Ira O. Racoma
PhD Candidate

“Targeting Glioblastoma Survival Signaling: A Novel Mechanism of Action of Thymoquinone”

May 7, 2013
Biomedical Research Tower, Room 105
1:30 pm

VITA

October 25, 1982 . . . . . . . . . . . . . . . . . . . . . . Born – San Carlos City, Philippines

May 2005 . . . . . . . . . . . . . . . . . . . . . . . . . . . . BS, Biochemistry, University of Nevada Las Vegas

COMMITTEE MEMBERS

Altaf A. Wani, PhD

Arnab Chakravarti, MD

Balveen Kaur, PhD

Robert M. Snapka, PhD
ABSTRACT

Glioblastoma is a grade IV glioma and remains the most aggressive and devastating cancer of the central nervous system with a median survival of 15 months. It is the most common malignant brain tumor diagnosed in adults and accounts for 23% of all primary brain tumors. Adding to this statistic is the number of recurring tumors, which occurs in a vast majority of cases. Glioblastomas are resistant to treatment due to the upregulation of survival pathways, decreased expression in pro-apoptotic proteins and overexpression of anti-apoptotic proteins.

There has been a growing interest in natural compounds with anti-cancer properties because they are relatively non-toxic to healthy cells and are available in a readily ingested form. The dietary phytochemical thymoquinone (TQ) is the primary bioactive component of *Nigella sativa* Linn seed (also known as black seed) oil which has been used for centuries in Middle Eastern, Indian and European countries for culinary purposes and to promote good health. We have previously shown that TQ induces apoptosis in HL-60 leukemia cells and MCF-7/DOX doxorubicin-resistant breast cancer cells.

The work presented in this thesis describes the mechanism of action TQ in apoptosis-resistant glioblastoma cells. On the molecular level, TQ induced intense DSBs and cell cycle alterations. We found that TQ mediated these effects on DNA and the cell cycle via arylation of target molecules, and not via generation of reactive oxygen species. Additionally, TQ did not exert the same detrimental effects on normal human astrocytes, confirming reports of the selectivity of TQ for cancer cells.

Glioblastoma are characterized by their resistance to apoptosis due to upregulation of several survival signaling pathways. In recent years, autophagy has emerged as a bona fide survival pathway for a number of tumors. TQ inhibited autophagy in glioblastoma cells, which was found to be a consequence of permeabilization of the lysosomal membrane. Additionally TQ induced the release of cathepsins into the cytosol which can mediate caspase-independent death in apoptosis-resistant cells.

Finally, TQ was tested *in vivo* by evaluating the survival time of mice with intra-cranial tumors. TQ resulted in a promising increase of survival time in treated mice. Orally administered drug did not result in adverse reactions and appears to be able to reach a neurological tumor site. The significance of this work was to investigate the modulation of a novel tumor survival pathway with a natural compound in the hopes of shedding light on new approaches to the treatment of a recalcitrant tumor.
RECENT ABSTRACTS AND PRESENTATION


---

RECENT PUBLICATIONS


2. **Racoma IO**, Snapka RM, Wani AA. Thymoquinone mediates cytotoxicity via arylation of key cellular molecules. (In preparation)


AWARDS AND HONORS

Ray Travel Award, The Ohio State University Council of Graduate Student, 2011