Slug transcription factor activates its own expression during epithelial to mesenchymal transition

Cancer is a highly aggressive and challenging disease. In several instances, symptoms are not evident until the disease progresses to an advanced stage and hence, it is amongst the leading causes of human mortality. Despite considerable attempts towards early detection and development of advanced therapy, metastatic relapses remain the most important challenge.

One of the mechanisms that have presently received considerable attention in studies on cancer metastases is epithelial to mesenchymal transition (EMT). EMT is a complex reprogramming process by which epithelial cells undergo loss of epithelial markers expression and gain mesenchymal markers to acquire new characteristics through corresponding morphogenetic changes including a migratory phenotype. Altered gene expression of epithelial markers and mesenchymal markers in EMT is brought about by specific transcription factors such as Slug that are now recognized as master regulators of the process. Expression of these regulators is often activated early in EMT and they play an essential role in progression of cancer.

Transcriptional repression mediated by Slug is believed to involve the five C2H2 zinc fingers (ZF1-ZF5) in its C-terminal DNA binding domain that interact with specific sequences (E-box element: 5'-CANNTG-3') in promoter region of target genes. Understanding these phenomena is important since Slug contributes to the invasive nature of tumor cells which facilitates metastasis during cancer progression.

In this study by Kumar et al, the transcription factor Slug not only acts as a transcriptional repressor, but also directly activates its own expression by preferential binding to specific E-box elements in the distal binding region of its own promoter. Moreover, the preferred order of binding to specific E-box elements within promoter further indicates in vitro affinity may not be predictive of similar binding in situ. This emphasizes the importance of the cellular context in target recognition and importantly, suggests that the genome comprises of far more potential transcription factor binding sites than can be really occupied in vivo. Most of these may be redundant and a fraction preferentially involved in target gene regulation under different conditions. Kumar et al. also identified that the first ZF of Slug does not contribute to its transcription-associated functions, while all remaining four ZFs are involved in regulating the expression of target genes with ZF3 and ZF4 likely to be more crucial than ZF2 or ZF5.

Functional analysis of E-boxes suggests that presence of these elements within the proximal promoter regions mediate transcriptional repression, while those in distal promoter regions may be involved in transcriptional activation. Such functional demarcations also rely on recruitment and association of cofactors (either co-repressors such as HDACs, CtBP1 or co-activators including CBP/p300, Smad4) in a context-specific manner. This finding in fact, provides an understanding about the modulation of Slug target gene profiles under varying cellular contexts.

In conclusion, we propose a model in which Slug activate its own expression by creating a positive feedback loop involving its distal promoter region and is supported by an association of co-activators which includes CBP/p300, Smad4 and transcription initiation complex RNA polymerase II, TFIIB. Thus, this loop may regulate not only EMT but can also other crucial cellular processes such as senescence, survival and stemness.

Publication

Auto-regulation of Slug mediates its activity during epithelial to mesenchymal transition.
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