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We study on the molecular toxicology and cancer biology.

Research

Our previous studies demonstrated that ATO induces c-Src activation to phosphorylation EGFR via ROS production **(Tseng et al. 2012)**, which can induce ERK1/2 activation to inactivate GSK-3*b* to increase c-Jun stability to be an adapter at the p21 promoter **(Huang et al. 2011)**. The sustained ERK1/2 phosphorylation can also stabilize c-Fos expression and dimerize with c-Jun to form a complex with p300/CBP to induce p21 expression and resultant apoptosis in human keratinocytic carcinoma A431 cells **(Huang et al. 2006; Liu and Huang 2006; Liu and Huang 2008a)**. Opposingly, ATO can activate JNK pathway to induce phosphorylation of N-terminus c-Jun (Ser63/73) to recruit TGIF/HDAC1 to the p21 promoter to suppress its transcriptional expression **(Huang et al. 2006; Huang et al. 2010; Liu and Huang 2006; Liu and Huang 2008b)**. That is, ATO-induced activation of JNK pathway antagonizes ERK-induced p21 expression and apoptosis. Therefore, we hypothesize that blockage of the negative regulators, such as JNK pathway and TGIF, can enhance ATO-induced cellular apoptosis.

HaCaT cells, an immortalized non-tumorigenic human keratinocyte, were continuously exposed to low-dose trivalent arsenic (ATO, 50-200 nM) for at least 4 weeks. We proved that low-dose ATO could stimulate malignant transformation of human HaCaT and rat fibroblast NIH3T3 cells, including increase of cellular proliferation, anchorage-independent growth, epithelial-to-mesenchymal transition markers alteration, MMPs activation, invadopodia formation, and migration/invasion activities **(Liu et al. 2015)**. In addition, TGIF expression via c-Src-dependent ROS production and EGFR-Y845 phosphorylation is involved in the events. Accordingly, we suggest that chronic exposure to low-level ATO (0.1~0.2 μM) can promote non-tumorigenic keratinocytic cells into transformation involving TGIF expression.

We further proved that TGIF can antagonize ATO-induced cellular apoptosis in human keratinocytes and hepatocellular carcinoma cells **(Huang et al. 2010; Liu and Huang 2008b; Liu et al. 2011)**. The

results indicate that TGIF might play a role in the carcinogenesis**.** TGIF, 5'TG3'-interacting factor, is one of the TALE (three-amino-acid loop extension) subfamily of atypical homeodomain proteins. It plays a role of transcriptional repressor/co-repressor to interact with Smad proteins, and then repress TGF-*b*-mediated signaling (Wotton et al. 2001). In addition, mutations in the TGIF gene have been found in patients with HPE (holoprosencephaly), a severe brain and craniofacial malformation associated with mental retardation (Gripp et al. 2000). Analysis ofthe specimens of 168 human upper urinary tract urothelial carcinoma (UTUC) by immunohistochemistry, we proved that overexpression of TGIF is associated with worse prognosis and progression of UTUC patients after radical nephroureterectomy **(Yeh et al. 2012)**. In addtion, the TGIF-induced cellular migration/invasion phenomena may be through the ROS production **(Huang et al. 2012)**. Furthermore, among the 168 human UTUC patients, 23 advanced stage patients who received the systemic chemotherapy treatment of the combination of gemcitabine and cisplatin (GC) were subjected for further chemotherapeutic drug sensitivity analysis. We demonstrated that alteration of TGIF and p-AKT^{Ser473} expression is correlated with poor prognosis and chemo-resistance in UTUC patients **(Yeh et al. 2016).**