Alveolar bone resorption caused by trauma or periodontal diseases has been a challenge for both dental clinicians and researchers. In this study, we investigate the bone regeneration through direct trans-differentiation from non-osteogenic cells to osteogenic cells by epigenetic modification. HGFs or 3T3-L1 cells treatment with 5'-aza-dC induced demethylation in the hypermethylated CpG islands of the osteogenic lineage marker genes RUNX2 and ALP, and subsequent BMP2 or Wnt3a treatment successfully drove to the osteoblasts lineage. Cell morphological changes viewed under microscopy and alkaline phosphatase and alizarin red S staining confirmed the osteoblastic change mediated by epigenetic modification as did real-time PCR, MSP, and ChIP assay, which demonstrated the altered methylation patterns in the RUNX2 and ALP promoter regions and their effect on gene expression. In vivo data indicated ectopic bone formation and increased bone volume, furthermore, RNA seq and MBD seq proved the process of trans-differentiation via epigenetic modification.

Collectively, our results indicate that epigenetic modification permits direct programming of non-osteoblasts into osteoblasts, suggesting that this approach might open a novel therapeutic avenue in alveolar bone regeneration.

**Trans-differentiation via epigenetic approach for alveolar bone regeneration**

*in vitro, in vivo, and in silico studies*

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I. Epigenetics

II. Induced pluripotent stem cell vs. Trans-differentiation

III. Strategy for trans-differentiation

**Experimental Works Flow**

**Methods & Results**

**Fig. 2. 5'-aza-dC and sequential bone morphogenetic protein 2 (BMP2) treatment stimulate osteogenesis**

**Adipocyte -> Osteoblast**

**Fig. 1. CpG methylation state in the promoter correlates with gene expression level**

**Fibroblast -> Osteoblast**

**Fig. 3. 5'-aza-dC and sequential Wnt3a mitigate osteoporotic character in old mice**

**Fig. 4. Genome-wide analysis: Epigenetic modification regulates gene expression**