Specific Chromatin Remodeling Complexes Mediate Glucocorticoid Receptor Dependent Transcription In Vivo

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In the eukaryotic nucleus DNA, the hereditary material of the cell is compacted and stored via its association with histone and non-histone proteins in a dynamic polymer called chromatin. The packaging of DNA into chromatin creates a highly inhibitory environment for many trans-acting factors to access target DNA sites during nuclear processes such as transcription. Consequently, modulation of this chromatin structure plays an important role in control of these processes including steroid receptor-mediated activation and repression of transcription. We have developed model systems to study the mechanisms by which steroid receptors control many physiological activities by regulating gene expression within a higher order chromatin organization. Our studies have focused on the glucocorticoid receptor (GR) and its ability to remodel chromatin which is mediated by the BRG1 ATPase as part of the human SWI/SNF complex. Using novel cell lines with an integrated gene reporter systems, we demonstrate that transactivation from a chromatin template requires an intact BRG1 remodeling activity, which induces regions of hypersensitivity and transcription factor loading. Analyses of the BRG1 associated factors (BAFs) demonstrate that specific BAFs mediate interactions between the complex and the nuclear receptors that are necessary and sufficient for receptor functions in vivo. In addition, the BRG1 remodeling activity required for GR-mediated transactivation cannot be substituted by other ATP-dependent remodeling proteins. These studies place the targeted remodeling of gene promoters at the heart of the transcriptional responses required for steroid receptor action in vivo.