Title: Multi-omics approaches to identify pollution-associated alterations in tumour metabolism

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Introduction

Human activity is associated with the production of xenobiotic pollutants that contribute to the contamination of ecosystems. Organisms, such as humans, are exposed to these pollutants throughout their entire life. These xenobiotics (drugs, pesticides, plastics, etc.) have been demonstrated to have multiple effects on human health. However, the full extent of their impact on the pathogenesis remains unclear (Koual et al., 2020).
The sources of xenobiotics are ubiquitous and include air, food and beverages, packaging, cosmetics and cleaning products, fertilisers and pesticides, and industrial wastes. These substances enter into the human body mainly through inhalation, ingestion and direct-contact. A rising number of epidemiological and molecular studies support the hypothesis that there is an increase in the incidence of cancer linked to xenobiotics exposure (Baj et al., 2022).
The carcinogenic effect could be highlighted in different tissues, however, this project is focused on lung cancer, hepatocarcinoma and breast cancer, given the rising incidence and mortality of these pathologies. Atmospheric pollutants are the main cause of lung cancer in non-smokers. Interestingly, according to (Berg et al., 2023), while the global number of smokers is decreasing, there is an increase in lung cancer cases, following the rise of air pollution. Moreover, given the central role of the liver in the metabolism of substances, the development of hepatocarcinoma is particularly sensitive to cytotoxic substances. It has been demonstrated that secondary metabolites deriving from the metabolism of this compound have a central role in the appearance of precancerous lesions (Baj et al., 2022). Furthermore, numerous studies have indicated a link between these pollutants and the insurgence and progression of breast cancer (Koual et al., 2020).
Cancer has many metabolic consequences where both the mesenchyme and the associated microenvironment (TME) contribute to radical metabolic changes in order to sustain tumour development through a complex cross-talk (Wang et al., 2021). An increasing number of studies have demonstrated a direct effect of single xenobiotics on the reprogramming of tumour metabolism. However, the joint effect (exposome) of these chemicals has not yet been characterised. One potential mechanism for this metabolic reprogramming is the activation of an immune response against xenobiotics. For instance, T $CD8^+$ tissue-resident lymphocytes in the liver are activated by pollutants, and their activation is linked to the rise of precancerous lesions (Baj et al., 2022). There is a growing interest in tumour metabolism as well as the study of TME finding new and potential therapeutic targets.

Objectives

The objective of this project is to highlight the role of tumour metabolism and the TME in the development and progression of cancer associated with xenobiotics. A robust computational approach will be employed to analyse proteomics and transcriptomics data to identify key molecular mechanisms that could be used as therapeutic targets. The project will be developed in three phases over the course of three years:

1. Data retrieval and analysis: I will conduct a systematic literature review to identify datasets of single-cell, spatial and RNA sequencing, and also assays proteomics related

to lung, breast and liver cancer. In particular, the aim is to identify experiments characterised by the exposure of patients to pollutants, with a focus on the exposome. The collected data will be precisely analysed to extract useful information about the metabolically active cellular populations and their molecular profiles. This will enable the discovery of overlapping altered mechanisms in different types of cancer.

2. Development of network models: the second year will be focused on the creation of computational models to simulate the cellular response to alterations (e.g., inhibition or activation) of metabolic and signalling pathways of interest. The data collected during phase two will be used to build and evaluate the models. The network models will then be used to predict the effect of potential therapeutic compounds or xenobiotics on tumour progression.
3. Further analysis, thesis writing and publication of the results: the third year will be dedicated to a comprehensive analysis of the results, which will form the basis of the thesis. Additionally, I will participate in conferences to disseminate the findings.

Methods

The project will be primarily computational, with the objective of precisely characterising the tumour and TME and their metabolic assets. I will initially focus on a comprehensive literature review and a detailed analysis of the experimental design, encompassing both proteomics and transcriptomics approaches. Subsequently, the data extracted will be analysed by advanced bioinformatics techniques with the objective of profiling the complete cellular dynamics associated with the tissue studied.
The development of mathematical models and machine learning techniques will be performed to simulate the cellular response to stimuli.

Expected results

This project expects to elucidate, through bioinformatic analysis of multi-omics data from xenobiotic-exposed cancers, key metabolic pathways and shared therapeutic targets across lung, breast, and liver cancers. This step should identify potential therapeutic targets. Additionally, computational models will be developed to predict cellular responses to targeted interventions, ultimately advancing our understanding of the exposome's role in tumour metabolism.