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Molecular Analysis of Silent Information Regulators

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Introduction

A group of non-essential genes necessary in trans for the transcriptional suppression of the silent mating type loci, HML and HMR in budding yeast, are known as silent information regulators (SIR). At least three SIR proteins, Sir2p, Sir3p, and Sir4p, are known to modulate chromatin shape to suppress transcription at several loci. In subtelomeric regions and at the HM loci, the Sir2/3/4 complex crosslinks to and immunoprecipitates with suppressed genes. Sir1p, which is much less common and only appears to have an impact on the mating type loci, interacts with the N-terminal domain of Sir4p and may also be a component of the complex. Regarding transcription, it is generally accepted that SIR-mediated silence entails the compacting of the chromatin fibre into a state that is resistant to RNA polymerases. This model is based on a number of findings. First, a variety of enzymatic probes have less access to HM and telomeric loci than they do to active loci. Second, in vivo foot printing research reveals highly organised nucleosomal arrays at silencer-adjacent suppressed HM loci. When the loci were depressed, these analyses discovered alterations in nucleosomal organisation close to the silencers as well as a few rather small modifications in the promoter region.

Description

Although there have been no reports to far of mutations in the core domains of histones that affect silence, there may be other characteristics of nucleosomal structure that contribute to the recruitment or binding of the SIR complex. There is substantial evidence in favour of a spreading paradigm for SIR dependent effects with regard to repression at a shortened telomere. However, there are some key differences between mating type repression at the HM loci and Sir2p-dependent silencing in the rDNA. Our understanding of the primary role of SIRs at telomeres may have been skewed by the use of transcriptional silencing experiments as the readout for the presence of SIR proteins. In addition to derepressing TPE, the lack of Sir3p or Sir4p also causes telomere shortening and increased chromosomal loss. Consequently, it is conceivable that the SIR complex is a fundamental part of a higher-order telomeric structure, whose main job is to maintain chromosomal ends and guarantee normal mitotic segregation. In fact, targeting a Sir4p subdomain to a vector improves the stability of the plasmid during mitosis, pointing to a potential role for Sir4p anchoring in mitotic segregation [1-4].

Although it has been conclusively demonstrated that Sir2p helps to silence Pol II-reporter genes that have been intentionally placed within the rDNA, its function in regulating rDNA transcription is less clear. The fact that a mutation of UAF, a transcription factor that binds to the upstream element of the rRNA promoter, enables a switch from Pol I- to Pol II-dependent transcription of the locus, provides one line of evidence that Sir2p affects the endogenous rDNA expression. The frequency of polymerase switching increases with loss of Sir2p, and this is accompanied by a quick increase in the number of rDNA repeats, an occurrence required for effective cell growth in the absence of Pol I transcription. It is interesting to note that longer SIR2 copy numbers in yeast are correlated with longer replicative lifespan, which may also be brought on by modifications to the rDNA chromatin structure. According to research from the Guarente laboratory, yeast has a shorter lifespan when autonomously reproducing rDNA episomes accumulate, which is most likely a result of high recombination rates. Since lifespan extension in response to caloric restriction depends on both SIR2 and NPT1, a component of the NAD-synthesis pathway, lifespan regulation may also be influenced by nutritional levels [1,5].

As NAD levels decrease, one would anticipate that Sir2p would work less effectively and that rDNA recombination or excision may increase. There are still questions regarding two crucial facets of Sir2p's enzymatic activity. The nature of its physiological substrate(s) is the subject of the first query, and the specificity of various Sir2 family members is the subject of the second. Given the proven link between HM locus silencing at telomeres and hypoacetylated H3 and H4 at the tails of histones and Sir2p targets, this hypothesis is appealing. However, it is important to keep in mind that neither the physiological targets of Sir2p, histone tails, nor the causes of the sir2-specific silencing abnormalities, lack of histone deacetylation, have been proven. It will be fascinating to find out whether inherent substrate specificity exists given that the majority of species contain at least four or five Sir2p-like enzymes, some of which have a highly constrained subcellular distribution [2,3].

Conclusion

We must concede complete ignorance when it comes to the mechanisms that bring together the SIR complex with nucleosomes to form a repressed chromatin structure, despite our growing understanding of the individual SIR proteins. Although there is conflicting evidence regarding whether Sir2p and Sir3p can assemble into a stable complex, it has been demonstrated that Sir3p and Sir4p can both form homo- and heterodimers as well as that Sir2p can bind Sir4p. Recently, in vitro homo-multimerization of Sir2p was proven utilising two differently labelled recombinant Sir2p proteins. The ratio of each component per nucleosome unit inside a suppressed domain is currently unknown, despite the fact that SIRs appear to spread along nucleosomes. because more and more modifying enzymes are becoming linked to the silencing event.

Acknowledgement

None.

Conflict of Interest

The author reported no potential conflict of interest.

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