DNA DAMAGE

Wrap-around care

The existence of regions of DNA that are difficult to replicate is exemplified by chromosome fragile sites. These sites are overtly sensitive to small changes in the rate of DNA synthesis and can result in breaks in mitotic chromosomes. Recent data have shown that these regions can be connected by ultrafine DNA bridges (UFBs) and that this connection could enable the segregation of regions of under-replicated DNA. However, it is unclear what the fate of these regions is after mitosis. Jiri Bartek, Jiri Lukas and colleagues noted that a number of publications have reported the presence of distinct regions in the nucleus that contain the DNA double-strand break (DSB) repair protein 53BP1. Having established that 53BP1 was joined in these regions by a host of proteins that are involved in DNA repair, the authors looked for the instigators of the DNA damage. Using various approaches they found that low levels of replication stress maximally increased the number of 53BP1 ‘nuclear bodies’. Surprisingly, these bodies did not arise in the S and G2 phases of the cell cycle, which would be expected if they marked stalled replication forks that had collapsed

and resulted in DSBs, but were instead prominent in G1, during which DNA does not replicate. Moreover, there was a striking consistency between the position and number of the 53BP1 nuclear bodies in daughter cells, but this pattern changed in subsequent mitoses.

So, what do the 53BP1 nuclear bodies mark? Further investigations showed that 53BP1 can be found at fragile sites under conditions of mild replication stress. In addition, gaps or breaks at fragile sites in mitotic chromosomes were marked by proteins involved in DSB repair, such as γ H2AX, and these foci correlate with 53BP1 nuclear bodies present in G1. It seems that 53BP1 nuclear bodies function to shield the regions of DNA breaks that are induced by replication stress, as knock down of 53BP1 increases the amount of unrepaired DNA at fragile sites.

The authors conclude that in addition to the formation of UFBs in mitosis, 53BP1 nuclear bodies mark DNA and chromatin lesions that arise as a result of under-replicated DNA and sequester these into nuclear compartments that might enable the repair of these lesions

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ahead of the next S phase. Failure of this mechanism could increase genomic instability and sits well with the finding that somatic homozygous deletions in cancers are associated with fragile sites.

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ORIGINAL RESEARCH PAPER Lukas, C. et al. 53BP1 nuclear bodies form around DNA lesions generated by mitotic transmission of chromosomes under replication stress. *Nature Cell Biol.* 13 Feb 2011 (doi:10.1038/ncb2201)

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