Version 2.0

Abstract

Back to Hit List

Grant Number: 1Z01AG000649-01
PI Name: WANG, WEIDONG
PI Email:
PI Title:
Project Title: Studies of human NURD Chromatin Remodeling Complex in Gene Regulation

Abstract: In eucaryotes, genes are packed within chromatin. Formation of nucleosomes and higher order chromatin structures can render the DNA inaccessible to transcription factors and RNA polymerases. The repressive chromatin structure must be remodeled to allow transcription to occur. Two classes of chromatin-remodeling complexes have been discovered: one, histone acetyltransferase and deacetylases which covalently modify histones by adding or removing an acetyl group from histone tails; two, the ATP-dependent remodeling complexes which use the energy of ATP to disrupt nucleosome structures. Before our study, it was generally believed that ATP-dependent complexes are only involved in gene activation by making DNA more accessible to transcription activators. In this work, we have purified a new human complex, named NURD, which contains both ATP-dependent nucleosome disruption activity and histone deacetylase activity (which is usually associated withtranscriptional repression). The deacetylase activity is stimulated by ATP on nucleosomal templates, suggesting that in this instance nucleosome disruption helps the deacetylase to access its substrates (Molecular Cell 2:851, 1998). In addition, one subunit of NURD was identified as MTA1, a metastasis-associated protein with a region similar to the nuclear receptor corepressor, N-CoR; and antibodies against NURD partially relieve transcriptional repression mediated by thyroid hormone receptor. Our results demonstrate that ATP- dependent chromatin-remodeling can participate in transcriptional repression by assisting repressors in gaining access to chromatin. - Chromatin, NURD, CHD, histone deacetylase, transcription, Cancer

Thesaurus Terms:
acyltransferase, chromatin, genetic transcription, histone, nucleosome
adenosine triphosphate, hormone receptor, metastasis, thyroid hormone, transcription factor
tissue /cell culture

Institution:
Fiscal Year: 1999
Department:
Project Start:
Project End:
ICD: NATIONAL INSTITUTE ON AGING
IRG: LG

Version 2.0

Abstract

Back to Hit List

Grant Number: 1Z01AG000650-01
PI Name: WANG, WEIDONG
PI Email:
PI Title:
Project Title: Structural and Functional Studies of Human SWI/SNF Chromatin Remodeling

Abstract: The ATP-dependent chromatin-remodeling complexes play important roles in gene regulation by opening chromatin structures for transcriptional activators or repressors. The prototype of this type of complexes is the SWI/SNF complex, which was found from diverse organisms, including yeast, Drosophila, mouse and human. It is required for proper expression of homeotic genes and segmentation in Drosophila. Mutation in one subunit of the complex causes pediatric rhabdoid cancer in human. I have purified several human SWI/SNF-related complexes previously at Stanford. By microsequencing, my colleagues and I have identified and cloned most of the subunits from the major form of the complex. In the continuation of this project, we have microsequenced and cloned its largest subunit, BAF250. Sequence analysis revealed that BAF250 contains a DNA binding domain similar to yeast SWI1, and several LXXLL motifs which have been previously shown to be able to interact nuclear hormone receptors. Using transient transfection assays, we found that BAF250 facilitates transcriptional activation by glucocorticoid receptor (GR). The region containing LXXLL motifs of BAF250 also interacts with GR in vitro. This work suggests that BAF250 may be a targeting subunit of hSWI/SNF, and may mediate the recruitment of the complex to DNA-bound glucocorticoid receptors. - Chromatin, SWI/SNF, BAF250, transcription

Thesaurus Terms:
chromatin, corticosteroid receptor, genetic transcription, intermolecular interaction, transcription factor
adenosine triphosphate, nucleic acid sequence
human tissue, molecular cloning, tissue /cell culture

Institution:
Fiscal Year: 1999
Department:
Project Start:
Project End:
ICD: NATIONAL INSTITUTE ON AGING
IRG: LG

Version 2.0

Abstract

Back to Hit List

Grant Number:	1Z01AG000651-01
PI Name:	WANG, WEIDONG
PI Email:	
PI Title:	
Project Title:	Identification and Characterization of human Rsc Chromatin Remodeling Complex

Abstract: The ATP-dependent Chromatin-remodeling complex, Rsc, was originally identified in yeast. It has similar subunit composition as SWI/SNF: 2 subunits are shared between the two complexes and at least 4 others are homologues of each other. However, the function of Rsc is distinct from SWI/SNF. Rsc is essential to the mitotic growth of yeast, whereas SWI/SNF is not. The rsc mutants are arrested at G2/M transition during the cell cycle and this arrest is dependent on the spindle-checkpoint gene. They are also more sensitive to microtubule-destabilizing drugs. These data suggest that Rsc may play a role in mitosis perhaps by stabilizing mitotic spindle formation. We have previously purified several ATP-dependent chromatin remodeling complexes from human which are closely-related to either yeast SWI/SNF or Rsc. By microsequencing and cloning, we now identified one subunit of a particular complex is a human homologue of yeast Rsc subunits, Rsc1 and Rsc2. We subsequently identified many other subunits of human Rsc complex and found many of them are identical to those in human SWI/SNF. Preliminary data suggest that human Rsc may directly participate in mitosis by binding to microtubules. We are continuing to investigate this part of the mechanism. - Chromatin, SWI/SNF, Rsc, transcription, mitosis

Thesaurus Terms:
cell cycle, cell cycle protein, chromatin
adenosine triphosphate, microtubule, mitotic spindle, mutant, nucleic acid sequence
molecular cloning, tissue /cell culture

Institution:
Fiscal Year: 1999
Department:
Project Start:
Project End:
ICD: NATIONAL INSTITUTE ON AGING
IRG: LG

Version 2.0

Abstract

Back to Hit List

Grant Number: 1Z01AG000652-01
PI Name: WANG, WEIDONG
PI Email:
PI Title:
Project Title: Identification of a Complex Involved in Werner Syndrome

Abstract: The Werner Syndrome (WS) is a rare human genetic disease with many features of premature aging. It has been considered by many researchers as a useful model for human aging studies. The gene that caused WS phenotype has recently been cloned and was named WRN. It encodes a protein homologous to RecQ family of helicases. Indeed, the recombinant WRN protein produced using baculovirus expression system contains a DNA helicase activity as well as an exonuclease activity. Interestingly, analysis of different WS patients suggests that some WRN mutations may impair the interactions between WRN and other proteins. This raised a possibility that WRN functions within a multisubunit protein complex in vivo. We investigated this possibility by using gel-filtration chromatography. Our data showed that WRN exists in a large protein complex of 2 MDa in human HeLa nuclear extract. In order to fully understand the mechanism of the WRN helicase, we believe that it is critical to purify the entire machine which the WRN is only a part of. The WRN-associated proteins within this machine may play key roles in the cellular process in which WRN participates. We have now successfully purified one such complex and identified all its subunits by microsequencing. Characterization of this complex will be crucial for our understanding of how WRN functions, as well as how mutations in WRN cause the premature aging phenotype in WS patients - Werner, RecQ, helicase, Aging

Thesaurus Terms:
Werner's syndrome, exonuclease, gene mutation, helicase
nucleic acid sequence, recombinant protein
Baculoviridae, HeLa cell, Insecta, gel filtration chromatography, molecular cloning

Institution:
Fiscal Year: 1999
Department:
Project Start:
Project End:
ICD: NATIONAL INSTITUTE ON AGING
IRG: LG