Call for Excellence Doctoral Scholarship – MuSkLE / InnovInOnco

Skeletal striated muscle resistance to metastasis: understanding the mechanisms and cellular interplays involved

Host Laboratories
InnovInCo: Lab#1: CRCL; KidsCaN – Cancer Neuroscience and Metastasis in Pediatric Malignancies
MuSkLE: Lab#2: INMG; Metabolic regulations of adult muscle stem cell fate

PhD supervisors
Céline Delloye-Bourgeois (CRCN CNRS; celine.delloye@lyon.unicancer.fr)
Elise Belaidi (PU UCBL; elise.belaidi@univ-lyon1.fr)

Project description
Metastasis is the leading cause of death from cancer. Secondary tumor sites are formed by cancer cells that have "escaped" from the primary site, having acquired specific migration, invasion and proliferative capacities that enable them to colonize and adapt themselves to certain distant tissues. While most cancers metastasize to organs such as the lung, liver or brain, skeletal striated muscle appears resistant to metastasis. Skeletal striated muscle cells (SMC) have the unique property to contract, thereby inducing metabolic changes in their physiologic hypoxic microenvironment, which could influence tumor metastatic potential and/or the propensity of healthy tissue to be colonized.
Since metastases rarely establish within the muscle, we propose to explore the impact of microenvironment modifications induced by SMC contraction on the metastatic process using a unique, innovative and original device that we developed in the lab. Our multimodal *ex vivo* model combines an isolated muscle contraction system with a cell culture device in hypoxic conditions, mimicking the muscle microenvironment. This will enable us to uncover the mechanisms of resistance of SMCs to the metastatic process and to further built upon these mechanisms to counteract the metastatic process in highly-affected sites. We will combine this paradigm with an *in vivo* model based on the micro-grafting of human tumor cells into the avian embryo. This model enables the experimental recapitulation and tracking of the entire metastatic cascade *in vivo* (Ben Amar 2022, Villalard 2024) while allowing manipulation of the identified candidate cellular and molecular mechanisms.
This study will enable us to: 1) characterize the steps (invasion, migration, dormancy/proliferation) of the metastatic cascade influenced by skeletal muscle contraction, and explore the subsequent role of the crosstalk between energetic metabolic and hypoxia in the SMC microenvironment; 2) identify associated changes in the metabolic profile of the muscle microenvironment in order to highlight key targets which could be modulated to blunt the metastatic cascade. Understanding the protective processes set up by SMCs in the face of metastatic development will provide major insights into the mechanisms of tumor dissemination and open up prospects for anti-metastatic treatments.

Consortium
Céline Delloye-Bourgeois is a CNRS researcher and leads a team at the CRCL dedicated to pediatric cancer research. Her ERC team explores the multi-layered interplay between the embryonic microenvironment, where pediatric nervous system cancers arise, and their unique metastatic properties. She has developed a series of in vivo and ex vivo models that recapitulate the entire metastatic cascade, enabling the investigation of functional and physical interactions between metastatic cancer cells and the various tissues and microenvironments they traverse during metastasis.
Elise Belaidi is a full professor in physiology (pharmacy faculty, Lyon). She is an expert in the field of hypoxia research. She explores the role of hypoxia Inducible Factor in adaptive to maladaptive response to hypoxia in several models such as cardiac diseases and metastases (Moulin 2020). Especially, she explores the impact of hypoxia on cellular metabolic response from transcription regulation to mitochondrial function (Moulin 2022). As an expert, she has been invited in national and international conferences (n=14 since 2019).

References
- Ben Amar D, Thoinet K, Villalard B, Imbaud O, Costechareyre C, Jarrosson L, Reynaud F, Novion Ducassou J, Couté Y, Brunet JF, Combaret V, Corradini N, Delloye-Bourgeois C*, Castellani V*. Environmental cues from neural crest derivatives act as metastatic triggers in an embryonic neuroblastoma model. Nat Commun. 2022 May 10;13(1):2549.
- Moulin S, Thomas A, Wagner S, Arzt M, Dubouchaud H, Lamarche F, Bouyon S, Vial G, Godin-Ribuot D, Pépin JL, Arnaud C, Belaidi E. Intermittent Hypoxia-Induced Cardiomyocyte Death Is Mediated by HIF-1 Dependent MAM Disruption. Antioxidants (Basel). 2022 Jul 27;11(8):1462.
- Moulin S, Thomas A, Arnaud C, Arzt M, Wagner S, Maier LS, Pépin JL, Godin-Ribuot D, Gaucher J, Belaidi E. Cooperation Between Hypoxia-Inducible Factor 1α and Activating Transcription Factor 4 in Sleep Apnea-Mediated Myocardial Injury Can J Cardiol. 2020 Jun;36(6):936-940.
- Villalard B, Boltjes A, Reynaud F, Imbaud O, Thoinet K, Timmerman I, Croze S, Theoulle E, Atzeni G, Lachuer J, Molenaar JJ, Tytgat GAM, Delloye-Bourgeois C*, Castellani V*. Neuroblastoma plasticity during metastatic progression stems from the dynamics of an early sympathetic transcriptomic trajectory. Nat Commun. 2024 Nov 6;15(1):9570.