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Non-homologous end joining of complex DNA double-strand breaks with proximal thymine glycol and interplay with base excision repair

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DNA double-strand breaks induced by ionizing radiation are often accompanied by ancillary oxidative base damage that may prevent or delay their repair. In order to better define the features that make some DSBs repair-resistant, XLF-prevent or delay their repair. In order to better define the features that make some DSBs repair-resistant, XLF-dependent non-homologous end joining of blunt-ended DSB substrates having the oxidatively modified non-planar base thymine glycol at the first (Tg1), second (Tg2), third (Tg3) or fifth (Tg5) positions from one 3_terminus, was examined in human whole-cell extracts. Tg at the third position had little effect on end-joining even when present on both ends of the break. However, Tg as the terminal or penultimate base was a major barrier to end joining (>10-fold reduction in ligated products) and an absolute barrier when present at both ends. Dideoxy trapping of base excision repair intermediates indicated that Tg was excised from Tg1, Tg2 and Tg3 largely if not exclusively after DSB ligation. However, Tg was rapidly excised from the Tg5 substrate, resulting in a reduced level of DSB ligation, as well as slow concomitant resection of the opposite strand. Ligase reactions containing only purified Ku, XRCC4, ligase IV and XLF showed that ligation of Tg3 and Tg5 was efficient and only partially XLF-dependent, whereas ligation of Tg1 and Tg2 was inefficient and only detectable in the presence of XLF. Overall, the results suggest that promoting ligation of DSBs with proximal base damage may be an important function of XLF, but that Tg can still be a major impediment to repair, being relatively resistant to both trimming and ligation. Moreover, it appears that base excision repair of Tg can sometimes interfere with repair of DSBs that would otherwise be readily rejoined.

Biography

Mohammed Al Mohaini is an Assistant Professor of Pharmacology at KSAU-HS, Saudi Arabia. His research interest is on "The effect of cancer chemotherapeutic drugs on the DNA especially the repair of DNA double-strand breaks induced by these compounds".

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