Analysis of spatial transcriptomics (Visium) data to study the spatial heterogeneity of oral cavity cancers

Équipe : Analyse intégrée de la dynamique des cancers (chef d'équipe : Pr Pierre Saintigny, médecin chercheur, oncologue médical au Centre Léon Bérard où il coordonne le Département de Médecine Translationnelle ; https://www.crcl.fr/en/teri-department/integrated-analysis-of-the-dynamics-of-cancer-2/).

Unité : Centre de Recherche en Cancérologie de Lyon (CRCL), Département Échappement Tumoral, résistance et Immunité, UMR INSERM 1052 / CNRS 5286 Mixte CLB, Lyon France (https://www.crcl.fr/)

Contacts : yannick.lemeitour@lyon.unicancer.fr ; karene.mahtouk@univ-lyon1.fr

Profil recherché : Étudiant de master 1 ou master 2 ayant des bonnes connaissances en bio-informatique, notamment avec le langage R.

Période : 3 à 6 mois selon le profil, disponible à partir de janvier 2023

General context of the team

The goal of our research team is to understand the longitudinal dynamics of head and neck cancers in order to prevent the transformation of pre-malignant lesions, the development of secondary primary tumors and to improve the efficacy of treatments. Our strategy is to integrate clinical, pathological and molecular parameters to best describe the dynamic changes during early stages of tumorigenesis and under the pressure of treatment selection for patients.

Context of the proposed internship

One of our specific objectives is to understand the diversity and heterogeneity of head and neck cancers, in particular those of the oral cavity (OSCC, for oral squamous cell carcinoma) in order to better understand the pathogenesis of OSCC, to improve patient stratification and therapeutic strategies. Tumor heterogeneity refers to the composition of the tumor cells themselves but also to the composition of the immune microenvironment. In addition, there is inter-patient heterogeneity, partly related to distinct environmental factors such as tobacco and alcohol consumption. Despite their strong association with tobacco and alcohol consumption ("SD" patients for smoker/drinker), 10-15% of head and neck cancers are diagnosed in non-smokers and non-drinkers (NSND) patients and the pathogenesis of these tumors remains poorly understood. Conventional high-throughput RNA sequencing (RNAseq) technology has enabled significant advances in the field of cancer. However, this technology measures the expression level at the tissue level and averages the expression profiles of all cells in the tissue. In recent years, another technology has emerged that allows the sequencing of the transcriptome of a single cell: single sell RNA Seq (scRNA-Seq). This innovative technology has become the method of choice for studying tumor heterogeneity. However, the isolation of single cells during the necessary tissue dissociation step of scRNA-seq destroys information on their spatial localization within native tissue and their proximities to each other, which is critical for understanding cellular microenvironment and cell–cell interactions. Current spatial transcriptomics approaches, like Visium, cannot yet provide deep transcriptomic information on precisely localized single cells in tissue; however, they can shed light on the niches enriched for distinct gene sets. When used in combination, scRNA-seq and spatial transcriptomics can thus localize transcriptionally characterized single cells

within their native tissue context. Integrating scRNA-seq and spatial transcriptomics (Visium) data may therefore increase our understanding of the roles of specific cell subpopulations.

Hypothesis and internship project

In this context, we are interested in studying the tumor heterogeneity of OSCC at different levels, and in the context of two different etiologies: association or not with smoking and alcohol consumption. Our hypothesis, based on previous work of the team, is that the main biological difference between OSCC of non-smoker and non-drinker (NSND) and so-called smoker/drinker (SD) patients lies in the immune microenvironment, suggesting a higher clinical benefit of immunotherapy in OSCC of NSND patients. To address this hypothesis, we generated scRNAseq and Visium data from 11 whole tumor biopsies of OSCC patient. The main focus of this work will be the analysis of these Visium data using, when needed, the already analyzed scRNAseq data. The data analysis will be oriented around two main aspects:

1) Implementing statistical techniques for spatial data analysis. The objectives of the internship will be:
   - To use neighborhood and promixity between relevant cell type and cluster
   - To quantify spatial correlation (using Moran's I or Geary's C) for genes, cell type and/or cluster of interest
   - To perform a comparative analysis of these result between SD vs NSND patients

2) Validation of already available scRNAseq data. The objectives of the internship will be:
   - To analyze subpopulation of the tumor microenvironment (immune cells and cancer associated fibroblasts)
   - To analyze the tumor cells heterogeneity
   - To perform a comparative analysis of these result between SD vs NSND patients

The following knowledge will be required:

- Strong knowledge in statistics and bioinformatics
- Strong foundation in Omics
- Good mastery of R + ggplot2/tidyverse
- Scientific knowledge/curiosity in the field of oncology and immunology would be appreciated
- Curiosity in the research of adequate statistical and algorithmic tools as well as a facility for their implementation and a critical mind on the results is a highly appreciated quality

Environment and supervision:

You will be supervised by a teacher-researcher in immunology (Karène Mahtouk, PhD), a third year PhD student (Yannick Le Meitour) and a bioinformatics engineer (Lucas Michon, INSA Lyon alumnus). Your place in a translational research team will help you to understand the clinical aspects necessary to carry out this work, and will also teach you how to popularize your results to make them accessible to non-bioinformaticians.