the release of ssDNA fragments from stalled replication forks.