INTRODUCTION

The trophic effects of steroid hormones on hormone-dependent cancers are mediated by specific nuclear receptors (NRs), which act as transcriptional regulators. Androgen (AR), estrogen (ER), and progesterone (PR) receptors possess sequence-specific binding affinity for hormone response elements upstream of hormone-responsive genes. Thus, the principal mechanism of action of steroid hormones is the regulation of gene expression (1), with NRs acting as signal transducers. This simple concept encompasses a remarkably intricate biochemical mechanism, which involves numerous proteins in addition to the NRs themselves. Recently, efforts in a number of laboratories have begun to delineate the complex process by which signals impinging on steroid receptors regulate transcription.

Steroid receptors belong to the NR superfamily, and have a similar structure, containing distinct domains (regions A–F) (1). Transcriptional activation properties are associated with two regions, the ligand-independent N-terminal AF-1 domain, and the ligand-dependent C-terminal AF-2 domain. NRs bind to DNA as homo- or heterodimers, which form on ligand binding. Although ER, for example, can interact directly with components of the basal transcriptional apparatus (2,3), it has become increasingly apparent that NRs do not act in isolation to alter transcription at their response elements. Instead, they function as part of a multimeric protein complex that serves to transmit the hormone signal to the basal transcriptional machinery. Accessory factors, termed co-activators or co-repressors, regulate the effects of NRs on transcription, and are an essential part of the mechanism mediating hormone action. Disturbances in the integrity of this mechanism may be of critical importance to the biology of hormone-responsive cancers by affecting their sensitivity to endocrine signals and disrupting the integration of signaling pathways.
Fig. 1. The regulation of transcription by a NR at the promoter of a hormone-responsive gene involves changes in the co-repressor complex bound to chromatin. In the inactive state, the receptor is engaged with a co-repressor complex with histone deacetylase activity. On ligand binding, the receptor (NR) undergoes a conformational change, and binds co-activators with a histone acetyltransferase activity, and affinity for the basal transcriptional machinery favoring the initiation of transcription.

Recognition of the complexity of the apparatus mediating NR transcription has been driven by several biochemical approaches. Older studies, using reporter genes in transient transfection assays, demonstrated interference between NRs (squelching), which suggested the existence of limiting intermediary factors essential for NR transactivation. Using the yeast two-hybrid system, a long list of proteins that interact with NRs have been isolated. Supplementing this list are proteins that have been isolated by direct biochemical analysis of purified transcriptional complexes, as well as molecules that also have the ability to regulate viral oncoproteins and non-steroid signaling pathways, notably the E1A binding protein, p300, and the related molecule, CREB-binding protein (CBP).

The precise roles of several of these proteins remain to be determined. However, because ligand binding is the critical event in NR signaling, the subsequent discussion focuses primarily on the network of factors that associate with NRs on ligand binding (Fig. 1). A general picture has emerged in which NRs participate in multimeric protein complexes. In the nonliganded state, association with co-repressors leads to the formation of an inhibitory complex \((4,5)\). On receptor formation by ligand binding (or via ligand-independent pathways), an activating complex forms, which promotes transcription. Chromatin modification by histone acetylation and deacetylation has emerged as an important biochemical aspect of the process. The unliganded chromatin-bound NR co-repressor complex maintains a condensed chromatin state through its histone deacetylase activity. In contrast, liganded NRs recruit histone acetyltransferase (HAT) components of the co-activator complex. Decondensation of acetylated chromatin presumably facilitates access to the DNA template by transcriptional proteins. Ligand activation of receptor can be conceptualized as promoting HAT activity over histone deacetylase activity. The combinatorial utilization of various possible co-regulators in specific cell types establishes the pattern of hormone responsiveness. In addition to complexes with HAT