PREDICTION OF ARSENIC-MODULATED MOLECULAR NETWORKS INVOLVING TRANSCRIPTION FACTORS EXPRESSED IN ONSET OF KERATINO CYTE DIFFERENTIATION

Udensi K. Udensi, Hari HP Cohly, Barbara E. Graham-Evans and Raphael D. Isokpehi

RCMI Center for Environmental Health, Jackson State University, Jackson, Mississippi, USA

Abstract: Human exposure to inorganic arsenic induces skin cancer. In our previous investigation, we established a chronic HaCaT keratinocyte cell culture (exposure to 0.5 mg/L arsenic trioxide up to passage 22) and used DNA microarray gene expression experiments combined with quantitative PCR to identify genes regulated by arsenic trioxide. As a follow-on investigation, we have focused on genes encoding membrane proteins as they could bind to arsenic at the cell surface and lead to changes in cellular biological pathways. Two genes encoding membrane proteins, Interleukin 1 receptor, type II (IL1R2) and Tumor necrosis factor (ligand) superfamily, member 18 (TNFSF18) were confirmed with q-PCR to be up-regulated in HaCaT cells exposed to low chronic dose of arsenic trioxide. Disulfide-containing proteins are attractive drug and diagnostic candidates as their interactions are potent and specific. Since arsenic has high affinity to bind to sulfur atoms of cysteine residues, detecting disulfide bonds between cysteine residues could be an arsenic insult marker in proteins whose functions are altered by arsenic exposure. Thus, disulfide bond formation between cysteines residues present in IL1R2 and TNFSF18 were determined. Further, to identify functional pathways that could be affected by arsenic interaction with these two proteins, molecular interaction network maps were reconstructed. Based on the agreement of software for disulfide bond prediction and X-ray diffraction, we identified as potential arsenic targets, the disulfide bonds Cys157-Cys207 and Cys24-Cys80 in IL1R2 and TNFSF18 respectively. Reconstruction of molecular interaction networks containing IL1R2 and TNFSF18 revealed interconnections to E2F4, a cell cycle–expressed, oncogenic transcription factor. The known predominant expression of E2F4 in the onset of keratinocyte differentiation raises the possibility that arsenic perturbation of molecular interactions that include E2F4 could alter keratinocyte differentiation pathways. This report provides insights into previously unknown gene markers that may explain the mechanisms of arsenic-induced dermal disorders including skin cancer.

Keywords: Arsenic trioxide, cysteines, disulfide bond prediction, HaCaT cell, gene networks and immune response genes.

Acknowledgements: Research Centers in Minority Institutions (RCMI) – Center for Environmental Health at Jackson State University (NIH-NCRR 2G12RR013459); Mississippi NSF-EPSCoR Grant Awards (EPS-0903787); Pittsburgh Supercomputing Centre’s National Resource for Biomedical Supercomputing (T36 GM008789); National Center for Integrative Biomedical Informatics (U54DA021519); U.S. Department of Homeland Security Science & Technology Directorate (2007-ST-104-000007; 2009-ST-062-000014; 2009-ST-104-000021).