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CELL CYCLE

A centrosome-integrity checkpoint

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URLs

CDK2
http://ca.expasy.org/uniprot/P24941

P21
http://ca.expasy.org/uniprot/P38936

P53
http://ca.expasy.org/uniprot/P04637

> "…loss of centrosome integrity activates a checkpoint that inhibits G1–S progression."

Centrosomes are best known for their role as microtubule-organizing centres, but recent studies have implied that they also function in cell-cycle progression from G1 into S phase. A new study by Stephen Doxsey and colleagues now provides evidence that loss of centrosome integrity activates a checkpoint that inhibits G1–S progression.

The Doxsey group depleted 15 different centrosome proteins in human cells and found that all depletions but one caused cell-cycle arrest in G1 phase. Expression of a centrosome protein construct that disrupts centrosomes in a dominant-negative manner gave similar results. In addition, the G1 arrest was specifically 'rescued' by re-expression of the targeted gene. The targeted centrosome proteins were localized to different centrosomal sites, which implies that no single centrosome substructure is responsible for the arrest.

Next, the authors showed that arrest was induced postmitotically in cells that expressed the dominant-negative centrosome protein construct. The G1 arrest was accompanied by reduced CDK2–cyclin A activity, but not cyclin A levels, which implied the presence of a CDK inhibitor. Indeed, loss of the CDK inhibitor p21 suppressed the G1 arrest, which implicates p21 in the inhibition of CDK2–cyclin A activity.

Immunofluorescence imaging revealed that all G1-arrested cells showed one or more centrosome defects, such as centriole loss, centriole separation and centriole fragmentation. Centrosomes have specific functions during G1, namely centrosome duplication and primary cilia assembly, both of which were also defective in the G1-arrested cells. Defects in centrosome structure and function therefore seem to correlate closely with centrosome-associated G1 arrest.

But what is the regulatory pathway that inhibits cell-cycle progression in centrosome-defective cells? Doxsey and colleagues observed the nuclear translocation of p53 in small interfering RNA-treated cells, but not in control cells, prior to G1 arrest. Also, cells that contained mutated p53 did not undergo G1 arrest, and when cells were concurrently depleted of centrosomal proteins and p53, G1 arrest was also suppressed. These findings indicate that centrosome-associated G1 arrest is p53 dependent.

In cells depleted of centrosomal proteins, p53 was activated by the phosphorylation of residue Ser33 — a known substrate of p38 kinase. This phosphorylation was not observed in control cells, and inhibition or depletion of p38 before centrosome depletion suppressed G1 arrest. Using immunofluorescence microscopy, the authors showed that, in response to centrosomal protein depletion, the p38-phosphorylated form of p53 accumulated at centrosomes before it translocated to the nucleus. This implies a multistep p53- and p38-dependent pathway for centrosome-associated cell-cycle arrest.

So, the authors propose the existence of a cell-cycle checkpoint that monitors centrosome integrity and controls G1–S progression. The regulatory pathway involves the activation of p53 by p38 and, in turn, p53 activates p21, which inhibits the CDK2–cyclin A complex. Indeed, tumour cells that lack p53 frequently show the consequences of checkpoint abrogation, including spindle defects and aneuploidy.

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ORIGINAL RESEARCH PAPER Mikule, K. *et al.* Loss of centrosome integrity induces p38–p53–p21-dependent G1–S arrest. *Nature Cell Biol.* 24 Dec 2006 (doi:10.1038/ncb1529)

WEB SITE

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