

Abstract

Caspase-activated DNase (CAD) and its inhibitor (ICAD) are essential regulators of apoptosis, playing a pivotal role in DNA fragmentation and cellular disintegration. Under proapoptotic conditions, caspase-3 cleaves ICAD within the CAD-ICAD heterodimer, releasing CAD to form homodimers which induce double-strand breaks (DSBs) in nuclear DNA. Beyond apoptosis, the involvement of CAD also has been recognized in cellular differentiation and senescence. In these contexts, ICAD undergoes partial cleavage, allowing for limited CAD activation and controlled DNA damage that contributes to specific cell fate decisions. More recently, CAD-ICAD heterodimers have been shown to serve an additional function in cancer cells. Phosphorylation of specific serine residues on ICAD enables CAD to induce DNA lesions even in its heterodimeric form. These lesions activate DNA damage response that arrest cell cycle progression, giving cancer cells time to repair their genomes. This thesis recapitalizes current knowledge on the functions of CAD and ICAD in apoptosis, differentiation, senescence, and emerging involvement in cell cycle regulation. It also explores the evolutionary origins of the CAD-ICAD system, proposing that its role in DNA damage modulation and cell cycle control may not be limited to malignancy, but could represent a conserved feature across diverse species.