Unraveling a potential relationship between repression of PPAR$\gamma$ activity via interaction with N-CoR/SMRT and enhancement of bone formation may provide new therapeutic targets in treating osteoporosis in the aging population. An important area for exploration involves regulation of PPAR$\gamma$ transcriptional activity via ubiquitin-proteasome-dependent degradation. The ubiquitin-proteasome system is responsible for the degradation of short-lived proteins in eukaryotes, including the nuclear receptors (reviewed in [67]). PPAR$\gamma$ is targeted for degradation under basal [68] and ligand-activated conditions [69]. Recent studies show that components of the ubiquitin-proteasome system responsible for targeting substrates for degradation also function as nuclear receptor coactivators and corepressors [70–72]. Indeed, subunits of the N-CoR/SMRT complex are ubiquitin ligases that target substrates for degradation by the 26S proteasome [72]. These components, TBL1/TBLR1 (transducin $\beta$-like 1/transducin $\beta$-like 1 related protein), are required for exchange of corepressors for coactivators upon ligand binding for a number of nuclear receptors, including PPAR$\gamma$ [72]. TBL1/TBLR1 act as adaptors for recruiting components of the ubiquitin-proteasome system to the liganded receptor [72]. In addition, deletion of TBL1 from mouse embryonic stem cells precludes the ability of these cells to undergo adipogenesis as judged by staining for neutral lipids and decreased gene expression of PPAR$\gamma$ and PPAR$\gamma$ targets such as adipsin [72]. Given the reciprocal relationship between adipogenesis and osteogenesis, these results suggest a role for interactions of components of the ubiquitin-proteasome system with PPAR$\gamma$ (and other nuclear receptors) in determining the balance between bone and fat formation.

## OTHER COREGULATORS OF PPAR$\gamma$

Additional components of the transcriptional complex also influence PPAR$\gamma$ activity and the differentiation of mesenchymal stem cells into either adipocytes or osteoblasts. New findings have identified a coactivator protein, known as the transcriptional coactivator with PDZ binding motif (TAZ), that is shared between Runx2 and PPAR$\gamma$ [73, 74]. In murine cell models, the TAZ protein localized to the osteocalcin promoter in the presence of bone morphogenic protein-2 (BMP-2) and coactivated Runx2 and osteogenesis while directly suppressing PPAR$\gamma$ and adipogenesis [73]. Although not structurally related to $\beta$-catenin, TAZ is proposed to be functionally similar to $\beta$-catenin as a regulatory switch in determining the balance between osteoblast and adipocyte development [74]. Wnt signaling stimulates osteogenesis by induction of osteogenic factors such as Runx2 [75] while suppressing adipogenesis in mesenchymal stem cells [76, 77]. Activation of the Wnt signaling pathway leads to activation of $\beta$-catenin, which interferes with PPAR$\gamma$ transcriptional activity [78]. Conversely, suppression of Wnt signaling [77] and activation of PPAR$\gamma$ [78] destabilize $\beta$-catenin, resulting in adipogenesis. Future studies will be needed to determine if $\beta$-catenin functions as a direct corepressor of PPAR$\gamma$ activity in a manner analogous to the TAZ protein. Finally, ligand-activated PPAR$\gamma$ itself suppresses both the expression and activity of Runx2 [79], adding another regulatory layer to the balance between bone and fat formation.

Any exploration of PPAR$\gamma$'s influence over bone formation must take into account the effect of oxygen tension on the development of fat and bone. It is here that the reciprocal relationship between bone and fat formation seems to disappear. The bone marrow mesenchymal stem cells (bone marrow MSC) are normally exposed to oxygen tensions lower than the atmospheric oxygen tension of 21%. In vitro studies indicate that low oxygen levels block induction of adipogenesis from human and murine MSCs [80]. Human MSCs accumulate lipid inclusions at low oxygen tensions, but the appearance of lipids is unaccompanied by expression of PPAR$\gamma$ or the downstream PPAR$\gamma$ target genes required for adipogenesis [81]. Adipogenesis is similarly inhibited under low oxygen conditions in human adipose-derived mesenchymal stem cells (ASC) [82]. However, reduced oxygen tension is also associated with decreased osteogenesis in the human ASCs [82, 83], suggesting parallel regulation of bone and fat development under these conditions. While hypoxic conditions (2% oxygen) do not inhibit Runx2 transcriptional activity [84], PPAR$\gamma$ transcriptional activity is inhibited under the same conditions [85]. PPAR$\gamma$ inhibition is mediated by HIF-1$\alpha$, a hypoxia inducible transcription factor governing a range of cellular responses to low oxygen levels [85]. HIF-1$\alpha$ mediated repression of PPAR$\gamma$ activity depends on an HIF-1$\alpha$ regulated transcriptional repressor, DEC1/Stra13 [85]. Interestingly, HIF-1$\alpha$/DEC1 inhibition of PPAR$\gamma$ under hypoxic conditions does not involve histone deacetylation, raising the possibility that the classical nuclear receptor coactivators and corepressors are not required in this process.

## CONCLUSIONS AND FUTURE QUESTIONS

These observations suggest that regulation of PPAR$\gamma$ activity may lie at the heart of determining if bone and fat development proceed along parallel or reciprocal directions. Efforts to understand the regulation of PPAR$\gamma$ transcriptional activity have uncovered interplay of PPAR$\gamma$ and other nuclear hormone receptors that is intricately regulated by a range of coregulators. The coregulators extend beyond the classical coactivators and corepressors to include enzymes of the ubiquitin-proteasome system, components of the Wnt and BMP-2 signaling pathways, $\beta$-catenin and TAZ, and oxygen-sensing factors such as DEC1/Stra13. As research progresses in defining the role of PPAR$\gamma$ and other nuclear hormone receptors in osteogenesis, some of the questions to be answered will include the following

(1) Will new insights into MSC adipogenesis and osteogenesis be gained as the ligands for "orphan" nuclear hormone receptors are identified?
(2) How do additional components of the transcriptional apparatus, such as histone acetylases and histone deacetylases, contribute to the effects of PPAR$\gamma$ and related nuclear hormone receptors?
(3) How does ubiquitin-proteasomal targeting of PPAR$\gamma$ and related nuclear hormone receptors coordinately regulate MSC adipogenesis and osteogenesis?