rylation, leading to enhanced androgen and growth factor response in prostate cancer cells. All these variants have been implicated in androgen-insensitive prostate cancer cell growth, which will be discussed in detail below.

AR primarily resides in the cytoplasm as a dimer and a complex with heat shock (such as HSP-90) and other chaperone proteins, which are tethered to cytoskeletal proteins, such as filamin A that interacts directly with AR and facilitates AR translocation to the nucleus. Upon androgen binding, the complex is disrupted and the liganded AR as a dimer becomes phosphorylated, along with several co-regulators, and enters the nucleus where it interacts with the DNA at certain androgen response elements (AREs) affecting the transcription of a number of genes, such as PSA.

The DBD domains of the receptor dimer recognize hexameric binding sites (organized in inverted repeats) separated by three nucleotides. The classical consensus sequence for ARE is 5'-TGTTCT-3' and is also the same for glucocorticoid, mineralocorticoid and progestagen receptors. However, for AR there are also selective AREs which seem to be partial direct repeats of the above motif and to bind the DBD of AR but not that of the glucocorticoid receptor.

Additionally, AR can be trans-activated by growth factors (i.e. EGF, IGF, KGF) and cytokine (i.e. IL6) signaling. Indeed, AR has been described as the target of several MAPKs such as Akt/PKB, PKA, PKC (Figure 2). This cross-talk of AR with growth factor signaling events is extensively studied since it has been associated with metastatic and hormone resistant disease state (see below and Reference for a review).

Finally, during the last decade membrane initiated androgen actions have been described in several cell...