LPC\_Géraldine FARGE

Maintenance of human mitochondrial DNA: a single-molecule study

Mitochondria contain their own genome (mtDNA) encoding 13 proteins involved in the production of ATP. To ensure a faithful replication of their genome, mitochondria contain an unique enzymatic machinery (replisome) and mutations affecting the function of this replisome have been associated with a large group of diseases in which the stability and maintenance of mtDNA are affected, such as neuropathy, optic atrophy or cardiomyopathy.

The objective of this phD project is to elucidate the molecular structure-function mechanisms by which specific mutations in the human replisome affect the integrity of mtDNA and cause pathologies. More precisely, we will characterize the functions of several mutants of the mitochondrial helicase and of the single-stranded DNA binding protein (mtSSB). For this, we will use a dynamic and functional approach using biophysical techniques on the scale of the single molecule: acoustic force spectroscopy (AFS), for the manipulation of single molecules, and TIRF microscopy, for the visualization of fluorescent proteins. Combined with the structural approach (electron microscopy) also carried out in the laboratory, this project will provide a better understanding of the mechanisms by which mutations in mtDNA maintenance proteins cause mtDNA instability in mitochondrial pathologies.