Letter to the Editor

Radiat Oncol J 2012;30(4):226-227
http://dx.doi.org/10.3857/roj.2012.30.4.226
pISSN 2234-1900 · eISSN 2234-3156

ROJ Radiation Oncology Journal

Troglitazone and tumor inhibition: an evolving concept in the management of systemic malignancies

Shailendra Kapoor

University of Illinois at Chicago, Chicago, IL, USA

The recent article by An et al. [1] provided for highly stimulating reading. Interestingly, recent data suggests that troglitazone may attenuate tumor growth in a number of systemic malignancies besides accentuating the radio-sensitivity of cervical carcinomas.

For instance, troglitazone attenuates tumor growth in gastric malignancies. It mediates this role by modulating the early growth response protein 1 (EGR-1) pathway. It accentuates nonsteroidal anti-inflammatory drug-activated gene 1 (NAG-1) expression within the cancerous cells [2]. As a result it augments intra-tumoral apoptosis within the gastric carcinomas. These effects are time dependent. Similar effects have been seen in colon carcinomas; it mediates this role by accentuating nuclear factor kappa B (NFκB) inactivation via attenuation of glycogen synthase kinase (GSK)-3β activity within the tumor cells. Intra-tumoral Bax levels are accentuated. As a result apoptosis is markedly augmented [3]. Cyclin B1 and cyclin D1 levels are attenuated. G0/G1 phase arrest is typically seen. Caspase-9 levels are typically accentuated. Troglitazone also decreases FLIP activity and thereby increase the sensitivity of the colon cancer cells to TRAIL induced apoptosis [4]. The anti-neoplastic activity of troglitazone is augmented by loss of X-linked inhibitor of apoptosis protein (XIAP) [5].

Similarly, troglitazone decreases tumor growth in breast cancers. It mediates this role by attenuating human telomerase reverse transcriptase (hTERT) expression within the mammary malignancies [6]. Telomerase activity is markedly reduced. Cdk2 and Cdk4 levels are markedly attenuated. As a result, increased G1 phase arrest is typically seen. In addition, it inhibits histone deacetylase resulting in attenuated phosphatidylinositol 3-kinase (PI3K) signaling [7]. p27 levels are accentuated [8]. These effects are dose dependent.

Similar effects are seen in prostate malignancies. Troglitazone primarily exerts these anti-neoplastic effects by accentuating intra-tumoral inactivation of NFκB. It mediates this role by suppression of GSK-3β expression [9]. Troglitazone also mediates this role by augmenting Erk phosphorylation within the cancerous cells. It also modulates p21 and c-*myc* expression [10]. It down-regulates expression of c-*myc*. As a result there is increased G0/G1 phase arrest [11]. These effects have been seen both *in vivo* and *in vitro*.

The above examples clearly illustrate the significant anti-neoplastic activity of troglitazone and the need for further studies in this regard.

References

1. An Z, Liu X, Song H, et al. Effect of troglitazone on radiation sensitivity in cervix cancer cells. Radiat Oncol J 2012;30:78-87.
2. Wang C, Wang J, Bai P. Troglitazone induces apoptosis in gastric cancer cells through the NAG-1 pathway. Mol Med Report 2011;4:93-7.

Received 2 December 2012, Accepted 6 December 2012.

Correspondence: Shailendra Kapoor, University of Illinois at Chicago, Chicago, IL, USA. Tel: +1-865-607-1014, Fax: +1-865-657-6767, E-mail: shailendrakapoor@yahoo.com

3. Ban JO, Kwak DH, Oh JH, et al. Suppression of NF-kappaB and GSK-3beta is involved in colon cancer cell growth inhibition by the PPAR agonist troglitazone. Chem Biol Interact 2010; 188:75-85.
4. Roth W, Grund K, Wiestler OD, Schirmacher P. The anti-diabetic drug troglitazone sensitizes colon cancer cells to TRAIL-induced apoptosis by down-regulating FLIP. Verh Dtsch Ges Pathol 2007;91:294-301.
5. Qiao L, Dai Y, Gu Q, et al. Loss of XIAP sensitizes colon cancer cells to PPARgamma independent antitumor effects of troglitazone and 15-PGJ2. Cancer Lett 2008;268:260-71.
6. Rashid-Kolvear F, Taboski MA, Nguyen J, Wang DY, Harrington LA, Done SJ. Troglitazone suppresses telomerase activity independently of PPARgamma in estrogen-receptor negative breast cancer cells. BMC Cancer 2010;10:390.
7. Davies GF, Ross AR, Arnason TG, Juurlink BH, Harkness TA. Troglitazone inhibits histone deacetylase activity in breast cancer cells. Cancer Lett 2010;288:236-50.
8. Yu HN, Lee YR, Noh EM, et al. Induction of G1 phase arrest and apoptosis in MDA-MB-231 breast cancer cells by troglitazone, a synthetic peroxisome proliferator-activated receptor gamma (PPARgamma) ligand. Cell Biol Int 2008;32:906-12.
9. Ban JO, Oh JH, Son SM, et al. Troglitazone, a PPAR agonist, inhibits human prostate cancer cell growth through inactivation of NFκB via suppression of GSK-3β expression. Cancer Biol Ther 2011;12:288-96.
10. Bolden A, Bernard L, Jones D, Akinyeke T, Stewart LV. The PPAR gamma agonist troglitazone regulates Erk 1/2 phosphorylation via a PPARγ-independent, MEK-dependent pathway in human prostate cancer cells. PPAR Res 2012;2012:929052.
11. Akinyeke TO, Stewart LV. Troglitazone suppresses c-Myc levels in human prostate cancer cells via a PPARγ-independent mechanism. Cancer Biol Ther 2011;11:1046-58.