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Polymeric micelles of a novel inhibitor of DNA repair enzyme, polynucleotide kinase/phosphatase (PNKP), for targeted treatment of non-small cell lung cancer as monotherapy or in combination with irinotecan

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INTRODUCTION

Concomitant disruption of polynucleotide kinase/phosphatase (PNKP), an enzyme involved in DNA repair, and the tumor suppressor protein phosphatase and tensin homologue (PTEN), lead to synthetic lethality in different cancer models[1]. Downregulation of PTEN is a frequent observation in non-small lung cancers (NSCLC), thus, pharmacological disruption of PNKP is expected to provide a viable and targeted mono-therapeutic strategy in NSCLC. Inhibition of PNKP can also make NSCLC more susceptible to cytotoxic effects of topoisomerase I inhibitors. Recently, the development of a potent PNKP inhibitor, namely A83B4C63, and its polymeric micellar formulations has been reported by our group[2].

OBJECTIVES

The aim of the present study was to develop polymeric micelles of A83B4C63 modified on their surface with a peptide sequence (i.e., H2009) for targeting $\alpha_v\beta_6$-integrins ($\alpha_v\beta_6$-INT) in NSCLC cells. We also assessed the activity of A83B4C63 in NSCLC cell lines showing different levels of PTEN expression as monotherapy or in combination with irinotecan.

METHODS

Polymeric micelles composed of poly(ethylene oxide)-poly(ε-caprolactone) (PEO-PCL) and poly(ethylene oxide)-poly(α-benzyl carboxylate-ε-caprolactone) (PEO-PBCL) were prepared for encapsulating A83B4C63 compound and characterized accordingly. The peptide H2009 was attached to the PEO block through thiol-maleimide "click" chemistry. Finally, the anti-cancer effect of A83B4C63 was assessed using the colony-forming assay in two NSCLC cell lines (i.e., H1975 and H1299) as a monotherapy or in combination with irinotecan.

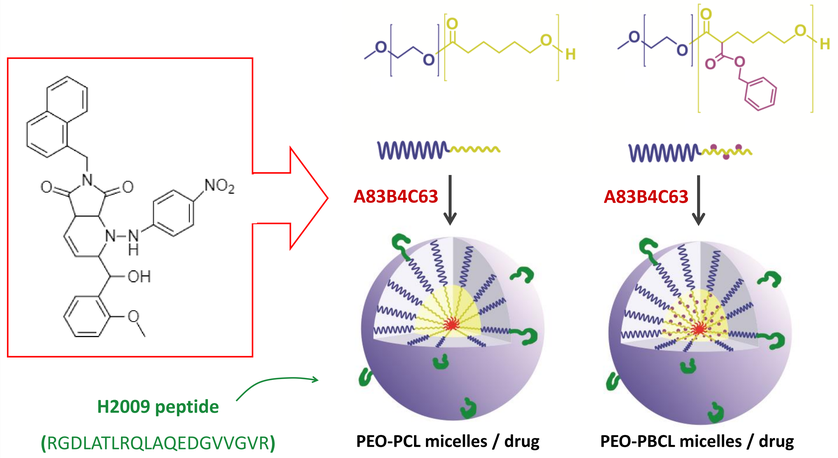

Figure 1. Representation of the nanoencapsulation of A83B4C63 drug into the polymeric micelles.

RESULTS

Table 1. Characterization of polymeric micelles.

Polymeric micelles	Size (nm)	EE (%)	DL (%)
Plain-PEO-PCL	56.5 ± 0.48	74.1	33.3
Plain-PEO-PBCL	51.4 ± 0.29	89.0	29.7
H2009-PEO-PBCL	68.5 ± 0.09	92.7	31.0

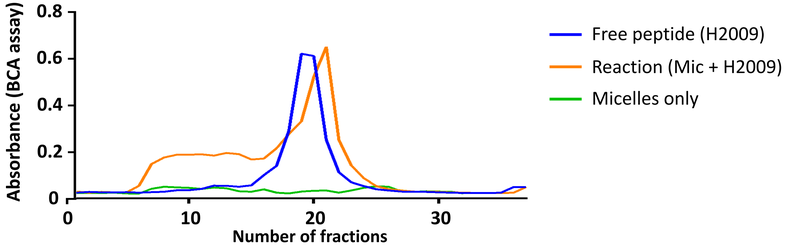

Figure 2. Size exclusion chromatograms (SEC) of H2009 peptide, PEO-PBCL and the reaction between them. The peptide was detected by BCA assay. The yield of H2009 attachment to the micelles was ~40%.

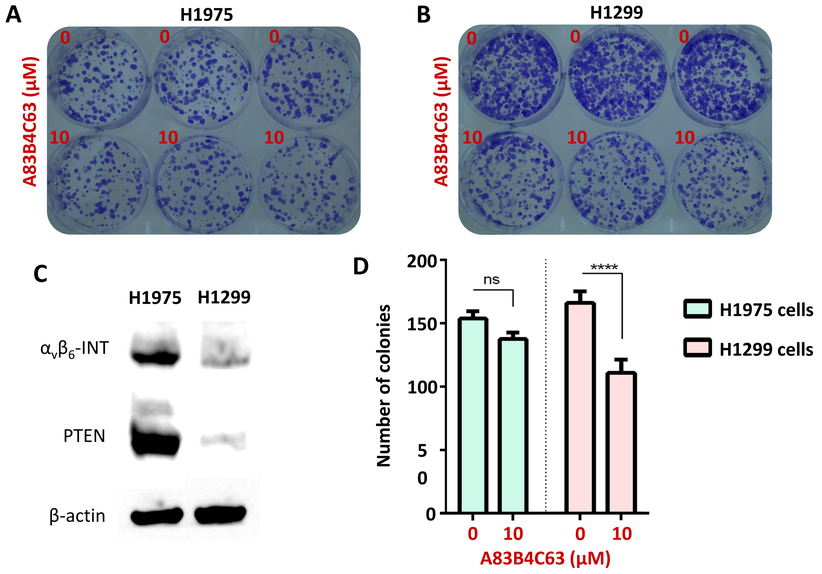

Figure 3. *In vitro* experiments in NSCLC cells. (A, B, and D): Effect of monotherapy using only A83B4C63 drug. (C): Identification of $\alpha_v\beta_6$-integrin and PTEN expression in two NSCLC cell lines.

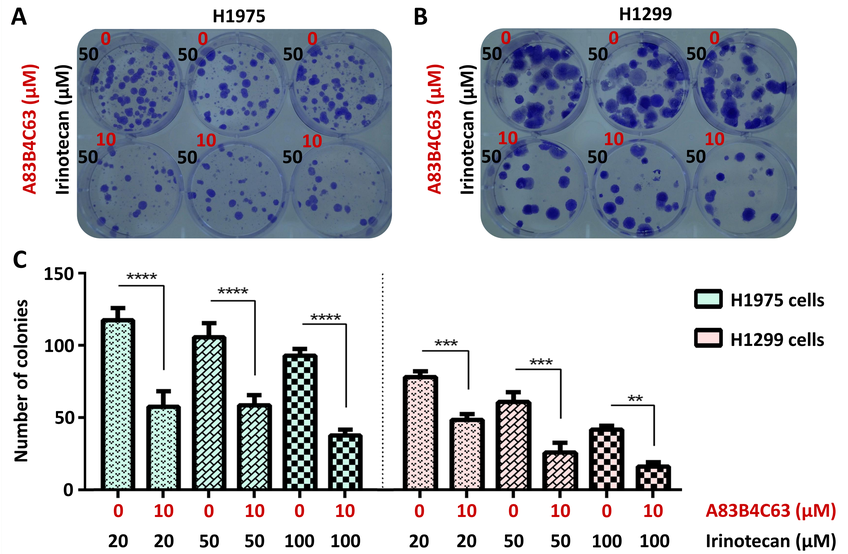

Figure 4. Sensitization strategy using A83B4C63 to irinotecan treatment in NSCLC cells. (A, B, and C): Effect of combination therapy using both drugs.

CONCLUSION

The results evidenced a synthetic lethal relationship between PTEN expression and A83B4C63 treatment in NSCLC cell lines. The chemo-sensitizing activity of A83B4C63 towards irinotecan in NSCLC cell lines was also significantly effective, particularly to the cell line with normal expression of PTEN. Interestingly, our data showed a successful generation of H2009-modified micelles for potential NSCLC targeted delivery of A83B4C63.

Taken together, this study indicates a potential for polymeric micellar formulations of A83B4C63 as mono-therapeutics in PTEN-deficient NSCLC cells and/or as targeted sensitizers to topoisomerase I inhibitors in NSCLC models.

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