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Host laboratory:
Lab : Laboratory of Chemistry and Biology of Metals

Host group/team:
Metals & Organ team

Title of the M2 research internship:
Study of copper homeostasis mechanisms in pulmonary cells

Project summary:
Copper (Cu) is an essential trace element used by enzymes to perform redox reactions but novel roles in cell differentiation and cancer development have been described in the last decade. As free Cu is highly detrimental, the cell develops homeostasis mechanisms to finely orchestrate Cu trafficking. Thus, soluble proteins called Cu chaperones convey and deliver Cu to target proteins. Among them, CCS provides Cu to SOD1, while Atox1 drives Cu to ATP7A and/or ATP7B proteins that transport Cu into the Golgi apparatus for the maturation of Cu proteins. Upon Cu overload, ATP7A or ATP7B can migrate to the plasma membrane to excrete excess Cu. The expression level and respective role of ATP7A and ATP7B is cell type-dependent and remains unknown for pulmonary cells. Moreover, we recently showed that both ATP7A and ATP7B are expressed in normal pulmonary cells but only ATP7A is expressed in cancer cells with resistance to chemotherapy and to Cu stress. In this project, we aim to identify the role of ATP7A and ATP7B in pulmonary cells and the modifications induced in the adenocarcinoma cell line expressing only ATP7A with the goal to understand how this favour their resistance. To reach these objectives, the student will determine the subcellular localization of ATP7A and ATP7B in the different cell lines and upon variation of Cu concentration (from Cu deprived to Cu excess) using confocal microscopy. In the same conditions, the distribution of the two chaperones CCS and Atox1 will be resolved thanks to super resolution fluorescence microscopy (dSTORM) that is required to obtain the intracellular distribution of these proteins. Finally, 2-colour dSTORM will be used to confirm possible colocalizations between Atox1 and ATP7A or ATP7B based on the results of previous experiments. These data will be combined with subcellular distribution of Cu from elemental imaging that will be acquired by a post-doctoral student in the lab. Overall, these results will participate in the understanding of Cu homeostasis in healthy and cancerous pulmonary cells.

Keywords:
Copper homeostasis, super resolution fluorescence microscopy, pulmonary cells

Relevant publications of the team:
Copper transport across cell membranes by calix[4]arene-based cationophores leading to potent biological activity. Renier N, Weyckmans Mele G, Lelièvre P, Boeckstaens M, Lavendomme R, Aydogan A, Dussein Y, Charbonnier P, Puillet Anselme L, Chovelon B, Castillo-Michel H, Tumanov N, Wouters J, Sancey L, Busser B, Maria Marini A, Veronesi G, Jabin I*, Deniaud A*, Valkenier H*. *ChemRxiv*, *2025*.

ATP7B-Deficient Hepatocytes Reveal the Importance of Protein Misfolding Induced at Low Copper Concentration. Charbonnier P, Chovelon B, Ravelet C, Ngo TD, Chevallet M, Deniaud A*. ***Cells****, 2022; 11(21). doi: 10.3390/cells11213400.*

Development, formulation, and cellular mechanism of a lipophilic copper chelator for the treatment of Wilson's disease. Gauthier L, Charbonnier P, Chevallet M, Delangle P, Texier I*, Gateau C*, Deniaud A*. ***Int. J. of Pharmaceutics****, 2021; 609.* doi: 10.1016/j.ijpharm.2021.121193.

The Multifaceted Roles of Copper in Cancer: A Trace Metal Element with Dysregulated Metabolism, but also a Target or a Bullet for Therapy. Lelièvre P, Sancey L, Coll JL, Deniaud A*, Busser B*. ***Cancers****. 2020; 12 (12), 3594. doi : 10.3390/cancers12123594.*