DNA Methylation Drives Osteochondrogenic Reprogramming in Keloid Pathogenesis and Reveals Therapeutic Potential of Decitabine

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Running Title

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BACKGROUND

Keloids are fibroproliferative disorders characterized by excessive extracellular matrix deposition, high recurrence, and aberrant osteochondrogenic differentiation. Although epigenetic dysregulation has been implicated in keloid pathogenesis, whether genome-wide DNA methylation drives pathological cellular reprogramming remains unclear.

METHODS

We performed genome-wide DNA methylation profiling and transcriptomic analysis of keloid tissues, matched primary keloid fibroblasts, and normal controls. Integrated methylome-transcriptome analyses were used to identify methylation-dependent transcriptional programs. Functional relevance was assessed using the DNA methyltransferase inhibitor decitabine (DAC) in vitro and in a keloid patient-derived xenograft (PDX) model.

RESULTS

Keloid tissues exhibited a globally hypermethylated DNA landscape, with differentially methylated regions enriched in pathways related to bone and cartilage development. Integrated methylome-transcriptome analyses demonstrated that DNA methylation functions as a central regulatory mechanism driving aberrant osteochondrogenic differentiation, identifying 211 genes whose expression was directly associated with promoter or gene-body DNA methylation and significantly enriched in osteochondrogenic pathways. Primary keloid fibroblasts partially retained these disease-associated epigenetic and transcriptional signatures, supporting their validity as a relevant in vitro model for epigenetic studies. Pharmacologic inhibition of DNA methylation with decitabine attenuated osteochondrogenic differentiation signatures, suppressed fibroblast proliferation and migration, and significantly reduced keloid growth and collagen deposition in PDX model.

CONCLUSION

Our findings identify DNA methylation as a central driver of aberrant osteochondrogenic reprogramming in keloid fibrosis and demonstrate that this pathological cell-fate program is therapeutically reversible. These results position keloids as a model of epigenetically driven fibrotic disease and support DNA methylation-targeted therapy as a rational strategy for preventing fibrosis progression and recurrence.