Hormones may act through either membrane-bound or nuclear receptor proteins. Whereas peptide hormones bind to receptors on the cell surface, small lipophilic hormones and vitamins such as steroids, retinoids and l-triiodothyronine enter the cell and bind to their respective intracellular receptor protein. All members of the nuclear hormone receptor superfamily (steroid, vitamin D (VDR), retinoid (RAR, RXR), thyroid (TR) and peroxisome proliferator-activated (PPAR) receptors) exert their action on target genes by binding to short, but specific, regulatory DNA sequences in the promoter region of hormone-regulated genes, thereby increasing or decreasing their transcription rate. However, in contrast to steroid hormone receptors, the RAR, RXR, TR, VDR and PPAR are capable of binding to DNA even in the absence of their cognate ligand. The molecular details of ligand-induced transcriptional activation have remained enigmatic because DNA binding of these unliganded receptors does not increase transcription and in some cases even decreases basal transcription of the target gene. The latter phenomenon of basal repression of transcription is particularly marked for TRs and this effect is believed to be important in mediating gene silencing, e.g. during development, where the expression of TRs precedes the production of thyroid hormone.

Given the above observations, it has been of considerable interest to identify co-activator and co-repressor proteins associating with nuclear hormone receptors in a ligand-dependent manner, thereby mediating an activating or inhibitory signal to the transcriptional machinery, respectively. In early and mid-1995, the first co-activator proteins for thyroid hormone and estrogen receptors were identified, including Trip1, p140 and p160 (1, 2). These factors were characterized by their ligand-dependent ability to associate with the respective nuclear receptor and consequently to increase transcription. As an extension of this line of investigations, the present articles report the cloning of co-repressor proteins involved in mediating basal repression of retinoid and thyroid hormone-regulated genes (3, 4). Using the yeast two-hybrid screening system, two distinct co-repressors were cloned—the nuclear receptor co-repressor (N-CoR) and the silencing mediator for RAR and TR (SMRT)—forming the new family of thyroid hormone- and retinoic acid-associated corepressors (TRACs). The N-CoR is a 270-kD protein without significant homology to any other known protein. It contains two transferable repression domains (N-terminal and in the center of the protein) as well as a C-terminal α-helical interaction domain required for dimerizing with the hinge region (junction between the DNA- and ligand-binding domain) of TR. A putative zinc-finger region is also present, suggesting that N-CoR might directly contact DNA. The SMRT protein has similar functional characteristics, but its molecular mass is only 168 kD. Both co-repressors are ubiquitously expressed in the nuclei at low levels.

Although the functional importance of these factors needs to be demonstrated in vivo, e.g. by knock-out experiments, a third paper in the same issue of Nature indicates that this is likely to be the case (5). Kurokawa et al. examined the paradoxical situation that an RXR-RAR heterodimer bound to a DR5 DNA-element activates transcription, whereas the RAR-RXR complex bound to a DR1 sequence does not (5). The authors demonstrate that retinoid receptors bound to either DNA element can associate with N-CoR in the absence of ligand. In the presence of retinoic acid, the complexes bound to either the DR1 or the DR5 sequences can form a ternary complex with the co-activators p140 and p160. Upon addition of retinoic acid, the RXR-RAR heterodimer bound to the DR5 dissociates from N-CoR, thereby activating transcription. In contrast, the DR1-bound RAR-RXR complex does not dissociate from the co-repressor, which continues to silence transcription in a dominant manner even in the presence of ligand.

A second set of experiments from the same investigators elegantly reinforces the biological relevance of TRACs. The viral protein v-erbA represents the oncogenic variant of the TR (also called c-erbA). It induces tumors in chicken in part by inhibiting TR-mediated cell differentiation in a dominant negative manner. However, a v-erbA point mutant in a position corresponding to the TR hinge region abolishes these effects of v-erbA. The present experiments now demonstrate that this mutation abolishes the interaction of v-erbA with its co-repressor SMRT, thereby strongly suggesting that the latter protein is the mediator of the constitutive basal repressor activity of v-erbA on T3-regulated genes.

The definitive physiological and possibly clinical relevance of these factors clearly remains to be demonstrated. However, it can be speculated that co-repressors might play an important role in gene silencing, e.g. during neuronal development, as well as in adding specificity to the sometimes promiscuous...
receptor-DNA interactions. In addition, it seems possible that the balance of co-activators to co-repressors could not only modulate the sensitivity of a given target organ to a particular hormone, but could also lead to situations of conditional cross-talk among different nuclear receptors under circumstances where one of these shared co-factors becomes limiting.

References

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Jérôme Bertherat, Service d’Endocrinologie, 8 INSERM CJF 92-08. CHU Cochin, 27 Rue du Fg-SV-Jacques, F-75014 Paris, France.