Author's response to reviews

Title: The cancer gene WWOX behaves as an inhibitor of SMAD3 transcriptional activity via direct binding

Authors:

Brent W Ferguson (bwferguson@mdanderson.org)
Xinsheng Gao (gaoxs@yahoo.com)
Maciej J Zelazowski (MJZelazowski@mdanderson.org)
Jaeho Lee (jhlee@mdanderson.org)
Collene R Jeter (cjeter@mdanderson.org)
Martin C Abba (mcabba@gmail.com)
C. Marcelo Aldaz (maaldaz@mdanderson.org)

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Author's response to reviews:

Dear BMC Cancer Editor:

Please find attached our manuscript entitled "The cancer gene WWOX behaves as an inhibitor of SMAD3 transcriptional activity via direct binding " by Brent W. Ferguson et al., which we are submitting for your consideration for publication as a Research Article in BMC Cancer.

In this report we describe that ablation of expression of the tumor suppressor gene WWOX in normal breast epithelial cells leads to a protransformation phenotype and to transcriptional activation of SMAD3 gene targets. Furthermore, we demonstrate that WWOX binds and regulates SMAD3 transcriptional activity by cytoplasmic sequestration. As a consequence we observed the upregulated expressions of multiple genes associated with advanced breast cancer progression.

We consider these findings very important for understanding the paradoxical effects of TGFβ signaling in breast cancer. TGFβ acts as an inhibitor of growth in normal mammary epithelium but transitions to being an enhancer of tumor progression in advanced breast cancer stages. The mechanisms behind this dichotomous behavior are not understood. We hypothesize that the progressive loss of WWOX expression observed in advanced breast cancer is a key event for deregulating TGFβ signaling and more importantly may explain some of the pro-metastatic effects resulting from TGFβ/SMAD3 hyperactive signaling in advance breast cancer by the selective activation of specific gene targets.

We believe that this manuscript will be of interest to BMC Cancer readers in general. Thank you for your time in considering our manuscript.

Sincerely yours,
C. Marcelo Aldaz, M.D., Ph.D.
Professor
Department of Molecular Carcinogenesis
University of Texas M.D. Anderson Cancer Center
Science Park - Research Division
Smithville, Texas 78957
(512) 237-9530 tele
(512) 237-2475 fax
E-mail: maaldaz@mdanderson.org