University of Massachusetts Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

INTERDISCIPLINARY GRADUATE PROGRAM

Ph.D. THESIS DEFENSE

JESSICA WEATHERBEE

MENTOR: Alonzo Ross, PhD

FRIDAY, 8/5/2016 10:00 a.m.

LRB room 816

"Exploiting DNA Repair and ER Stress Response Pathways to Induce Apoptosis in Glioblastoma Multiforme"

Glioblastoma multiforme (GBM) is a grade IV brain tumor characterized by a heterogeneous population of cells that are highly resistant, aggressive, and infiltrative. The current standard of care, which has not changed in over a decade, only provides GBM patients with 12-14 months survival post diagnosis.
We asked if the addition of a novel endoplasmic reticulum (ER) stress inducing agent, JLK1486, to the standard chemotherapy, temozolomide (TMZ), which induces DNA double strand breaks (DSBs), would enhance TMZ's efficacy.Because GBMs rely on the ER to mitigate their hypoxic environment and DNA repair to fix TMZ induced DSBs, we reasoned that DSBs occurring during heightened ER stress would be deleterious.

Combination of TMZ+JLK1486 reduced secondary sphere formation, decreased cell viability, and increased cell death due to apoptosis. We found that TMZ+JLK1486 prolonged ER stress induction, as indicated by elevated ER stress markers BiP, ATF4, and CHOP, while sustaining activation of the DNA damage response pathway. This combination produced unresolved DNA DSBs due to reduction in RAD51, a key DNA repair factor, which correlated with increased ER stress. The combination of TMZ+JLK1486 is a potential novel therapeutic combination and suggests an inverse relationship between ER stress and DNA repair pathways.

Mentor(s)

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Dissertation Exam Committee

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