B-01 Biology

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Histone H3 is a competitive Chk1 inhibitor that controls early embryonic cell cycle

Abstract:

The DNA damage checkpoint is crucial to protect genome integrity. However, the early embryos of many metazoans sacrifice this safeguard to allow for rapid cleavage divisions that are required for speedy development. These rapid cell cycles go on for a set number of divisions until the cell cycle is remodeled with the acquisition of DNA damage checkpoints. However, how DNA checkpoint activity is coordinated with progression of early development remains unclear. Here, we show that histone H3 dynamics couple developmental progression to DNA checkpoint activity, allowing for cell cycle remodeling at precisely the correct developmental time point in the early Drosophila embryo. We show that the excess pool of non-DNA-bound histones becomes depleted as the embryo undergoes cleavage divisions, leading to falling nuclear H3 concentrations. Using quantitative imaging, biochemistry, and mathematical modeling, we find that excess H3 N-terminal tail acts as a competitive inhibitor of Chk1 that controls DNA checkpoint activity. These results define Chk1 regulation by H3 as a key mechanism that couples Chk1 activity directly to developmental progression. Thus, our model provides a simple molecular mechanism for the longstanding problem of timing mechanism in early development.