

P015 Regulation of separase: securin-independent modes of regulating the giant protease that triggers anaphase
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Sister chromatids are held together by the ring-shaped cohesin complex, which likely entraps both DNA-double strands in its middle. This tie is resolved in anaphase when separase, a giant protease, becomes active and cleaves the kleisin subunit of cohesin. Previous models implied that premature activation of separase and, hence, chromosome missegregation are solely prevented by association of this cysteine endopeptidase with its inhibitor securin. However, dispensability of vertebrate securin strongly suggests additional means of separase regulation. Indeed, sister chromatid separation but not securin degradation is inhibited by phosphorylation-dependent binding of cyclin-dependent kinase 1 (Cdk1)/cyclin B1 to separase. Because securin and Cdk1/cyclin B1 interact with separase in a mutually exclusive manner, the degradation of both these protease inhibitors via the ubiquitin-proteasome-pathway plays an important role in activating separase at anaphase. We will present an in-depth biochemical characterization of the securin-independent inhibition of separase by Cdk1. In addition, the regulation of separase's proteolytic activity by auto-cleavage, association with protein phosphatase 2A, and antagonistic action of cohesin-protective shugoshin 2 will be discussed.