Chapter 5

Conclusion
In an effort to elucidate the effect of lithium on osteoblast differentiation, the present study revealed lithium-induced reprogramming of human bone marrow-derived mesenchymal stem cell transcriptome to favour osteogenesis while repressing adipogenic and chondrogenic programs. Lithium was found to inhibit GSK-3β resulting in stabilization and translocation of β-catenin to the nucleus and activation of Wnt signaling. Microarray-based gene expression profiling of lithium-treated mesenchymal stem cells uncovered critical osteogenesis regulating genes like ATF4, CLEC3B, PBX1, TWIST1, TBX3 and CEBPA. Among these genes, ATF4 and CLEC3B were identified as probable Wnt targets as they were also induced by Wnt3a, while down-regulation of PBX1 and TWIST1 (negative regulators of osteogenesis) occurred independent of Wnt signaling. Lithium pre-treatment primed the cells towards osteogenic lineage resulting in increased collagen-I synthesis, ALP activity and calcium deposition (mineralization) as summarized in Figure 5.1. Treatment of osteoblastic SaOS2 cells with lithium enhanced the gap junctional protein Connexin43, and increased collagen-I in association with osteogenic transcription factor Osterix. All these results support the hypothesis that short-term use of lithium primes mesenchymal stem cells enhancing their osteogenic potential. It also highlights the potential clinical applicability of lithium for treating orthopedic defects and in particular osteoporosis as lithium suppressed the expression of osteoclastogenic factors.

**Figure 5.1: Molecular events mediated by lithium regulating osteogenesis.**
Increase in expression or synthesis is indicated in green while decrease in expression is indicated in red.

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