AAP China Scholarship Council - CSC 2023

PROJET DE RECHERCHE DOCTORALE (PRD)

Titre du PRD : Molecular drivers of glioblastoma cell plasticity

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CO-TUTELLE INTERNATIONALE envisagée : ☐ OUI ☒ NON

DESCRIPTIF du PRD :

*Ce texte sera affiché en ligne à destination des candidates et candidats chinois : il ne doit pas excéder **2 pages** doit être rédigé en **ANGLAIS***

Metabolic control of glioblastoma cell plasticity

Glioblastoma (GB), the most common form of primary brain tumor in adults, is characterized by resistance to current treatments. One of the main causes of this therapeutic resistance is the significant intra-tumor heterogeneity of the functional states of GB cells. Recent studies, to which our team has contributed, have identified micro-territories within patient tumors in which GB cells in different functional states coexist: stem or non-stem cells, proliferative or non-proliferative, motile or static, pro-angiogenic or not, tumor-initiating or not, sensitive or resistant to therapies (1-8). These cell states are not specific to a particular mutational profile and are therefore detected in the tumors of all patients. The emergence of this functional heterogeneity is fuelled by the selection of genomic clones and by the differentiation of cancer stem cells, but also and mainly by the exceptional plasticity of GB cells. This plasticity allows GB cells to oscillate between different functional states in response to variations in their environment and to therapies (9, 10).

Each functional state depends on specific metabolic requirements. Any change in functional state is accompanied by significant variations in cellular metabolic activities. These metabolic variations are classically interpreted as simple adaptations to the cellular requirements of each functional state (11). However, we showed that variations in metabolic activity can also drive these cell state changes in GB and thus affect tumor development (7). These data highlight the central role played by metabolism in the adaptation of GB cells to changes in their microenvironment. The relevance of targeting metabolism for therapeutic purposes is supported by several studies (11) including ours (7, 12, 13) which show that tumor growth can be slowed by limiting the activity of key enzymes of deregulated metabolic pathways in GB. Our interest in metabolic deregulations is not only motivated by our work on its driving role in GB cell plasticity, but also by its location downstream of all signalling pathways that control cell behavior. We therefore consider metabolism as a unique opportunity to identify molecular players of plasticity common to different GB mutational profiles, and whose therapeutic targeting should therefore be relevant for a wide range of patients.

On this basis, the aim of this project is to map the metabolic modules underlying the functional states of GB cells in patients' tumors, with the ultimate goal to propose novel therapeutics targeting cellular plasticity. Our team has already developed computational approaches to model the metabolic profile of GB cells in a given functional state from single-cell transcriptomes (scRNA-seq).

The candidate will:

1. Participate in the reconstruction of the metabolic profile of GB cells according to their functional state

2. Evaluate experimentally in vitro and in vivo the predictions of computational analyses using a large panel of human GB models (patient-derived cells/PDCs, organoids and intracerebral PDC xenografts) and techniques.

References

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