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YOU ARE INVITED TO ATTEND THE

DEFENSE OF THE DOCTORAL

DISSERTATION

"Temozolomide exposed: glioblastoma-derived exosomes on hematopoiesis"

by

Marina Gergues

Molecular Biology, Genetics, & Cancer Track

B.S., 2013, Rutgers The State University of New Jersey
M.BS., 2015, Rutgers Graduate School of Biomedical Sciences

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Professor
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Wednesday, April 28th, 2021
1:00 P.M.
Zoom Link:
https://rutgers.zoom.us/j/99333589098?pwd=aHY0NmRQSEg3bWxJL3ZxNnZWV3BFdz09

Meeting ID: 993 3358 9098
Password: 850982

ABSTRACT

Glioblastoma (GBM), the most common and aggressive glioma, has an average survival rate of less than 15 months. The standard treatment for GBM includes maximal surgical resection followed by concurrent radiotherapy and chemotherapy with the alkylating agent, temozolomide (TMZ). Despite advances for new treatments, TMZ remains the frontline therapy, making TMZ resistance a clinical challenge. Part of GBM pathogenesis is caused by increased immune suppressor functions within the tumor microenvironment. The literature reports extensively on the immune suppressor cells within the tumor. However, there is little information on how GBM cells communicate with the bone marrow (BM) to enhance hematopoietic activity towards myeloid lineage and generate immune suppressor cells. To this end, this thesis tested the hypothesis that GBM instigates a pro-tumor immunity by releasing exosomes (GDE) that stimulate hematopoiesis towards myeloid differentiation. TMZ resistant GBM cells release significantly ($p<0.05$) more exosomes per cell as compared to TMZ sensitive cells. An *ex vivo* model of hematopoiesis with a transwell system containing healthy BM mononuclear cells in the outer wells and GBM cells in the inner wells, resulted in higher percentages of hematopoietic stem and progenitor cells (HSPCs), based on flow cytometry and clonogenic assay for myeloid progenitors. Hematopoietic activity was mediated by GDEs, resulting in significantly more common myeloid progenitor (CMP) and granulocyte/monocyte progenitor (GMP), and decreased megakaryocyte/erythrocyte progenitor (MEP). Since GBM is mostly diagnosed in the aging population with predominantly myeloid cells, we sought a possible explanation for responsiveness of the aged hematopoietic cells to GDEs. We interrogated a role of HMGB1, which is decreased in aged human hematopoietic cells. This was contrary to the role for HMGB1 to regulate hematopoietic homeostasis in young individuals, based on validation in mice, humanized with young hematopoietic system. These studies suggested that the aged BM is already prone to generate myeloid cells by GDEs. Thus, this thesis is significant in two critical ways: first, it unveils peripheral systemic effects caused by TMZ-resistant GBM; and second, it identifies GDEs and their contents as peripheral therapeutic target to prevent hematopoietic dysregulation associated with GBM immune evasion and tumor growth.