ÉCOLE NORMALE SUPÉRIEURE DE LYON

Master 2 Internship offer

Date of the offer: September 2024

Lab : team '**Developmental and Evolutionary Histories of Vertebrates'**
Dr. Eglantine Heude, Team Leader, permanent CNRS researcher (CR CNRS)
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https://igfl.ens-lyon.fr/equipes/eglantine-heude/development-evolutionary-histories-vertebrates?set_language=en&cl=en

Characterization of TGFβ signaling function during neck morphogenesis and sarcomagenesis

Head and neck sarcomas constitute rare malignant tumors of mesenchymal origin with poor prognosis. Rarity induces major challenges for diagnosis and limits the understanding of the molecular pathogenesis of sarcoma and its malignancy processes.

Recent studies have demonstrated that tumor subsets share transcriptomic similarities with their corresponding cell lineage embryonic origins and mimic the tissue-specific developmental programs. We will combine developmental and cancer biology approaches and state-of-the-art cell imaging tools to comprehensively analyze neck musculoskeletal morphogenesis and identify regulators of mesenchymal malignancy.

Using the similarities between tumor and normal embryonic development, both characterized by rapid cell expansion, we will investigate embryonic pathways that could be re-initiated during tumor formation and expansion.

TGFβ signaling appears critical for both neck tumorigenesis and musculoskeletal formation by modulating genetic networks involved in cell proliferation and differentiation.

In the present project we will combine *in vitro* and *in vivo* approaches in sarcoma cell lines and mouse embryos by inactivating TGFβ function to assess how TGFβ pathway dysregulation affects neck formation and disease progression.

We are currently generating new conditional mouse models using the Cre-Lox system to inactivate TGFβ signaling specifically in embryonic population of interest (Figure 1, CNC = neural crest and LPM= lateral plate mesoderm-derived cells). Embryos will be collected at key developmental stages and the phenotype of mutants will be investigated by immunofluorescence stainings for markers of skeletal, tendon and muscle development as well as of proliferation and apoptosis. Analysis will be performed on sections or on whole-mount clarified specimens and high resolution confocal or light-sheet microscopy.

In parallel, we will study the function of TGFβ pathway *in vitro* to determine how it is associated with cell impaired differentiation. Knockdowns (KD) of TGFβ signaling actors will be performed using siRNAs in undifferentiated pleomorphic sarcoma (UPS) and fibrosarcoma cell lines (Figure 1). Cell survival, proliferation, stemness as well as the ability to differentiate will be assessed with specific markers by immunofluorescent stainings and high resolution live and confocal imaging.

The collected data will allow a better understanding of the mechanisms behind TGFβ regulation during neck morphogenesis and will seek to highlight conserved developmental programs that could be re-activated during neck sarcomagenesis.

The student will work in close collaboration with a postdoctoral researcher in the team who is currently developing the present project under the supervision of E. Heude.

Candidates must have a strong background in cellular biology and fluorescent imaging approaches, and interest for developmental and cancer biology.

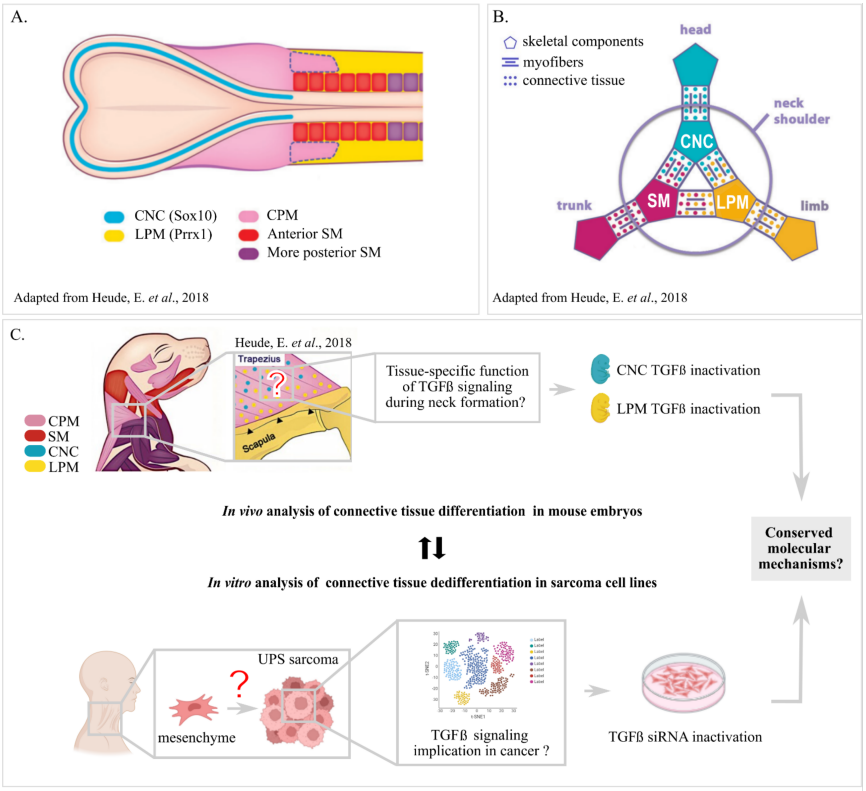

Figure 1. Musculoskeletal and connective tissue relationship during murine neck development and experimental approaches to investigate TGFβ function in neck morphogenesis and sarcomagenesis. (A) Schematic view of an early mouse embryo and cell populations forming the neck musculoskeletal system. (B) Model of muscle connectivity network showing the mixed origins of connective tissues in the neck region. (C) Embryonic origin of musculoskeletal derivatives in a mouse fetus and simplified experimental set-up to identify the molecular basis of neck morphogenesis and sarcomagenesis by studying the role of the TGFβ signaling pathway. Abbreviations: CNC, cephalic neural crest; LPM, lateral plate mesoderm; CPM, cardiopharyngeal mesoderm; SM, somitic mesoderm; UPS, undifferentiated pleomorphic sarcoma; siRNA, small interfering RNA.

Heude *et al.* (2018) Unique morphogenetic signatures define mammalian neck muscles and associated connective tissues. *eLife* Nov19 (https://elifesciences.org/articles/40179)