UFR de Chimie et de Biologie
UNIVERSITÉ Grenoble Alpes

Master's degree in Biology – Chemistry-Biology Department

Master 2 internship project
Year 2024-2025

Laboratory/Institute: IAB **Director:** P. Hainaut
Team: Épigénétique, Immunité, Métabolisme, Signalisation cellulaire et Cancer **Head of the team:** P. Hainaut
Name and status of the scientist in charge of the project: H. Menoni **HDR: yes** ☐ **no** ■
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Program of the Master's degree in Biology:

☐ Microbiology, Infectious Diseases and Immunology ☐ Structural Biology of Pathogens
■ Physiology, Epigenetics, Differentiation, Cancer ☐ Neurosciences and Neurobiology

Title of the project:

Molecular insight of Base Excision Repair (BER) initiation of oxidative DNA lesions in the nucleosomal context

Objectives:

We will address how a single DNA lesion localized in various nucleosomal DNA context is identified by DNA glycosylases. We aim to characterize i) the mode of recognition of 8-oxoG by OGG1 glycosylase in different sites around the nucleosome ; ii) the way CSB helps to access DNA lesion during BER initiation to initiate 8-oxoG excision at specific nucleosomal position determined *in silico*.

Abstract:

We will study BER on nucleosomal templates, in a pure and "tunable" system, currently impossible to obtain in living cells. The project will focus on the 8-oxoguanine glycosylase (OGG1), a bi-functional glycosylase excising 8-Oxoguanine (8-oxoG), the most abundant oxidative DNA damage. This enzyme can use nucleosomal DNA as its substrate to initiate the BER pathway, with a marked dependence on translational and presumably rotational position of the defect within the nucleosome particle. To further elucidate the mechanisms required to initiate BER, our collaborator at ENS Lyon (Dr. Gillet) already characterized the 8-oxoG structural and dynamical behavior in the nucleosome to analyze the most interesting 8-oxoG positions for OGG1 (and CSB) binding. We will now precisely measure when(-if) OGG1 is capable of targeting CSB remodeler specifically or if it is CSB that facilitates OGG1 glycolytic/AP-lyase activities at these positions.

Methods :

Production and purification of DNA templates with single 8-oxoG. Protein purification (i.e. OGG1, and CSB) will be performed using established protocols (collab. Team Palencia-IAB). Nucleosome reconstitution and biochemical repair experiments will be carried out on fluorescently labeled DNA.

Up to 3 relevant publications of the team:

Menoni, H., et al. The transcription-coupled DNA repair-initiating protein CSB promotes XRCC1 recruitment to oxidative DNA damage. **NAR** doi.org/10.1093/nar/gky579
Menoni, H. et al. BER of 8-oxoG in dinucleosomes **NAR** doi.org/10.1093/nar/gkr761
Menoni, H., Di Mascio, P., Cadet, J., Dimitrov, S., and Angelov, D. Chromatin associated mechanisms in base excision repair - nucleosome remodeling and DNA transcription, two key players. **Free Radic Biol Med** *107*, 159-169; 10.1016/j.freeradbiomed.2016.12.026

Requested domains of expertise (up to 5 keywords):

DNA Repair, Glycosylase, Nucleosome, Molecular biology and Biochemistry