Morgan S Schrock, DVM
PhD Candidate

Wwox Deficiency in Human Cancers: Role in Treatment Resistance

Thursday, March 23rd, 2017
James B050
10:00 am
VITA

June 5, 1984 . . . . . . . . . . . . . . . . . . . Born
    Muscatine, Ia

May 5, 2006 . . . . . . . . . . . . . . . . . . . Bachelor of Science
    Cedar Crest College

May 2, 2010 . . . . . . . . . . . . . . . . . . . Doctor of Veterinary Medicine
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COMMITTEE MEMBERS

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ABSTRACT

WWOX gene deletions occur in a variety of human cancer types, and reduced Wwox protein expression can be detected early during cancer development. In this study, loss of expression of the fragile site-encoded Wwox protein was found to contribute to radiation and cisplatin resistance of cells, responses that could be associated with cancer recurrence and poor outcome. We found that Wwox loss is followed by mild chromosome instability in genomes of mouse embryo fibroblast cells from Wwox-knockout mice. Human and mouse cells deficient for Wwox also exhibit significantly enhanced survival of ionizing radiation and bleomycin treatment, agents that induce double-strand breaks (DSBs). In a xenograft tumor model of irradiated cells, Wwox-deficient cancer cells exhibited significantly shorter tumor latencies, suggesting that Wwox-deficiency facilitates radiation resistance in vivo. In examining mechanisms underlying Ww ox-dependent survival differences, we found that Wwox-deficient cells exhibit enhanced homology directed repair (HDR) and single strand annealing (SSA) repair pathways, but reduced nonhomologous end-joining (NHEJ) and Alternative-NHEJ (Alt-NHJE) repair, suggesting that Wwox contributes to DNA DSB repair pathway choice. We also demonstrated interaction of Wwox with Brca1, a driver of HDR, and show via immunofluorescent detection of repair proteins at ionizing radiation-induced DNA damage foci that Wwox expression suppresses DSB repair at the end-resection step of HDR. We propose a genome caretaker function for Wwox, in which Brca1–Wwox interaction supports NHEJ as the dominant DSB repair pathway in Wwox-sufficient cells. This Wwox effect has important consequences in human disease: in a cohort of brain, ovarian and non-small cell lung cancer patients treated with radiation or cisplatin, Wwox deficiency significantly correlated with shorter overall survival times, indicating that dysregulation of DSB repair by Wwox-deficiency worsens patient outcome via treatment resistance.
RECENT ABSTRACTS AND PRESENTATIONS


RECENT PUBLICATIONS


3. Sun J*, Shen R*, Schrock MS*, Liu J, Pan X, Quimby D et al. (2016) Reduction in squamous cell carcinomas in mouse skin by dietary zinc supplementation. Cancer Med. 8; 2032-2042. Original research article *These authors contributed equally to this work


AWARDS AND HONORS

1. Graduate University Fellowship, The Ohio State University (2012)

FUTURE PLANS

My long-term career goal is to become an independent scientist with expertise in DNA damage pathways responsible for cancer development and recurrence. As a veterinarian, I also have an interest in animal models of human cancer—both genetically-engineered mouse models of cancer as well as spontaneous cancers that occur in pets. Following graduation, I will continue my training as a post-doctoral scientist where I can pursue these interests and prepare for a career in academic research.
DEDICATION

This thesis is dedicated to the many people who have enriched my life with opportunities for learning.

Uncle Rick and Aunt Marcia whose gifts of books nurtured my young mind,
My inspiring and terrifying 8th grade English teacher, Elsie Olán, whose lessons and assignments taught me the satisfaction of proper diction,
My grandpa Buckaroo, who lovingly took me along with him on sheep shows and nightly chores and whose passing taught me the heartbreak of cancer,
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My dad, who worked hard so my siblings and I could pursue our every interest,
My mother, who gave me every object, moment of time, and pearl of wisdom she had,
My husband, who has dedicated his life to learning about growing old with me,
And my children, whose lives teach me the importance of the future.