

# DNA-PK targeting virotherapy, a promising approach

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Submitted Apr 15, 2012. Accepted for publication May 02, 2012.

DOI: 10.3978/j.issn.2218-676X.2012.05.03

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Inhibition of DNA double strand break repair definitely increases radiosensitivity, which is a promising strategy to enhance therapeutic effects of radiotherapy to cancers. For this purpose, targeting the repair enzymes, especially DNA-PK, have been reported using compounds such as caffeine, wortmannin, antisense oligodeoxynucleotides, NU7026, IC87361, NU7441 (1-5). Those innovative drug developments and pre-clinical studies are promoting the implementation of DNA-PK inhibiting drugs as radiosensitizers. However, in order to prove their clinical efficacy, we have to overcome the obstacle of their lack of selectivity to cancer cells as well as to confirm their safety to normal tissues. In contrast, targeting DNA-PK has also been attempted by specific gene knockdown using siRNA or shRNA (6,7). In order to deliver particular genes to cancer cells only, the development of oncolytic viruses has been accelerated since the milestone report of Martuza published in 1991 (8). The greatest advantage of this strategy is its selectivity to cancer cells. Although it has now become a major and attractive trend of selective gene delivery method, clinical results have been disappointing so far even though its safety and pre-clinical results were shown to be promising. In this issue of TCR, Takashi Kon *et al.* (9) report that the oncolytic adenovirus which has an insert of antisense DNA-PK shRNA can significantly enhance radiosensitivity by inhibition of DNA-PK activity in colon cancer cells. An innovative finding of their work is that the delivery of oncolytic virus targeting DNA-PK was significantly improved when it was co-transfected with a different oncolytic virus which is targeted to telomerase. They mention that co-infection of two viruses would allow both vectors to selectively replicate in telomerase-positive cancer cells. Although the further precise mechanism of this

phenomenon remains to be clarified, this pre-clinical study clearly demonstrates that efficient delivery and specific gene knockdown can be achieved simultaneously with their method. Their work may also indicate that a strategy of unifying oncolytic virotherapy with conventional therapies such as radiotherapy is more practical than conducting virotherapy alone to eradicate cancers.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Translational Cancer Research*. The article did not undergo external peer review.

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.3978/j.issn.2218-676X.2012.05.03>). KT serves as an unpaid editorial board member of *Translational Cancer Research*. The author has no other conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Cite this article as:** Tsuboi K. DNA-PK targeting virotherapy, a promising approach. *Transl Cancer Res* 2012;1(1):2-3. DOI: 10.3978/j.issn.2218-676X.2012.05.03