

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

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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 (NF $\kappa$ B) inactivation via attenuation of glycogen synthase kinase (GSK)-3 $\beta$  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 NF $\kappa$ B. It mediates this role by suppression of GSK-3 $\beta$  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

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