REGIONAL CENTRE FOR BIOTECHNOLOGY

Seminar series

An ATR-mediated mechanical response controlling cell plasticity

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Abstract

Our genome is continuously damaged by environmental, endogenous agents as well as by the instrinsic instability of DNA. To counteract the deleterious effects of DNA damage, the cell is equipped with a wide variety of damage checkpoint responses to guard our genome. ATR is DNA damage sensor protein that prevents replication fork collapse, chromosome fragility and aberrant chromatin condensation. Yeast Mec1/ATR detaches transcribed chromatin from the nuclear envelope to counteract aberrant topological transitions when forks encounter transcribed genes. We found that active ATR, ATRIP and phosphorylated Chk1 associate with the nuclear envelope during S phase and prophase. Following osmotic stress, ATR relocalizes at the inner and outer nuclear membranes throughout the cell cycle. Mechanical stimulation of the plasma membrane causes accumulation of ATR at the nuclear envelope. ATR-mediated mechanosensing of membrane stress is independent of DNA damage. We propose that the mechanical forces owing to chromosome dynamics or plasma membrane stress convey to nuclear membranes and activate the ATR kinase. ATR counteract aberrant topological transitions at perinuclear chromatin by modulating nuclear envelope plasticity and chromatin association. Thus ATR is part of an integrated mechanical response coupling plasma membrane induced cytoskeleton response with epigenetic changes within the nucleus.