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The aberrant expression of ISWI regulatory subunit *RSF1* induces oncogenic reorganization of 3D genome that leads DNA repair defect

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Amplification of 11q13 locus is frequently found in breast and ovarian cancer. Among the potential oncogenes on 11q13 amplicon, *RSF1*, the regulatory subunit in ISWI family, is one of the putative oncogenes and is often overexpressed in various cancer types with a poor prognosis. However, the precise mechanism by which *RSF1* overexpression promotes cancer progression remains unclear. In this study, we investigated the impact of *RSF1* overexpression on chromatin architecture and its implications for the DNA damage response. Our findings revealed that *RSF1* overexpression increased CTCF and cohesin binding within topologically associating domains (TADs) by altering chromatin accessibility. In addition, SNF2h, the ATPase of ISWI family frequently overexpressed with RSF1 in ovarian carcinoma, was simultaneously enriched at *de novo* CTCF binding sites by *RSF1* overexpression. Consequently, Hi-C analyses demonstrated that individual TADs were often sub-compartmentalized by CTCF-mediated insulation. Upon DNA damage, super resolution imaging analyses showed that the altered 3D chromatin architecture failed to establish the chromatin microdomains of 53BP1 and BRCA1 repair proteins, leading to DNA repair defect. Thus, our study demonstrates that the aberrant expression of *RSF1* in cancer leads genomic instability through the formation of oncogenic 3D genome structure.