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Altered Force Sensing and Cell-cell Adhesion by Mutant ALK2 FOP Cells—Implications for Heterotopic Ossification

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Introduction

The rare genetic disease fibrodysplasia ossificans progressiva (FOP) dysregulates progenitor cells to form heterotopic bone in soft tissues. Microenvironment rigidity modulates lineage specification to direct cell fates. Soft substrates induce mesenchymal progenitor cells towards neuro-/adipogenic fates while stiff substrates promote chondro-/osteogenesis. Pathologic tissue stiffening occurs in fibrotic diseases when damaged tissue aberrantly acquires increased rigidity during wound healing. Similarly, injury-induced FOP lesions exhibit excessive fibroproliferation. Gain-of-function R206H mutations in the BMP receptor ALK2/ACVR1 cause FOP. Since BMP signaling both regulates and is regulated by cell tensional force, we hypothesized that altered ALK2 signaling as a consequence of the FOP mutation alters mechanical force sensing in progenitor cells and lowers the threshold for bone formation.

Methods

We used immortalized mouse embryonic fibroblasts (iMEFs) from ACVR1^{R206H} knock-in and WT embryos on varied matrix elasticity (soft/5kPa; moderate/15kPa, stiff/55kPa) and analyzed cell size, aspect ratio (AR), circularity, and solidity at low cell density.

Results

WT cells responded to increasing stiffness as expected with increased cell size and AR, and decreased circularity and solidity. However, FOP cells on soft substrates were similar to WT on stiff substrates, and FOP cells were overall less responsive to substrate rigidity. FOP iMEFs also showed a loss of contact inhibition, reduced cell-cell contacts, and loss of β-catenin at cell membranes.

Discussion

These data support that the combination of increased BMP signaling and misinterpretation of biomechanical signals in FOP cells lowers their threshold for commitment to chondro-/osteogenic lineages, resulting in an aberrant tissue repair response that leads to ectopic bone formation.