Thus the synergy in repression mediated by TR and CTCF may be different domains interacting independently with the CTCF zinc-finger correlates with the ability to bind to SIN3A and to repress gene activitity.

ternary complex and providing a large platform for histone deacetylases.

TR has not been determined. Here we show, that CTCF comprises TR mediated repression has been shown to involve the co-repressors The highly conserved zinc-finger protein, CTCF, is a candidate tumour suppressor protein that binds to divergent DNA sequences. CTCF has been shown to interact with SIN3A and to repress gene activity. The completion of these regulatory machines provides substantial insight into the molecular mechanisms by which chromatin is remodelled to achieve transcriptional silencing. More importantly deficiencies in the correct targeting of these complexes can be directly associated with pathological changes in gene expression in human development and disease (9).

5. Lee et al 1993 Acetylation promotes transcription factor access to nucleosomal DNA. Cell 72: 73-86
6. Tsu et al 1999 Acetylation promotes template transcription through chromatin fibres. Mol Cell. 18: 4629-4639
9. Wolffe and Masske 1999 Epigenetics in development and disease. Semin

E6  Mediation and modulation of thyroid hormone receptor repression

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The highly conserved zinc-finger protein, CTCF, is a candidate tumour suppressor protein that binds to divergent DNA sequences. CTCF has been connected to multiple functions in gene regulation including chromatin insulator activity and transcriptional enhancement and silencing. A specific property of CTCF is that some of the CTCF binding sites are found in the vicinity of thyroid hormone receptor (TR) binding sites. Interestingly both factors synergise in repression as well as in activation.

TR mediated repression has been shown to involve the co-repressors SMRT, N-CoR and Alien. These co-repressors in turn have been found to interact with SIN3 A.

Until now the functional role of CTCF in the synergy of repression with TR has not been determined. Here we show, that CTCF comprises autonomous silencing domains mediating transcriptional repression, when tethered to a promoter sequence. At least one of these domains, the zinc-finger region of CTCF, binds SIN3 A without binding to SMRT or N-CoR and recruits histone deacetylase activity. For SIN3 A we identified two different domains interacting independently with the CTCF zinc-finger cluster. The ability of regions of CTCF to retain deacetylase activity correlates with the ability to bind to SIN3A and to repress gene activity. Thus the synergy in repression mediated by TR and CTCF may be achieved by the multiple molecules of SIN3-A binding to the TR/CTCF ternary complex and providing a large platform for histone deacetylases.

E8  Structural Aspects of Agonism and Antagonism in the Oestrogen Receptor

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The oestrogen receptor is a ligand-inducible transcription factor that controls expression of a number of genes in a wide variety of tissues. Binding of the natural hormone, oestradiol, triggers dimerisation and nuclear location of the receptor and assembly of a functional transcriptional complex through recruitment of various coactivators. Studies in a number of laboratories are beginning to provide insight into the detailed structural mechanisms of nuclear receptor interactions and function.

We have determined the structure of the ligand binding domain of the a form of the oestrogen receptor (ERa) complexed to oestradiol and the selective oestrogen receptor modulator raloxifene. This has provided insights at the molecular level into some key aspects of the pharmacology and function of this molecule:

* Understanding the distinctive ERa pharmacophore*
* A rationale for the large range of molecules that bind to ERa*
* Description of the biologically active dimer*
* Structural basis for the antagonist action of molecules such as raloxifene*
* Indications of the site of interaction with some co-activators (see Brzozowski et al, Nature (1997), 389, 755-758)*

This presentation will review these structural results and discuss recent work including structural studies of the β isoform of the oestrogen receptor (ERβ) (see Pike et al (1999), Embo J. 18, 4628-4638) and of complexes probing the interactions between co-activators and lignad binding domains. The infrastructure of the Structural Biology Laboratory at York is supported by the BBSRC.

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