

Nuclear Receptor-Mediated Gene Regulation in Drug Metabolism

HONGBING WANG and WEN XIE

1 INTRODUCTION

1.1 General Features of Nuclear Receptors

The mammalian nuclear receptor (NR) superfamily contains nearly 50 structurally related members, including both receptors for which ligands are known and “orphan receptors” for which there are, as yet, no known ligands (Laudet *et al.*, 1992; Giguere, 1999). Regulation of gene expression at the transcriptional level by NRs has an important role in both cellular development and the body’s defensive systems, including drug metabolism and clearance (Kastner and Chambon, 1995; Mangelsdorf *et al.*, 1995; Honkakoski and Negishi, 2000; Moore *et al.*, 2000a). Members of the nuclear receptor family share several structural features. Two of the modulator domains are common structural motifs shared by most of the nuclear receptors (Fig. 1a). The highly conserved DNA-binding domain (DBD) that links the receptor to specific promoter regions of its target genes is termed hormone response elements (HREs) or xenobiotic response elements (XREs). As the most conserved domain of NRs, DBD can recognize the response elements that contain one or two consensus core half-sites related to the hexamer ACAACA (steroid receptors) or AGGTCA (estrogen receptors and other nuclear receptors) (Cairns *et al.*, 1991; Lee *et al.*, 1993). The HREs or XREs usually contain two NR half-sites of the consensus hexameric sequences, organized as inverted, everted, or direct repeats with a 3- to 6-base-pair spacing (Fig. 1b). The carboxy (C)-terminal portion of the receptor contains a less conserved ligand-binding domain (LBD), which interacts directly with hormones and xenobiotics. Remarkable variations in the shape and size of LBDs provide the structural basis for fitting a wide range of ligands with diverse chemical structures. It appears that the receptors that bind with high affinity to a specific ligand, such as estrogen receptor (ER) and thyroid hormone receptor (TR), have relatively small ligand-binding pockets, whereas the xenobiotic NRs, such as pregnane X receptor (PXR) and the peroxisome proliferator-activated receptors (PPARs), contain much larger and more flexible ligand-binding cavities that