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Lamin A/C deficiency re-wires transcription factor footprints and inhibits EMT

Recent studies suggest an involvement of nuclear lamins in the epithelial-to-mesenchymal transition (EMT) and cancer progression. However, the extent to which nuclear lamins, as genome organizers, are implicated in EMT remains both not consensual and unclear. We have addressed the role of A-type lamins (lamin A/C) in an MCF10A breast epithelial cell model of EMT induction by TGFβ. LMNA transcript levels correlate with expression of EMT markers and with poor prognosis of breast cancer survival. Lamin A/C depletion in MCF10A cells prevents acquisition of an EMT phenotype, establishment of an EMT transcriptome, and of histone modification changes elicited by TGFβ in lamina-associated domains. Lamin A/C depletion also extensively remodels chromatin accessibility detected by ATAC-seq, resulting in a general net opening of promoters of differentially expressed genes, yet attenuating TGFβ-induced increases in promoter accessibility. Absence of lamin A/C also extensively remodels transcription factor (TF) footprints, notably of FOS/JUN pioneer TFs of the AP-1 complex, SMAD2/3 and other factors previously not reported to be associated with EMT. Our footprint changes allude to TF retention, eviction or binding inhibition at/from target DNA binding sites in promoters and enhancers. Changes in TF binding behavior however occur in a manner not necessarily coupled to concurring changes in chromatin accessibility and H3K27 acetylation. We conclude that A-type lamins are essential for TGFβ-induced EMT in the MCF10A model, by enabling a chromatin accessibility landscape and TF binding behaviors at regulatory elements driving EMT gene expression.

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