Δ Unleashing ß-Catenin With a New Anti-Alzheimer Drug for Bone Tissue Regeneration

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Purpose: The Wnt/β-catenin signaling pathway is critical for bone regeneration. Being involved in several developmental processes, Wnt/β-catenin signaling must be safely targeted. Recent work has shown that Tideglusib, a selective and irreversible small molecule non-ATP [adenosine triphosphate]-competitive glycogen synthase kinase 3-β (GSK-3β) inhibitor currently in trial for Alzheimer's patients, can promote tooth growth and repair cavities. Despite some differences, bone and tooth formation exhibit some similarities; thus we hypothesize that this new drug can in theF same manner accelerate bone healing.

Methods: Biodegradable FDA [Food and Drug Administration]-approved collagen sponges filled with or without GSK-3β inhibitor (Tideglusib) were implanted in 1 x 2-mm unicortical femoral defects (n= 35 mature Wild-type male mice). Bone defect repair on control and experimental (GSK-3β inhibitor) groups was assessed after 1 week (n = 22), 2 weeks (n = 24), and 4 weeks (n = 24) with microCT and histological analysis for alkaline phosphatase (ALP, osteoblast activity), tartrate-resistant acid phosphatase (TRAP, osteoclasts), and immunohistochemistry to confirm the activation of the Wnt/β-catenin pathway.

Results: Our results showed that Tideglusib significantly enhanced cortical bone bridging (20.6 ± 2.3) when compared with the control (12.7 ± 1.9; P = 0.001). Activity of GSK-3β was effectively downregulated at day 7 and 14 (P = 0.04) resulting in a higher accumulation of active β-catenin at day 14 in the experimental group compared to the control (P = 0.03). Furthermore, the onset of ALP activity appears earlier in the experimental group (P = 0.02). At 4 weeks, we observed a significant drop in ALP in the experimental group (0.47 ± 0.05) compared to the control (1.01 ± 0.19; P = 0.02) and a decrease in osteoclasts (experimental = 1.32 ± 0.36; control = 2.23 ± 0.67; P = 0.04).

Conclusion: Local downregulation of GSK-3β by Tideglusib during bone defect repair resulted in significant increase in amount of new bone formation. The early upregulation of osteoblast activity is 1 explanation of bone healing augmentation. This is likely the effect of upregulation of β-catenin following pharmaceutical inhibition of GSK-3β. Indeed, it has been previously demonstrated that β-catenin activation positively regulates osteoblasts, once committed to the osteoblast lineage. As a GSK-3β inhibitor, Tideglusib demonstrates a different mechanism of action compared to other GSK-3β antagonists. Here, the treatment was applied immediately after the injury and did not interfere with precursor cells recruitment and commitment. This safe and FDA-approved drug could be used in prevention of nonunion in patients presenting with high risk for fracture-healing complications.

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