A novel role for SAMHD1 connecting DNA replication stress to inflammation

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SAMHD1 is a triphosphohydrolase that restricts HIV-1 infection in non-cycling cells. Mutations in SAMHD1 cause Aicardi-Goutières syndrome (AGS) and have been implicated in chronic lymphocytic leukemia (CLL). However, the molecular mechanisms involved remain unknown. We have characterized a novel function of SAMHD1 in DNA replication that is independent of its dNTPase activity. We show that SAMHD1 promotes the degradation of newly-synthesized DNA in a CycA/CDK-dependent manner. This function is epistatic to Mre11 and is counteracted by Rad51, a recombinase loaded by BRCA2 at stalled forks. SAMHD1 is required for Chk1 activation and for the recovery of stalled forks, indicating that it is a novel key player in the replication stress response. Moreover, we found that nascent DNA accumulates in the cytosol of SAMHD1-depleted cells in a RecQ1-dependent manner and activate type I interferon response. Together, these data suggests the existence of an unexpected link between replication stress, innate immunity and inflammation.