LINE1 expression and radio-response in rectal cancer cells

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Abstract

All patients diagnosed with locally advanced rectal cancer in the UK routinely receive radiotherapy as a pre-operative neoadjuvant with varied response rates and ¯˜20% of tumours showing no response or disease progression. Effective markers to predict radiotherapy response would not only protect non-responsive patients from the debilitating effect of unnecessary treatment but also avoid the risks associated with surgery in fully responsive patients. Ionising radiation drives a global decrease in methylation that is most pronounced at Long Interspersed Nuclear Elements-1 (LINE1s), a family of retrotransposons which are usually silenced in healthy cells. LINE1 hypomethylation is considered synonymous with LINE1 activation, however, LINE1 expression profiles have not been thoroughly characterised in irradiated cells. To investigate the relation between LINE1 expression and radio-response, we measured LINE1-5'UTR RNA in response to increasing radiation doses in two rectal cancer cell lines, the more sensitive SW837 and the more resistant HT55.

We observed an increase in LINE1-5'UTR RNA upon radiation in SW837 cells but not in HT55 cells. We then used CRISPR/Cas9 mediated HDR to generate SW837 cells stably expressing shRNAs designed on the endo453 sequence, a naturally occurring endogenous siRNA that specifically targets the LINE1 5'UTR. A decrease in LINE1-5'UTR containing RNAs and in ORF1P protein levels in SW837 cells constitutively expressing sh-endo453 are linked to an increased resistance to radiation compared to non-transfected cells.
We hypothesize that the rise in LINE1 expression contributes to increased radiosensitivity in SW837 cells. Further work is needed to validate these findings and determine whether LINE1/ORF1P expression can be utilised as a marker of response to radiation.

Keywords: Radioresponse, LINE1, endo453, rectal cancer, ORF1P

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