Abstract

The transforming growth factor-β (TGF-β) superfamily interacts with the nuclear receptor superfamily in a variety of cell types. The vitamin D receptor (VDR) and the peroxisome proliferator activated receptor-γ (PPAR-γ) are among the members of the nuclear receptor superfamily that after activation by their ligands interact with the TGF-β/Smad system to modulate cellular responses. This chapter discusses the importance of interactions between nuclear receptors and the TGF-β/Smad system in inflammation as well as in cancer. Crosstalk between the TGF-β/Smad system and nuclear receptors occurs at multiple levels and will be discussed later in this chapter when describing the role of nuclear receptors and their ligands such as vitamin D derivatives and triterpenoids on (a) modulation of TGF-β/Smad signaling, (b) interactions of nuclear receptors with Smads, and (c) the consequences of their interactions in diseases such as inflammation and cancer. Understanding crosstalk between the TGF-β/Smad system and the nuclear receptor superfamily may give new insights for the possible use of nuclear receptor ligands for the treatment and prevention of these and other diseases.

Key Words: TGF-β; Smad; cancer; inflammation; nuclear receptors.
1. TGF-β/Smad Signaling, Inflammation, and Cancer

The transforming growth factor-β (TGF-β) superfamily, including TGF-βs, activins, and bone morphogenetic proteins (BMPs), are multifunctional cytokines that affect inflammation, the immune response, cell growth, differentiation, apoptosis, and development as well as carcinogenesis (1,2). Upon stimulation by the ligands of the TGF-βs, activins, and BMPs, cells induce the formation of heteromeric complexes of transmembrane serine/threonine kinase type II and type I receptors, which then initiate signaling involving (a) receptor-regulated Smads (Smad2/3 for TGF-β and Smad1/5/8 for BMPs), (b) a co-Smad (Smad4), and (c) inhibitory Smads (Smad6 and Smad7). Smad complexes then translocate to the nucleus, where together with a coactivator or corepressor, regulate transcription of target genes (2–4). Although the Smad intracellular signaling molecules confer TGF-β signaling, biological effects of TGF-β in a variety of cells occur by either a Smad-dependent or Smad-independent pathway (2). Among many potential actions of TGF-β in different disease processes, this chapter will describe two disease processes that are regulated by both the nuclear receptor superfamily and the TGF-β/Smad system, namely carcinogenesis and inflammation.

1.1. TGF-β/Smad Signaling and Cancer

During carcinogenesis, the role of the TGF-β/Smad superfamily is complex. TGF-β is a potent inducer of apoptosis and growth inhibition in many epithelial cell types (2,5,6). Conversely, TGF-β stimulates the growth of certain stroma-fibroblast cell types (5,7). During mammary gland development, TGF-β regulates branching morphogenesis and differentiation by acting on both epithelial and stromal cells. At the end of pregnancy, it is known that TGF-β is a key molecule that induces apoptosis in mammary epithelial cells and stimulates matrix remodeling during involution (5). Maintaining TGF-β function as an inducer of apoptosis in the mammary gland is critical. Interestingly, during the early stages of breast cancer development, the transformed epithelial cells are sensitive to growth arrest by TGF-β, and TGF-β can act as a tumor suppressor (8,9). However, the growth inhibition and induction of apoptosis in epithelial cell types are lost with mutations and loss of gene expression for the formation of molecules of the TGF-β/Smad signaling pathway, resulting in uncontrolled cell proliferation with tumor formation (5,8,9). With the loss of growth inhibition that results from somatic mutations in the TGF-β/Smad pathway, unregulated proliferation of cells and surrounding stromal cells then increase their production of TGF-β with a resultant increase in angiogenesis, immunosuppression, invasion, and metastasis (7,10). Over 50% of pancreatic cancers and 30% of colorectal cancers are associated with mutations in Smad4, and many other cancers have mutations of other Smads in the pathway (11–15). Mutations in the TGF-β type II receptor have also been shown to occur in several types of cancer, including colorectal cancer, hereditary nonpolyposis colon cancer, gastric cancer, and endometrial cancer (16–18).

In addition to the mutations or deletions of Smads, loss of TGF-β type II receptor is also known to contribute to reduced TGF-β-induced cellular differentiation and growth inhibition (19). The loss of expression of type II receptor has also been associated with progressive malignant phenotype in gastric cancer and in T-cell lymphomas (19,20). It is clear that aberrant regulation or mutations in TGF-β/Smad signaling, either in Smads, TGF-βs, or receptors, is critical in carcinogenesis as well as in other disease processes (9,21–24). Even in the absence of mutations or deletions of players in the TGF-β/Smad system, the receptor-regulated Smad of TGF-β (Smad2/3) plays a role as a tumor suppressor at an early stage of breast carcinogenesis, but enhances metastasis at later stages in breast carcinogenesis (8,9,25). Although we understand that Smads, such as Smad2/3, may play