Signal Transduction

The SRF Target Gene Fhl2 Antagonizes RhoA/MAL-Dependent Activation of SRF

RhoA signaling regulates the activity of the transcription factor SRF (serum response factor) during muscle differentiation. How RhoA signaling is integrated at SRF target promoters to achieve muscle-lineage-specific expression is largely unknown. Using large-scale expression profiling combined with bioinformatic and biochemical approaches, we identified several SRF target genes, including Fhl2, encoding a transcriptional cofactor that is highly expressed in the heart. SRF binds the Fhl2 promoter in vivo and regulates Fhl2 expression in response to RhoA activation. FHL2 protein and SRF interact physically, and FHL2 binds the promoters of SRF-responsive smooth muscle (SM) genes, but not the promoters of immediate-early genes (IEGs), in response to RhoA. FHL2 antagonizes induction of SM genes, but not IEGs or cardiac genes, by competing with the coactivator MAL/MRTF-A for SRF binding. Our findings identify an autoregulatory mechanism to selectively regulate subsets of RhoA activated SRF target genes.

Study of ligand dependent ROR beta function

Retinoids regulate gene expression through binding to the nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs). In contrast, no ligands for the retinoic acid receptor-related orphan receptos beta and gamma (ROR beta and gamma) have been identified, yet structural data and structure-function analyses indicate that ROR is a ligand-regulated nuclear receptor. We found that all-trans retinoic acid (ATRA) and several retinoids bind to the ROR beta ligand-binding domain (LBD). The crystal structures of the complex with ATRA and with the synthetic analog ALRT 1550 reveal the binding modes of these ligands. ATRA and related retinoids inhibit ROR beta but not ROR alpha transcriptional activity suggesting that high-affinity, subtype-specific ligands could be designed for the identification of ROR beta target genes. Our results identify ROR beta as a retinoid-regulated nuclear receptor, providing a novel pathway for retinoid action.