Genome wide screen identifies USP28 and SPINT2 as novel factors mediating cell cycle arrest after whole genome doubling

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K. Seget-Trzensiok[I], S. Bernhard[I], C. Kuffer[II], Z. Storchova[I]

[I]TU Kaiserslautern, Kaiserslautern, Germany, [II]Max Planck Institute of Biochemistry, Munich, Germany

Growing body of evidence shows many solid tumors have undergone whole genome doubling (WGD) during their development. Tetraploid cells possessing doubled set of chromosomes are found in all stages of cancer, supporting a role of WGD in cancer evolution and progression. How exactly genome doubling events favour cancer development is not fully understood. Moreover, proliferation of newly arising tetraploids is limited by activation of the p53 tumor suppressor. We observed that less than 1% of cells were able to stably propagate after whole genome doubling. However, how tetraploids escape the p53-mediated cell cycle arrest remains poorly understood. To uncover the mechanisms contributing to the p53-dependent cell cycle arrest after whole genome doubling, we have performed an esiRNA genome wide screen in human cells. We have identified 140 candidate genes that might be involved in regulation of this cell cycle arrest. Further validation confirmed two genes that might regulate the p53 dependent arrest of tetraploid cells: USP28, coding for a deubiquitinase that was described to play a role in DNA damage as well as in response to loss of centrosome, and SPINT2, a tumor suppressor frequently inactivated in cancer. Depletion of these two candidates improves proliferation of tetraploid cells by independent mechanisms. Taken together, we describe novel players in regulation of cell cycle arrest upon tetraploidization, whose dysfunction may lead to tolerance of genome duplication.