The nurd complex

The NuRD Complex

The ability to access DNA of target genes by transcription factors and RNA polymerase is essential in the regulation of all processes that rely on DNA templates. This process has been termed as chromatin remodeling. Studies have been devoted to identifying the enzymatic activities and proteins that are involved in chromatin remodeling. Two enzymatic activities have since been identified to be involved in chromatin remodeling to allow access to DNA. The first one is ATP-dependent nucleosome remodeling which utilizes the energy derived from ATP hydrolysis to remove, displace, or destabilize nucleosomes resulting in a chromatin structure that is more accessible (Swygert and Peterson 2014). The second enzymatic process is termed histone tail modification in which Histone Deacetylase (HDAC) among other enzymes covalently modifies the core histone tails (Swygert and Peterson 2014). The core histone tails are susceptible to a variety of covalent modifications including acetylation, phosphorylation, methylation, and ubiquitination (Workman 2003).

The two activities, ATP-dependent nucleosome remodeling and histone tail modification, were first identified in ySWI/SNF complex from *Saccharomyces cerevisiae* . In 1998, a group of researchers identified the NuRD complex (Nucleosome Remodeling and histone Deacetylation). Upon purification and characterization of the NuRD complex, it was found that it possesses both nucleosome remodeling and histone deacetylase activities, with the ATP-dependent nucleosome remodeling coupled to the histone tail deacetylation function (Torchy, Hamiche, and Klaholz 2015). This makes the NuRD complex unique.

Components of The NuRD Complex

The NuRD complex has seven protein subunits:

1. Histone deacetylase proteins – either HDAC1 or HDAC2
2. histone-binding proteins - RbAp46 and RbAp48.
3. Metastasis-associated proteins MTA1/ MTA2/ MTA3
4. the methyl-CpG-binding domain protein MBD2/ MBD3
5. the chromo-helicase-DNA-binding protein CHD3 or CHD4 protein.
6. p66a/b proteins and
7. DOC-1 protein (Torchy, Hamiche, and Klaholz 2015).

CHD3 or CHD4. Chromo-helicase-DNA-binding protein proteins CHD3 or CHD4 are responsible for the ATP-dependent nucleosome remodeling activity. CHD proteins are also known as Mi-2. CHD/ Mi-2 proteins function as ATPase enzymes where they catalyze the hydrolysis of ATP and the resultant energy is utilized by the NuRD/ Mi-2 complex to destabilize the interactions between DNA and histone proteins that constitute the core of the nucleosome (Torchy, Hamiche, and Klaholz 2015). Besides functioning as an ATPase, Mi-2 also plays a role in targeting the NuRD complex to specific genes because many transcription factors have been reported to interact directly with Mi-2 (Walkman 2003). Mi-2 has also been reported to interact with many transcriptional factors in mammalian cells (Walkman 2003).

HDAC1 and HDAC2. These units are responsible for the histone deacetylation activity of the NuRD complex to disrupt chromatin. The two protein units share the two histone binding proteins RbAp46 and RbAp48. HDAC1 or HDAC2 together with RbAp46 or RbAp48 form a deacetylase core complex

which is capable of actively deacetylating histones (Workman 2003). One of the biochemical functions of MTA2 is to stimulate the histone deacetylase activity of this deacetylase core complex (Workman 2003). MTA2 contains SANT domain proteins; hence these proteins are likely to function as deacetylase modulators (Workman 2003).

MTA1 and MTA2. Besides being involved in the deacetylation of histones, these proteins are associated with metastasis suggesting that the NuRD complex plays some roles in regulating cell growth and the development of cancer. MTA and MTA2 have been shown to be involved. MTAI was identified due to its high expression level in metastasis cell lines, hence a metastasis protein (Lai and Wade 2014). Studies indicate that one mechanism by which MTAI regulates cell growth and cancer metastasis is estrogen receptor-mediated transcriptional repression (Lai and Wade 2014). MTA2 has been shown to interact directly with the tumor suppressor p53 and it modulates its steady-state acetylation level. Over-expression of MTA2 has been associated with deacetylation of p53 (Workman 2003). This correlates with impaired ability of p53 to arrest cell growth and to mediate apoptosis.

RbAp46 and RbAp4. These proteins are associated with histone deacetylases given their high affinity for histones and their presence in various deacetylation and remodeling complexes (Torchy, Hamiche, and Klaholz 2015). They also play a role in the regulation of the Ras pathway, as studies have demonstrated their role in antagonizing the Ras pathway which is responsible for cell growth, differentiation, and survival (Workman 2003). Another function of RbAp proteins that has been demonstrated in studies is to bring histone metabolic enzymes to histones (Workman 2003).

MBD2 and MBD3: MBD2 predominantly binds to methylated DNA, leading to a repression of
gene expression while MBD3 predominantly binds to non-methylated DNA, and is associated with active transcription (Torchy, Hamiche, and Klaholz 2015). Recent studies have demonstrated the interaction between MBD2 and MBD3 suggesting that MBD3 may target the NuRD complex to methylated DNA indirectly through MBD2 (Torchy, Hamiche, and Klaholz 2015). MBD3 also plays an important role in maintaining the integrity of the NuRD complex (Workman 2003).

Taken together, the nucleosome remodeling and deacetylation activities suggest that the NuRD complex is involved in various biological processes including repression of transcription, embryonic development, cellular differentiation, or tumor regulation. With advances in genetics, great progress in understanding the biochemical and biological function of the NuRD complex is expected in the near future.

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