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A Dimerized Coiled-Coil Domain and an Adjoining Part of Geminin Interact with Two Sites on Cdt1 for DNA Replication Inhibition. Kunchithapadam Swaminathan^{1,2}, Ping Yuan¹, Sandeep Saxena³, Suman Kumar Dhar³, Takeshi Senga³, David Takeda³, Howard Robinson⁴, Sally Kornbluth⁵ and Anindya Dutta³, ¹Inst. of Molecular and Cell Biology, ²Dept. of Biological Sciences, National Univ. of Singapore, Singapore, ³Dept. of Biochemistry and Molecular Genetics, Univ. of Virginia, Charlottesville, VA, ⁴Brookhaven National Lab., Upton, NY, ⁵Dept. of Pharmacology and Cancer Biology, Duke Univ. Medical Center, Durham NC.

Geminin is a cellular protein that associates with Cdt1 and inhibits Mcm2-7 loading during S phase. It prevents multiple cycles of replication per cell-cycle and prevents episome replication. It also directly inhibits the HoxA11 transcription factor. We report the crystal structure of the dimerization domain of geminin¹, which forms a parallel coiled-coil homo-dimer with atypical residues in the dimer interface. Point mutations that disrupt the dimerization abolish interaction with Cdt1 and the inhibition of replication. An array of glutamic acid residues on the coiled-coil domain surface interacts with positive charges in the middle of Cdt1. An adjoining region interacts independently with the N-terminal 100 residues of Cdt1. Both interactions are essential for replication inhibition. The negative residues on the coiled-coil domain and a different part of geminin are also required for interaction with HoxA11. Therefore a rigid cylinder with negative surface charges is a critical component of a bipartite interaction interface between geminin and its cellular targets.

1. Ping, Y. *et al.* (2004). *Molecular Cell*, in press.