Author's response to reviews

Title: Activation of the steroid and xenobiotic receptor, SXR, induces apoptosis in breast cancer cells.

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Author's response to reviews: see over
Dear Dr. Norton:

Enclosed please find our original article entitled “Activation of the steroid and xenobiotic receptor, SXR, induces apoptosis in breast cancer cells” by Suman Verma, Michelle M. Tabb, and Bruce Blumberg for consideration as a research article in BMC Cancer. This article was originally submitted to Breast Cancer Research and has been transferred by their editorial team to BMC Cancer on our behalf.

We believe that this paper will be of interest to the readership of BMC Cancer because it demonstrates a novel link between the nuclear Steroid and Xenobiotic Receptor (SXR) and breast cancer. SXR is a key regulator of the body’s response to drugs, bioactive dietary components and xenobiotic chemicals, mediating the breakdown of these compounds by inducing catabolic enzymes in the liver and intestine. The role of SXR in other tissues was mostly unknown until recently when we and other groups showed that SXR has functions other than its conventional role in metabolism in these tissues. For example SXR helps in maintaining homeostasis in bone, decreases chemically-induced fibrogenesis in the liver and decreases apoptosis induced by anti-cancer agents in endometrial cancer. Here for the first time we show that activation of SXR induces apoptosis in breast cancer cells. The apoptosis induced by SXR activators is mediated through a nitric oxide and p53 dependent mechanism in p53 wild type breast cancer cell lines. Loss- and gain-of-function studies confirm the key role of SXR as a central player in this mechanistic pathway of inhibiting breast cancer growth. These findings reveal a novel biological function for SXR and suggest that a subset of SXR activators may function as effective therapeutic and chemopreventative agents for certain types of breast cancers. At present, very little is known about the function of SXR in breast beyond a suggestion that it may play a role in drug resistance. Our results provide a plausible mechanism for the decreased proliferation of breast cancer cells by SXR. These findings are very important because many commonly used drugs, including chemotherapeutic drugs and dietary and environmental compounds activate SXR. The ability of dietary and xenobiotic chemicals to activate and antagonize SXR could have important implications for linking diet and lifestyle factors with breast cancer.

On behalf of my co-authors, I certify that the enclosed material has not been submitted for publication elsewhere. Neither has it been published in whole or in part elsewhere. I attest to the fact that all authors listed on the title page have read the manuscript and approved the final version to submit to BMC Cancer. We also agree that the contents of this manuscript will not be copyrighted, submitted, or published elsewhere; while acceptance by BMC Cancer is under consideration.
We recommend Dr. Ana Soto (Tufts University), Dr. Barry Forman (City of Hope National Cancer Center) and Dr. Powel Brown (Baylor University) to review this article.

Thank you for considering our manuscript.

Sincerely yours,

Bruce Blumberg