The mechanism of SIRT6-mediated de-2-hydroxyisobutyrylation modification of hnRNP-Q1 in regulating the progression of cervical cancer

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Abstract

This study aimed to elucidate HPV-associated pathogenesis and identify potential molecular targets for cervical cancer therapy. We investigated the oncogenic mechanism of HPV E6/E7 by focusing on its regulation of 2-hydroxyisobutyrylation in hnRNP Q1. We further demonstrated that HPV E6/E7 modulates SIRT6-mediated de-2-hydroxyisobutyrylation of hnRNP Q1, thereby promoting cervical cancer cell invasion and angiogenesis. Our results illustrated that hnRNP-Q1 and SIRT6 as important regulators of tumorigenesis during cervical cancer pathogenesis and establish the scientific basis for targeting these molecules for treating CC.

Results

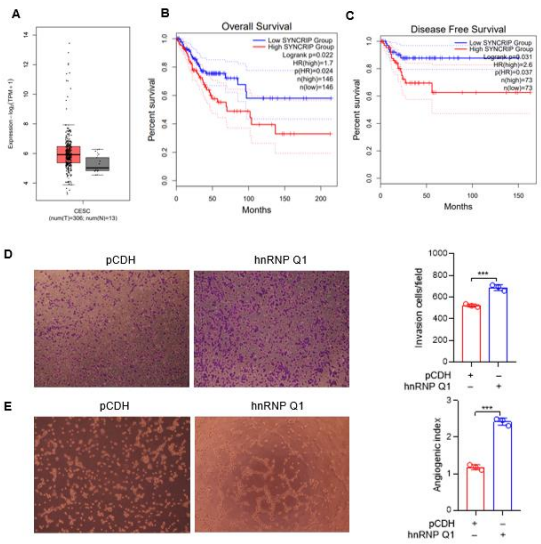

Fig1. High expression of hnRNP Q1 in cervical cancer correlates with poor prognosis and promotes cancer cell invasion and angiogenesis.
(A) Expression pattern of hnRNP Q1 in cervical cancer tissues.
(B) Overall survival is lower in cervical cancer patients with high hnRNP Q1 expression than in those with low expression ($p < 0.05$).
(C) Disease-free survival is lower in cervical cancer patients with high hnRNP Q1 expression than in those with low expression ($p < 0.05$).
(D) Representative images and quantitative results of Transwell invasion assay in hnRNP Q1-overexpressing and control cells (***$P < 0.001$).
(E) Representative images and quantitative results of tube formation assay in hnRNP Q1-overexpressing and control cells (***$P < 0.001$).

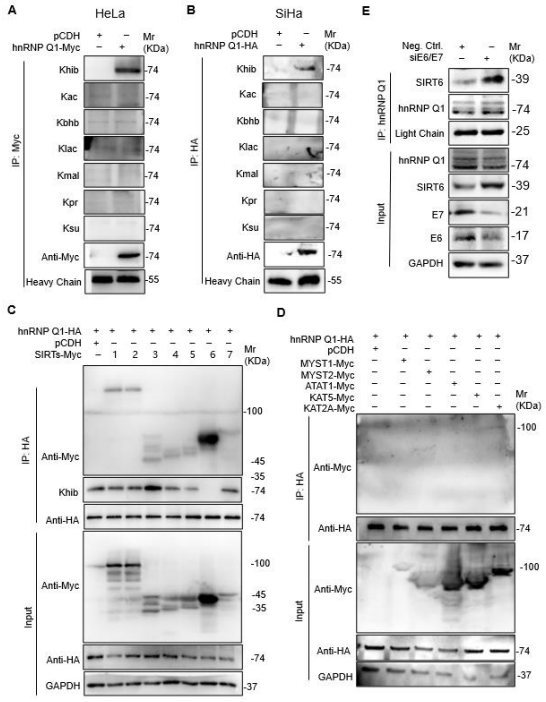

Fig2. SIRT6 regulates the de-2-hydroxyisobutyrylation modification of the hnRNP-Q1, and HPV E6/E7 is involved in regulating the level of this modification.
(A) hnRNP Q1 protein undergoes 2-hydroxyisobutyrylation in HeLa cell lines.
(B) hnRNP Q1 protein undergoes 2-hydroxyisobutyrylation in SiHa cell lines.
(C) SIRT6 regulates the de-2-hydroxyisobutyrylation of hnRNP Q1.
(D) Lysine acyltransferases MYST1、MYST2、ATAT1、KAT5 and KAT2A do not bind to hnRNP Q1 protein.
(E) HPV E6/E7 inhibits the interaction between SIRT6 and hnRNP Q1 protein.

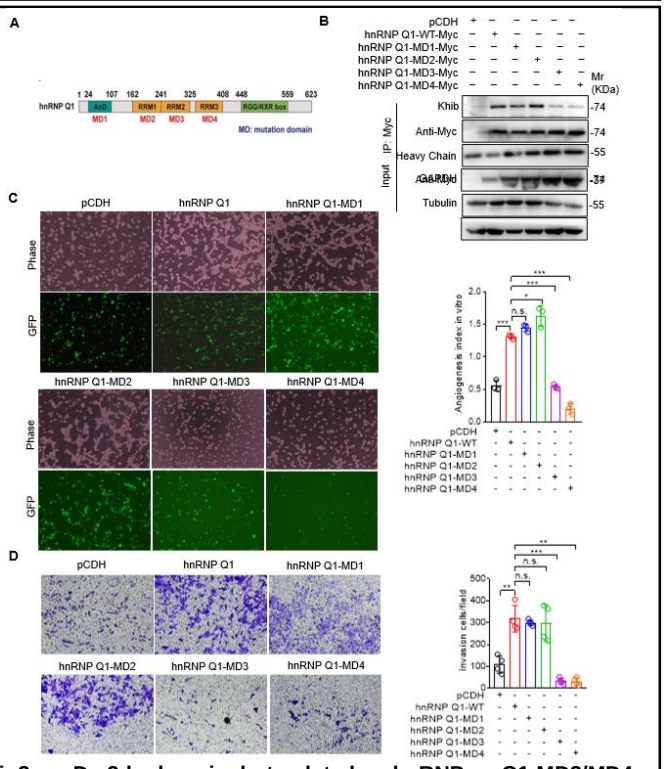

Fig3. De-2-hydroxyisobutyrylated hnRNP Q1-MD3/MD4 domains suppress the invasion and angiogenesis in cervical cancer cells.
(A) Schematic diagram of lysine mutation sites in hnRNP Q1 protein.
(B) Effect of lysine mutations within hnRNP Q1-MD1, -MD2, -MD3, and -MD4 on the 2-hydroxyisobutyrylation level of hnRNP Q1 detected by Co-IP.
(C) Tube formation assay and quantitative analysis in six groups of cells (pCDH, hnRNP Q1, hnRNP Q1-MD1/-MD2/-MD3/-MD4). ***$P < 0.001$, **$P < 0.01$, *$P < 0.1$; n.s., not significant.
(D) Matrigel invasion assay and quantitative analysis in six groups of cells (pCDH, hnRNP Q1, hnRNP Q1-MD1/-MD2/-MD3/-MD4). ***$P < 0.001$, **$P < 0.01$; n.s., not significant.

Conclusions

- High hnRNP Q1 expression is associated with poor prognosis and facilitates invasion and angiogenesis in cervical cancer.
- SIRT6 mediates de-2-hydroxyisobutyrylation of hnRNP Q1, which is regulated by HPV E6/E7.
- De-2-hydroxyisobutyrylation within the MD3/MD4 domains of hnRNP Q1 contributes to tumorigenesis in cervical cancer.

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