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Role of ubiquitin-conjugating enzymes in chromosome instability and breast cancer metastasis

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Introduction

Chromosome Instability (CIN) is a hallmark of cancer being aneuploidy found in most of the tumors. In addition, high levels of CIN in primary tumors predict poor outcome in several cancer types, including breast cancer (BC). During last years, it has been demonstrated the role of aneuploidy during primary tumor generation in some transgenic mouse models. However, the role and functional consequences of CIN and aneuploidy during the metastatic process has not been deeply explored.

Material and Methods

- CIN70 signature (Carter et al 2006, Nat Genet) was obtained by analyzing RNA expression data from paired primary and metastatic tissues from BC (Cejalvo et al 2017, Cancer Research).
- Previous screening from the group identified several candidate genes potentially relevant for BC dormancy in dormant bone metastatic BC cells (DBM)(Gawrzak et al 2018, Nat Cell Biol).
- WB and IF were performed for analysis of mitosis and study of chromosome segregation.
- Cells were labeled with GFP-Luciferease for tracking tumor cells in mice.

Results and Discussions

We compared a signature of chromosome instability (CIN70) between paired primary and metastatic tissues form BC. CIN70 score is clearly increased in metastasis, emphasizing the importance of aneuploidy for the acquisition of the traits required for cancer metastasis in BC. Additionally, taking advantage from a previous loss of function screening approach in DBM cells we have identified an Ubiquitin-conjugating enzyme (UBE) as a candidate gene to control metastasis in BC. UBE has a pivotal role during cell division by controlling the stability of key mitotic players. UBE abrogation prolongs the spindle assembly checkpoint in several BC lines, thus delaying mitosis exit. Further analysis shows that UBE depletion impaired the normal segregation of chromosomes during cell division increasing aneuploidy rates. Interestingly, in vivo studies with different BC cell lines show an increase in the metastatic abilities of UBE downregulated cells.

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