Abstract

In animals, some of the most critical regulators of gene expression are nuclear hormone receptors (NRs) and their coregulators, specifically the Mediator complex. Of particular interest are the NRs implicated in metabolic and developmental regulation and in carcinogenesis: thyroid hormone receptors (TRs) and retinoid X receptors (RXRs). In this work, I venture to elucidate some aspects of gene expression regulation by these NRs: the degree of evolutionary conservation of signalling based on NRs and their coregulators; the mechanisms of negative regulation by NRs; and possible implications of these findings for clinical medicine. State-of-the-art bioinformatical, genome editing and microscopic techniques are applied at three levels of animal evolution to study NRs and Mediator. Reverse genomics in human patients suffering from the syndrome of resistance to thyroid hormones β are used to infer the structure and function of TRβ subdomains. Alignments, binding studies and *in vivo* experiments in *Trichoplax adhaerens* allow identification of a close orthologue of human RXR at the basis of metazoan evolution. Employing database queries, genome editing and microscopy, we describe a correct orthologue of the Mediator subunit 28 in *Caenorhabditis elegans*, indicating a complete homology of the Mediator complex between nematodes and human. Analysing the results between species, we provide further indications that regulation by the NR-Mediator axis is conserved throughout *metazoa*, and we propose a hypothetical working model of the negative regulation by NRs.