THE EFFICACY OF DIFFERENT DELIVERY SYSTEMS FOR FGF-2 TO TREAT AGE-RELATED INHIBITION OF BONE FORMATION DURING DISTRACTION OSTEOGENESIS IN THE RAT TibIAL LENGTHENING MODEL

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Introduction: In young rats, gradual distraction of a mid tibial osteotomy produces a gradient of new bone formation (DO) across the entire cross-section that bridges the distraction gap. The new bone forms primarily by direct intramembranous bone from the periosteum and endosteum. Histological zones include a central fibrous interzone (FIZ) connecting mirror image zones of proliferating progenitor cells (PMF) leading to coupled osteogenesis and angiogenesis in longitudinal microcolumns of bone and sinusoids (MCF), parallel to the distraction force. FGF-2 and two of its high affinity receptors (FGFR1 and 2) are specifically expressed at the transition from proliferating cells to more differentiated osteoblasts and endothelial cells.

In older rats, the endosteal contribution (ENB) to the new bone bridge is dramatically deficient, while the periosteal component (PNB) is maintained, similar to senile osteoporosis. FGF-2 is deficient systemically and locally in old rats undergoing DO, whereas the receptors are still present.

We hypothesized that 1) administration of exogenous FGF-2 could re-stimulate deficient ENB in older rats and that 2) different delivery systems could be used to enhance the effect. We decided to administer the FGF-2 at the index operation to simulate the clinical situation, to avoid secondary damage to the local biology by injection during distraction and to reproduce the in situ findings of early expression seen in young rats.

Methods: Our standard model for unilateral tibial lengthening uses a two ring external fixator, proximal and distal transverse wires, a low energy mid-diaphyseal osteotomy, gradual manual distraction at 0.2mm bid and evaluation of bone formation at the end of distraction (14days).

We have also standardized radiographic and histological techniques for quantitating bone formation using videomicroscopy and NIH Image.

We randomly assigned old rats to the following groups: 1) systemic (Sys) FGF-2 via osmotic pump/catheter (n=8), 2) local extraperiosteal (EP) FGF-2 via osmotic pump/catheter to a drill hole (n=8), and 4) local intramedullary injection in hyaluronate carrier (Oss) (n=10). All test groups were controlled using the delivery vehicle without FGF-2.

Young rats were used as the normal baseline for measuring new bone in vivo.

Results: Systemic FGF-2 administration increased circulating levels of serum FGF-2 measured by ELISA (21.73±20.99 pg/ml vs. 3.88±20.33 pg/ml in controls, P<0.001). ENB in old rats was re-stimulated in all test groups (as recommended from fracture studies in rats).

Discussion: Local administration of FGF-2 may introduce higher local concentrations at the site of DO increasing the effect on new bone formation. Early administration of FGF-2 for a short duration, 2-7 days was effective in significantly increasing ENB. The carrier itself may have some effect on the mode of ENB.

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