

Suffering the Slings and Arrows: Role of Host Cell Functions in Post-Integration Repair. René Daniel, Konstantin D. Taganov, James Greger, Richard A. Katz, and Anna Marie Skalka.* Fox Chase Cancer Center, Institute for Cancer Research, 333 Cottman Avenue, Philadelphia, PA 19111-2497 U.S.A.

The joining of retroviral and host DNA, mediated by the viral integrase, creates a discontinuity in the host cell chromatin. It appears that this discontinuity is sensed as DNA damage by the cell: our previous results have provided strong evidence that post-integration repair of this lesion is mediated mainly via components of the cellular non-homologous end-joining pathway. An ATM (ataxia- telangiectasia mutated)-dependent, alternative pathway has also been implicated, which we hypothesize may depend on components of the homologous recombination repair system. Finally, computational simulations as well as evidence of a requirement for ATR (ATM and Rad-related) function in post-integration repair suggest a link with cellular DNA replication. Based on these results we have proposed a model for post-integration repair in cycling cells. A brief description of the approaches used in these studies and key observations will be presented, along with further tests of this model. Knowledge of how retroviruses exploit the relevant host functions can provide new insight into cellular DNA damage response and repair mechanisms and may identify cellular targets for antiviral drug development.

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