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Structural Mechanism for Inactivation and Activation of CAD/DFF40 in the Apoptotic Pathway

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CAD/DFF40 is responsible for the degradation of chromosomal DNA into nucleosomal fragments and subsequent chromatin condensation during apoptosis. It exists as an inactive complex with its inhibitor ICAD/DFF45 in proliferating cells but becomes activated upon cleavage of ICAD/DFF45 into three domains by caspases in dying cells. The molecular mechanism underlying the control and activation of CAD/DFF40 was unknown. Here, the crystal structure of activated CAD/DFF40 reveals that it is a pair of molecular scissors with a deep active site crevice that appears ideal for distinguishing internucleosomal DNA from nucleosomal DNA. Ensuing studies show that ICAD/DFF45 sequesters the nonfunctional CAD/DFF40 monomer and is also able to disassemble the functional CAD/DFF40 dimer. This capacity requires the involvement of the middle domain of ICAD/DFF45, which by itself cannot remain bound to CAD/DFF40 due to low binding affinity for the enzyme. Thus, the consequence of the caspase cleavage of ICAD/DFF45 is a self-assembly of CAD/DFF40 into the active dimer.