

Structural studies of transcription complexes: the TFIID transcription/DNA repair factor in the context of transcription and its regulation

A post-doctoral position is available for two years at IGBMC (Strasbourg) to study the structure of transcription complexes. Gene expression is mainly modulated at the transcription level and this step determines the onset of normal cellular processes as well as the evolution towards pathologic situations. The objective of this proposal is to study the molecular structure of large multiprotein complexes involved in DNA transcription and repair in order to better understand the mode of action of these assemblies. TFIID is a multiprotein complex involved in transcription initiation by RNA polymerases I and II, in nucleotide excision repair (NER) and probably in cell cycle regulation. TFIID is present in all eukaryotic genomes and is composed of ten subunits with a total molecular weight of 460 kDa. It can be resolved into two functional and structural entities: the core-TFIID with two helicase activities (XPB and XPD) and a kinase complex (CAK). The XPB and XPD subunits catalyse promoter opening in transcription initiation or allow strand separation around the DNA lesion in the context of DNA repair by NER. Inherited mutations in the XPB and XPD subunit of the core-TFIID yield the rare genetic disorder Xeroderma pigmentosum (XP), Cockayne syndrome (CS) or Trichothiodystrophy (TTD). While all the XPD mutations are detrimental for the XPD helicase activity explaining the NER defect, some of them also result in distinct transcriptional defects. Indeed mutations in XPD result in a drop in the ability of certain NRs to be phosphorylated by TFIID and to mediate transcription explaining, at least partially, the developmental defects in the XPD-deficient patients. The effect of XPD mutations on the activity of nuclear receptors has important implications for interpretation of the phenotypes observed in patients with altered XPD.

This project aims at better understanding the molecular architecture of the TFIID factor, either alone or in complex with its partners, mainly by cryo-electron microscopy, X-ray crystallography and through a panel of biochemical (immuno-precipitations, gel-shift assays, SRP, ...) and biophysical (gel-filtration, light scattering, analytical ultracentrifugation, SANS, SAX...) approaches. An important aspect will be devoted to the identification, production, purification and characterization of eukaryotic complexes: (i) usage of the E. coli and baculovirus expression system for the production of recombinant complexes, (ii) usage of stable cell lines for the purification of endogenous complexes and the potential identification of new partners that will lead to stable and homogenous samples. The candidate will thus work in a highly competitive environment with access to cutting edge technologies at the interface between molecular biology and structural biology. The pluri-disciplinary approach is a chance to interact with different methodologies during this project.

Highly motivated can apply by sending an e-mail to Arnaud.POTERSZMAN@igbmc.fr

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