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Up-regulation of KRT14 Promotes EMT in Basal Muscle-invasive Bladder Cancer through IGF2BP1/FTO Dependence on Methyladenosine-modified SNAI1

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Abstract : Basal muscle-invasive bladder cancer (BMIBC) is considered one of the subtypes of BC with the highest metastatic rate and the poorest prognosis. Therefore, elucidating the mechanisms underlying BMIBC metastasis and identifying novel precision therapeutic targets are current research hotspots and challenges to cancer researchers. Through a series of in vitro and in vivo functional experiments, we have identified the crucial role of KRT14 in the high invasiveness and adverse prognosis of BMIBC. We found that the K294 site within the IGF2BP1-KH2 domain is responsible for reading the conserved genetic information carried by D226/E227 in the KRT14 nuclear export signal (NES). Activation of the KRT14-IGF2BP1 signaling axis is essential for IGF2BP1-mediated stabilization of SNAI1 mRNA through FTO modification. Additionally, IGF2BP1 forms a positive feedback loop by stabilizing its own mRNA, thereby accelerating the invasion and metastasis of BMIBC. Collectively, our study identifies the KRT14/IGF2BP1/FTO/Snail signaling axis as an essential regulatory mechanism associated with poor prognosis in BMIBC, providing a theoretical basis for KRT14 and its downstream regulated molecules as therapeutic targets for BMIBC and the development of corresponding targeted therapies.

Keywords : BMIBC, KRT4, IFGF2BP1, DNA methylation
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