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GENOME STABILITY

Cyclin' on mRNA

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> "the regulation of MRE11 protein levels was independent of CDK activity"

Cyclin A2, a key regulator of the cell cycle, is highly expressed from S phase to early mitosis and has been associated with tumorigenesis. Cyclin A2–cyclin-dependent kinase (CDK) complexes (with CDK1 and CDK2) drive the initiation and progression of chromosome duplication and later promote the initiation of mitosis. van Deursen and colleagues now report that cyclin A2 regulates DNA replication through RNA binding and independently of kinase activity, revealing that independent catalytic and non-catalytic functions of cyclin A2 are important for proper mitotic progression and genome duplication, and thus the maintenance of genome stability.

The authors used a combination of knockout (*Ccna2*$^{-}$) and hypomorphic (*Ccna2*^{H}) alleles to downregulate cyclin A2 expression in mice without causing major developmental defects. Consistent with previous reports suggesting a link between cyclin A2 and malignant growth, *Ccna2*$^{-/H}$ mice had a marked increase in tumour incidence. Moreover, mouse embryonic fibroblasts (MEFs) derived from these mice, which express only ~25% of normal cyclin A2 levels, were predisposed to two types of chromosome segregation errors: lagging chromosomes and chromatin bridges.

So how do low cyclin A2 levels cause such errors? During spindle formation, *Ccna2*$^{-/H}$ MEFs displayed markedly delayed centrosome movement to opposite poles, which results in a high frequency of asymmetrical spindles and lagging chromosomes. The authors found that such defects were caused by reduced loading of the motor protein EG5 at centrosomes in prophase, owing to reduced EG5 phosphorylation by cyclin A2–CDK. Indeed, restoration of normal cyclin A2 levels restored EG5 phosphorylation and corrected EG5 loading and centrosomal movement.

The formation of chromatin bridges, by contrast, was attributed to DNA replication defects. Compared with *Ccna2*$^{+/+}$ MEFs, *Ccna2*$^{-/H}$ MEFs displayed more frequent stalling of replication forks and lower efficiency of fork restart, and accumulated more DNA double-stranded breaks (DSBs). *Ccna2*$^{-/H}$ MEFs had reduced levels of MRE11 and RAD50, two components of the MRN complex, which is crucial for fork restart and DSB repair. *Mre11* and *Rad50* mRNA expression and distribution were normal, but their abundance in polysomes was reduced, suggesting decreased translation. Immunoprecipitation assays showed that cyclin A2 selectively and directly bound to the 3′ untranslated region (UTR) of *Mre11* transcripts. This interaction promoted translation, presumably by facilitating the recruitment of the translation initiation factor eIF4A2, as cyclin A2 was found to interact with both the *Mre11* 3′ UTR and eIF4A2. Importantly, the regulation of MRE11 protein levels was independent of CDK activity.

Thus, cyclin A2 coordinates two separate functions that are key for genome stability. It ensures accurate chromosome segregation through CDK activation, and proper DNA replication and repair through previously uncharacterized kinase-independent RNA-binding activity.

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ORIGINAL ARTICLE Kanakkanthara, A. *et al.* Cyclin A2 is an RNA binding protein that controls *Mre11* mRNA translation. *Science* **353**, 1549–1552 (2016)

FURTHER READING Hydbring, P., Malumbres, M. & Sicinski, P. Non-canonical functions of cell cycle cyclins and cyclin-dependent kinases. *Nat. Rev. Mol. Cell Biol.* **17**, 280–292 (2016)