Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Uncovering the role of ANXA4 in glioblastoma recurrence

Synopsis:

Glioblastoma (GB) is the most frequent primary malignant brain tumor[1], accounting for 16% of all central nervous system (CNS) primary tumors[2]. Despite substantial advances in the comprehension of disease biology and the current standard-of-care, including surgery followed by radiation and chemotherapy[3], the median overall survival (OS) of these patients is around 15-18 months[4,5] and the 5-year survival is only 5%[6]. This poor prognosis has been mainly attributed to high tumor invasion of the surrounding healthy brain[7] and the development of therapeutic resistance mechanisms by cancer cells[8,9]. These two characteristics lead to tumor recurrence after surgery[7]. Recurrent GB are usually inoperable and are left without therapeutic options. Therefore, there is an unmet medical need for more effective treatment approaches for recurrent GB patients.

Previously, our team has performed RNA sequencing in 8 paired GB samples (primary and matched recurrences) to identify genes differentially expressed in recurrent tumors that may play a role in resistance to therapy. Tumor tissues in this discovery cohort were collected in the Department of Neurosurgery at Hospital de Santa Maria, Unidade Local de Saúde de Santa Maria (ULSSM), snap frozen and stored in our Brain Tumor Bank at Biobanco-iMM CAML. Based on available literature, public data sets on GB, and after our initial validation of the identified genes, we have selected *ANXA4* to be further studied.

Therefore, in this project we hypothesize that high expression levels of ANXA4 in GB tumors are associated with increased resistance to standard therapy, leading to tumor recurrence and a worse patient outcome. In this proposal, the main goal is to study the role of ANXA4 in GB recurrence. To accomplish this, the work plan has 3 objectives: 1) Validate the clinical relevance of ANXA4 by quantifying its protein levels by immunohistochemistry in an independent validation cohort of primary and recurrent matched samples of GB patients, and correlate these levels with time to relapse (progression-free survival) and overall survival; 2) In vitro functional validation of ANXA4 role in the development of therapeutic resistance using a commercially available GB cell line (U87 cells) with overexpression of ANXA4 treated with temozolomide (TMZ) and/or radiation; and 3) In vivo functional validation of ANXA4 role in GB progression using an orthotopic NSG mice model injected with the U87 cell line with overexpression of ANXA4 and treated with (TMZ) and/or radiotherapy (RT).

At the end of this project, we expect that the results obtained may contribute to validate ANXA4 as an important player in GB recurrence. These results can pave the way for future research in the identification of novel and more effective targeted therapies, improving the outcome of GB patients.

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