Homeodomain protein TGIF is required for Canonical Wnt signaling-induced bone formation

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Background
The homeodomain protein TGIF regulates several physiological processes and plays crucial roles in cell fate determination and tissue homeostasis. To identify TGIF interacting partners, we undertook a yeast two hybrid approach using human TGIF as bait. Screening of a human placental cDNA library repeatedly recovered Axin2, a prominent antagonist of Wnt signaling.

To determine whether TGIF binds Axin2 in mammalian cells, we immunoprecipitation and Luciferase assay experiments to identify the interaction domains (Fig 1). Similar to Axin2, the interaction of Axin1 with TGIF was selectively increased by canonical Wnt (Fig 1).

Aim
Given that Wnt signaling is a potent regulator of osteoblast differentiation and bone formation, we then tested whether TGIF was capable to enhance this pathway in osteoblasts (OBs) and bone formation in vitro and in vivo.

Results

• Interaction of TGIF with Axin1/Axin2
• TGIF Interferes with the Nucleocytoplasmic Transit of Axin1/Axin2
• TGIF activates canonical Wnt signaling.
• Wnt signaling induces TGIF expression.
• TGIF promotes osteoblast differentiation and bone formation

Conclusion
Activation of Wnt signaling induced the expression of TGIF itself in many cell lines, revealing an ability of TGIF to govern a feed-forward loop that sustains Wnt signaling.

This study therefore establishes TGIF as a component of the Wnt signaling machinery that is required for efficient Wnt-induced osteoblast differentiation and bone formation.

Acknowledgements
M.-Z.Z. is recipient of a fellowship from the China Scholarship Council. This work was supported by INSERM, CNRS, ARC, La Ligue, NIH R01-AR059070 to A.A. and NIH R01-AR48218 to R.B.