PhD Research Proposal Form
China Scholarship Council (CSC) - ENS Group

FIELD: Biology

Thesis subject title:

Characterizing the role of specialized ribosomes and ribosome-associated proteins during the interferon response.

Name of the French doctoral school :
BIOLOGIE MOLÉCULAIRE INTÉGRATIVE ET CELLULAIRE (BMIC)

Name of the Research team :
Website : http://rmi2lab.weebly.com or https://www.ens-lyon.fr/LBMC/equipes/rna-metabolism-in-immunity-and-infection-rmi2/presentation?set_language=en&cl=en

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Lab Language : English/French

Research Proposal Abstract :
Ribosomes, the cellular machinery responsible for protein synthesis, play a pivotal role in the regulation of gene expression and cellular responses to various stimuli. Interferons (IFNs), key components of the innate immune system, are critical for mounting antiviral defences. While the role of interferons in the activation of cellular antiviral pathways is well established, their specific impact on ribosomes and their associated proteins is unknown. This study aims to elucidate the molecular mechanisms underlying interferon-mediated modulation of ribosomal function and its consequences for antiviral responses.
We have conducted a comprehensive analysis of ribosome-associated proteins upon interferon treatment using a combination of proteomic profiling and functional approaches. Our results reveal that interferon signaling significantly alters the composition of ribosomal subunits and associated proteins. In particular, we identified several novel ribosome-associated proteins that exhibit dynamic changes in their association to ribosomes upon interferon stimulation. These proteins are involved in diverse cellular processes, including translation regulation, RNA metabolism and innate immune signalling. Notably, interferon treatment promotes the recruitment of DDX60 and DDX60L to ribosomes, thereby enhancing their antiviral potential.

Based on these preliminary results, our thesis project aims at characterizing the functional roles of the above-mentioned ribosome-associated factors. To this aim, we plan on performing mutagenesis analyses in order to identify the residues involved in ribosome association and mutate them to

monitor the functional consequences of losing ribosome association. We also plan on performing Cryo-EM studies to characterize the precise position of the identified factors on ribosomes and understand their functional role. Finally, ribosome profiling coupled with RNA-seq in conditions where the ribosome-associated factors are depleted or not from cells, will allow us to understand their impact in modulating mRNA translation.

Overall, our findings will provide mechanistic insights into the dynamic interplay between interferon signalling, ribosomes, and their associated proteins, shedding light on the complex regulatory network governing antiviral responses.

References :

1. **Shaping the Innate Immune Response Through Post-Transcriptional Regulation of Gene Expression Mediated by RNA-Binding Proteins.** Guillemin A, Kumar A, Wencker M, Ricci EP. Front Immunol. 2022 Jan 11;12:796012. doi: 10.3389/fimmu.2021.796012. ECollection 2021. PMID: 35087521

2. **Ribosome dynamics and mRNA turnover, a complex relationship under constant cellular scrutiny.** Morris C, Cluet D, Ricci EP. Wiley Interdiscip Rev RNA. 2021 Nov;12(6):e1658. doi: 10.1002/wrna.1658. Epub 2021 May 5. PMID: 33949788

3. **The long non-coding RNA LUCAT1 is a negative feedback regulator of interferon responses in humans.** Agarwal S, Vierbuchen T, Ghosh S, Chan J, Jiang Z, Kandasamy RK, Ricci E, Fitzgerald KA. Nat Commun. 2020 Dec 11;11(1):6348. doi: 10.1038/s41467-020-20165-5. PMID: 33311506

4. **Genome editing in primary cells and in vivo using viral-derived Nanoblades loaded with Cas9-sgRNA ribonucleoproteins.** Mangeot PE, Risson V, Fusil F, Marnef A, Laurent E, Blin J, Mournetas V, Massouridès E, Sohier TJM, Corbin A, Aubé F, Teixeira M, Pinset C, Schaeffer L, Legube G, Cosset FL, Verhoeyen E, Ohlmann T, Ricci EP. Nat Commun. 2019 Jan 3;10 (1):45 doi: 10.1038/s41467-018-07845-z. PMID: 30604748

Type of PhD :

1.Full PhD

- Joint PhD/cotutelle (leading to a double diploma) : YES
- Regular PhD (leading to a single French diploma) : YES

2. Visiting PhD (for students enrolled at a Chinese institution who will be invited to a French institution to carry out a mobility period) : NO