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Transcriptional and posttranscriptional upregulation of p27 mediates growth inhibition of isorhapontigenin (ISO) in human bladder cancer cells

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There are few approved drugs available for the treatment of muscle invasive bladder cancer (MIBC). Recently, we have demonstrated that Isorhapontigenin (ISO), a new derivative isolated from the Chinese herb *Gnetum cleistostachyum*, effectively induces cell-cycle arrest at the G0/G1 phase and inhibits anchorage-independent cell growth through the miR-137/Sp1/cyclin D1 axis in human MIBC cells both *in vitro* and in vivo. Herein, we show that treatment of MIBC cells with ISO resulted in a significant upregulation of p27, a key cyclin-dependent kinase (CDK) inhibitor. Importantly, knockdown of p27 caused a decline in the ISO-induced G0-G1 growth arrest and reversed ISO suppression of anchorage-independent growth in MIBC cells. Mechanistic studies revealed that ISO promoted p27 expression at mRNA transcription level through an increase in the direct binding of FOXO1 to its promoter, while knockdown of FOXO1 attenuated ISO inhibition of MIBC cell growth. On the other hand, ISO upregulated the 3'UTR activity of p27 which was accompanied by a reduction of miR-182 expression. In line with these observations, ectopic expression of miR-182 did significantly block p27 3'UTR activity, whereas mutation of the miR-182 binding site at p27 3'UTR effectively reversed this inhibition and led to a significant loss of ISO induction effect on its activity, indicating that miR-182 is able to bind directly to p27 3'UTR and repress its activity in MIBC cells. Accordingly, ectopic expression of miR-182 also attenuated ISO upregulation of p27 expression and impaired ISO inhibition of BC cell growth. These studies reveal that p27 expression is transcriptionally upregulated by enhancing binding of FOXO1 to its promoter, and that it is post-transcriptionally induced through decreasing binding of miR-182 to its mRNA 3'UTR upon ISO treatment. Our results not only provide novel insight into understanding of the underlying mechanism related to regulation of MIBC cell growth, they also identify a new role and mechanisms underlying ISO inhibition of the growth.

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