KRAB-ZNF / KAP Interaction

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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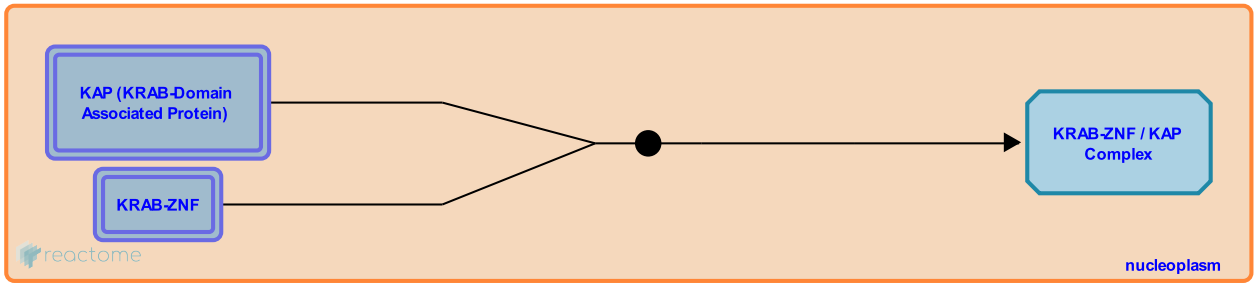
KRAB-ZNF / KAP Interaction ↗

Stable identifier: R-HSA-975040

Type: binding

Compartments: nucleoplasm



Formation of the KRAB ZNF / KAP1 Corepressor Complex:

Transcription factors which contain tandem copies of the C2H2 zinc finger DNA binding motif (ZNFs) are the most abundant class of TFs in the human proteome, comprising more than 1000 members. The KRAB ZNF proteins are the largest subset of these (with 423 members) and are defined by having an additional conserved domain, the KRAB domain (Bellefroid,1991, Margolin, 1994, Urrutia, 2003, Huntley, 2006). The Kruppel Associated Box (KRAB) domain is a transcription repression domain (Margolin, 1994) which mediates the recruitment of a specific and dedicated co repressor protein for the KRAB-ZNF family - KAP1 - which is required for transcriptional repression and gene silencing (Friedman, 1996).

The larger family of ZNF transcription factors are present in almost all metazoans and generally their DNA binding specificities and transcription regulation functions are conserved from Drosophila to humans. Although the biological functions of most ZNF TFs is not known, they often function biochemically as sequence specific DNA binding proteins and can be activators, or more oftenly observed, repressors of transcription, depending on cellular context. Transcriptional repression is mediated via specific protein protein interaction surfaces in the ZNF that function as repression domains, by recruiting specific co repressors, such as KAP1 in humans (Friedman, 1996), and dCTBP in Drosophila (Nibu, 1998).

In contrast to the larger ZNF family, the KRAB-ZNFs only appear much later in vertebrate evolution: genes encoding the primordial KRAB ZNF subfamily first arose in tetrapods and the family has been greatly expanded in numbers and complexity in mammals. Interestingly,a large fraction of KRAB-ZNFs are found only in primates. In addition to their rapid and dynamic evolutionary history, comparative genomics and expression studies of primate KRAB-ZNFs suggest that these genes have played a significant role in shaping primate specific traits (Huntley, 2006, Nowick, 2009).

The biochemical pathway utilized by KRAB-ZNFs is well defined and probably nearly identical for each member: All KRAB-ZNF proteins which have been studied in detail are repressors and utilize the KRAB domain to bind the KAP1 co-repressor. This interaction is direct, of high affinity, and is obligate for the KRAB-ZNF to function as a repressor when bound to DNA in vivo (Peng, 2000a,b).. The KAP1co-repressor appears to function as a scaffold protein to assemble and coordinate multiple enzymes (histone de-acetylases, histone methyltransferases and heterochromatin proteins) which target and modify chromatin structure thus leading to a compacted, silent state (Lechner, 2000; Schultz, 2001 Schultz, 2002 , Ayyanathan, 2003). The post-translational modification of KAP1 by SUMO controls its ability to assemble the enzymatic apparatus in chromatin (Ivanov, 2007; Zeng, 2008). It is formally possible that some KRAB ZNF proteins may have additional functional domains that recruit coactivators in specific contexts, given that such bifunctionality is common for many classes of DNA binding transcription factors,. However, there is no experimental evidence for this yet.

There also is good evidence that the KRAB ZNF-KAP1 complex proteins can have long range gene silencing functions, by nucleating chromatin complexes that inactivate transcription of large numbers of genes over large distances by assembling silent heterochromatin (Ayyanathan, 2003). Although KAP1 was originally identified as a mediator of specific gene transcription repression, subsequent studies have shown that KAP1 also is involved in the recruitment of homologues of the HP1 protein family (Ryan, 1999, Ayyanathan, 2003; Lechner, 2000). These nonhistone heterochromatin associated proteins were first shown to have an epigenetic gene silencing function in Drosophila and more recently in mammalian cells . These studies suggest that KRAB ZNF proteins and KAP1 may also be involved in large scale chromatin regulation and gene silencing, not just in gene specific transcriptional

repression. Whether this is a general property of most or all KRAB ZNF proteins will require additional studies.

Finally, several KRAB containing ZNFs in mammals also contain a conserved SCAN domain which, like the KRAB domain also functions as a protein protein interaction domain. (Edelstein, 2005, Peng, 2000a,b). The SCAN domain does not participate in KAP1 binding but rather functions to mediate homodimerization, or selective heterodimerization with other SCAN containing proteins. However, the biochemical and biological functions of the SCAN domain in KRAB-ZNF mediated repression are not known.

Remaining Questions: The single most important unanswered question for KRAB-ZNFDs is to determine their biological functions. While the mechanism utilized by the KRAB ZNF / KAP1 protein complex to mediate gene specific transcription repression is well understood , much less known about the specific biological pathways they control. Preliminary evidence from recent whole genome analysis of the target genes for the KRAB- ZNF263 protein suggest that it can have both positive and negative effects on transcriptional regulation of its target genes (Frietze, 2010). Presumably, each KRAB-ZNF, via its array of zinc fingers can bind to specific DNA recognition sequences in target promoters. This, combined with highly tissue specific expression of each gene, makes the potential transcriptome controlled by the 423 KRAB-ZNFs extremely large.

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