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Joint Event

2nd International Conference on

Tissue Science and Molecular Biology, Stem Cells & Separation Techniques

June 06-07, 2019 | London, UK

Biomed Res, Volume 30
ISSN: 0976-1683

Investigation into the mechanism regulating mitotic DNA synthesis (MiDAS)

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All multicellular organisms develop via proliferation-dependent growth, which requires full genome duplication for each mitotic division. Cells with unreplicated DNA fragments may occasionally proceed to mitosis by bypassing canonical checkpoint activation. The resulting under-replicated regions are particularly prevalent following replication stress, as seen for instance, in cancer cells. They can be fixed by a recently characterized mechanism-mitotic DNA synthesis (MiDAS). Here, we investigate the upstream regulation of this process in osteosarcoma cells following induction of aphidicolin-mediated replicative stress and cell synchronisation. Candidate components of the cell-cycle regulating machinery were ablated using RNAi and MiDAS was quantified using EdU incorporation during mitosis. Collectively, our results expose a vital role of BRCA2 and the UBR5 complex in regulating MiDAS, which facilitates a last-resort protective response to unreplicated genome regions in mitosis. Mechanistically, we propose that BRCA2-mediated RAD51 phosphorylation and UBR5-dependent chromatin clearance promote MiDAS. Our results uncover new potential factors that could be exploited therapeutically in cancer treatment.

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