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Review

# Keeping things quiet: Roles of NuRD and Sin3 co-repressor complexes during mammalian development

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ABSTRACT

Gene inactivation studies of mammalian histone and DNA-modifying proteins have demonstrated a role for many such proteins in embryonic development. Post-implantation embryonic lethality implies a role for epigenetic factors in differentiation and in development of specific lineages or tissues. However a handful of chromatin-modifying enzymes have been found to be required in pre- or peri-implantation embryos. This is significant as implantation is the time when inner cell mass cells of the blastocyst exit pluripotency and begin to commit to form the various lineages that will eventually form the adult animal. These observations indicate a critical role for chromatin-modifying proteins in the earliest lineage decisions of mammalian development, and/or in the formation of the first embryonic cell types. Recent work has shown that the two major class I histone deacetylase-containing co-repressor complexes, the NuRD and Sin3 complexes, are both required at peri-implantation stages of mouse development, demonstrating the importance of histone deacetylation in cell fate decisions. Over the past 10 years both genetic and biochemical studies have revealed surprisingly divergent roles for these two co-repressors in mammalian cells. In this review we will summarise the evidence that the two major class I histone deacetylase complexes in mammalian cells, the NuRD and Sin3 complexes, play important roles in distinct aspects of embryonic development.

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*Abbreviations:* Hdac, histone deacetylase; ESCells, embryonic stem cells; ICM, inner cell mass; dpc, days post coitum; MEF, mouse embryonic fibroblast.

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## 1. The NuRD complex

A decade ago the first purifications were reported of an abundant histone deacetylase complex that was distinct from the best-characterised deacetylase complex at the time, namely the Sin3 complex. The analogous Mi-2, NRD, NuRD and NuRD complexes were purified from *Xenopus* egg, HeLa cell and SW13 cell nuclear extracts, respectively (Tong et al., 1998; Wade et al., 1998; Xue et al., 1998; Zhang et al., 1998). The complex has become known as the NuRD (nucleosome remodelling and histone deacetylation) complex and, as the name suggests, couples the two main chromatin-modifying activities, chromatin remodelling and histone modification.

Independent purifications of the NuRD complex did not produce identical compositions, as there were subtle variations in each of the purifications. Nonetheless, the defining components of the complex are an Mi-2 chromatin remodelling subunit, an Mbd3 subunit and Mta subunit (Fig. 1A). Mta subunits (e.g. Mta1, Mta2 or Mta3) appear to be mutually exclusive within NuRD, possibly contributing to functional diversity of NuRD complexes (Bowen et al., 2004; Fujita et al., 2004). Mbd3 can be replaced by related protein Mbd2, forming the Mecp1 complex (Feng and Zhang, 2001; Le Guezennec et al., 2006a). The original purifications of NuRD did not identify Mbd2, indicating that Mecp1 accounts for only a small subfraction of the total NuRD in mammalian cells (Tong et al., 1998; Wade et al., 1998; Xue et al., 1998; Zhang et al., 1998). As Mbd2 has been shown to be dispensable for normal mammalian development (Hendrich et al., 2001), Mbd2 and Mecp1 will not be considered further in this review. NuRD also contains a core histone deacetylase complex comprised of Hdac1, Hdac2, Rbbp7 (formerly known as RbAp46) and Rbbp4 (formerly RbAp48). These core proteins are also found in the Sin3 complex. Additionally the presence of the Gatad2a and Gatad2b proteins (formerly kown as p66α and p66β) is often reported for NuRD purifications. While NuRD has been purified from mammalian, amphibian and insect cells, subunits of the complex have also been described in other organisms including plants and worms implying that NuRD is broadly conserved among plants and animals.

## 2. The Mi-2 nucleosome remodelling proteins

Mi-2 is a key component of the NuRD complex as it contains both the ATPase, chromatin remodelling activity and physically associates with histone deacetylases. Originally identified as an autoantigen in dermatomyositis (Seelig et al., 1995), it is the largest subunit of the NuRD complex. Mammalian genomes are capable of encoding two Mi-2 proteins: Mi-2α (encoded by the *Chd3* gene) and Mi-2β (encoded by the *Chd4* gene) (Seelig et al., 1996). The latter is the form predominantly associated with the mammalian NuRD complex (Feng and Zhang, 2001; Zhang et al., 1998), although Mi-2α has been shown to be a member of the NuRD complex in a variety of human cell lines (Le Guezennec et al., 2006a; Tong et al., 1998; Xue et al., 1998). Whether functional or cell type-specific differences exist between Mi-2α- and Mi-2β-containing NuRD complexes remains to be determined. Mi-2 proteins belong to the CHD (chromo-helicase–ATP–DNA binding) family, which is conserved from yeast to humans. Structurally, Mi-2α and Mi-2β both contain two PHD (plant homeo domain)-zinc finger domains, two chromodomains and a SWI2/SNF2-type ATPase/helicase domain, the latter being responsible for the nucleosome remodelling activity (Wang and Zhang, 2001). The chromodomains of *Drosophila melanogaster* dMi-2 have been reported to have DNA-binding ability (Bouazoune et al., 2002), but the role of the chromodomains in the mammalian Mi-2 proteins remains to be determined. Similarly, the function(s) of the PHD fingers has not yet been demonstrated.

## 3. Transcriptional regulation and the role of Mi-2β and the NuRD complex

Since its purification in 1998, numerous different functions for NuRD have been postulated, although its main function is as a transcriptional repressor complex (Denslow and Wade, 2007). As histone deacetylation is generally correlated with transcriptional repression, the presence of two Hdacs in the complex implicates it in transcriptional repression. The remodelling activity of NuRD may be required to allow access of the deacetylases to the histone tails. Indeed, histone deacetylation of nucleosomal substrates by Mi-2 complexes is stimulated by ATP hydrolysis. Importantly, the NuRD complex represents one of the most abundant forms of a deacetylase complex in amphibian eggs and cultured mammalian cells (Wade et al., 1998; Zhang et al., 1998). This implicates it as a possible general co-repressor complex.

Evidence for a repressive function of NuRD also comes from physical interaction studies. In murine lymphocytes, Mi-2β was uncovered as interacting with *Ikaros* and *Aiolos*, which are zinc finger DNA-binding factors and potent repressors required for lymphoid cell development (Kim et al., 1999). Ikaros is able to bind DNA in a sequence-specific manner and is also associated with pericentric heterochromatin in cycling T-cells, indicating that it might be involved in a more general silencing mechanism. Indeed, mammalian NuRD has been shown to interact with a variety of other transcriptional repressors (Fig. 1A) implicating it as a widely used repressor in a variety of cell types.

Mi-2β has also been implicated in transcriptional activation. Biochemical analysis revealed that the amino-terminus of Mi-2β had transcriptional activating ability in reporter assays by interacting with Brg-1 (Shimono et al., 2003). Williams et al. (2004) showed that Mi-2β is required for several steps during T cell development, playing a direct role in promoting *CD4* gene expression. This experiment defines a role for Mi-2β in gene activation in vivo. Whether this represents a NuRD-independent function of Mi-2β, or possibly implicates deacetylase function in transcriptional activation (e.g. Metivier et al., 2003; reviewed in Smith, 2008) remains to be demonstrated.

## 4. Developmental roles of the NuRD complex

Development requires the stable repression and activation of genes in different cell types. Transcriptional repression by the NuRD complex has been connected with developmental roles in numerous model systems (Table 1). In *D. melanogaster*, dMi-2 appears to function with Hb and Polycomb group proteins in HOX gene repression during embryo patterning (Kehle et al., 1998). dMi-2 is essential for embryogenesis as mutants arrest as first or second instar larvae, and is also required for germ cell development (Kehle et al., 1998). In *Caenorhabditis elegans*, mutations in the Mi-2 homologue *let-418* revealed it to be required for proper vulval development (Solari and Ahringer, 2000; von Zelewsky et al., 2000). Genetic approaches have shown that *let-418* is an essential gene and is required for larval viability. Additionally, *let-418* is required for maintenance of germline-soma distinctions in *C. elegans* as *let-418* deficient animals show inappropriate expression of germline-specific genes in somatic cells (Unhavaithaya et al., 2002). The *Pickle* (aka *Gymnos*) gene of *Arabidopsis thaliana* has been identified as a Mi-2 homologue (Eshed et al., 1999; Ogas et al., 1999). It has a similar role to *let-418*, as *Pickle* mutants express embryonic characteristics in root meristem cells (Ogas et al., 1997, 1999). Hence,

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