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CELL SIGNALLING

Signalling to cell cycle arrest

During mitosis, duplicated centrosomes organize a bipolar spindle, which is crucial for maintaining the fidelity of chromosome segregation. In non-transformed cells, centrosome loss leads to p53-mediated cell cycle arrest, which might protect from genomic instability induced by aberrant mitosis in the absence of centrosomes. However, the mechanisms through which centrosome loss is sensed and signals to cell cycle arrest are poorly understood.

To identify molecular components of the response to centrosome loss, the Holland, Oegema and Tsou groups performed independent, genome-wide CRISPR–Cas9-mediated knockout screens for the suppression of cell cycle arrest following centrosome loss in human retinal pigment epithelial (RPE) cells. All three groups identified p53-binding protein 1 (53BP1; also known as TP53BP1) and the deubiquitylase ubiquitin carboxyl-terminal hydrolase 28 (USP28) as top hits. Apart from mediating cell cycle arrest in centrosome depleted cells, both 53BP1 and USP28 were necessary for the stabilization of p53 in these cells. In more detail, the Tsou group revealed that USP28 acts downstream of 53BP1 and that its deubiquitylase activity is necessary for p53 stabilization. They also showed that USP28 directly deubiquitylates p53 *in vitro*.

Prolonged mitosis, exceeding a defined threshold (~90 minutes in RPE cells), activates a 'mitotic timer' that senses aberrant mitosis and prevents cell cycle re-entry, thereby arresting cells in G1 phase. Notably, both 53BP1 and USP28 were found to be important for the activation of this mitotic timer, as their knockout abolished cell cycle arrest following prolonged mitosis in response to various insults. In addition, the role of the 53BP1–USP28–p53 signalling axis in mediating cell cycle arrest was found to be independent of the function of these proteins in DNA damage response. This indicates that both centrosome loss and mitotic delay induce cell cycle arrest through the 53BP1–USP28–p53 signalling axis, and that this response is independent of DNA damage. Interestingly, in centrosome-depleted cells, mitotic timer activation was not clearly correlated with cell cycle stalling. This suggests that it is perhaps the cumulative stress of consecutive, prolonged mitoses, each occurring below the mitotic timer activation cut-off, that signals to induce cell cycle arrest when centrosomes are depleted.

Together, these studies delineate a signalling axis that governs cell cycle arrest in response to insults associated with mitotic delay, such as centrosome loss. Moving forward, it would be important to uncover a direct trigger (or triggers) mediating this cell cycle arrest.

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ORIGINAL ARTICLES Lambrus, B. G. *et al.* A USP28–53BP1–p53–p21 signaling axis arrests growth after centrosome loss or prolonged mitosis. *J. Cell Biol.* **214**, 143–153 (2016) | Meitinger, . *et al.* 53BP1 and USP28 mediate p53 activation and G1 arrest after centrosome loss or extended mitotic duration. *J. Cell Biol.* **214**, 155–166 (2016) | Fong, C. S. *et al.* 53BP1 and USP28 mediate p53-dependent cell cycle arrest in response to centrosome loss and prolonged mitosis. *eLife* **5**, e16270 (2016)