ARSENIC INDUCED SKIN LESIONS AND ITS ASSOCIATION TO INFLAMMATORY CYTOKINES

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Introduction

Arsenic is a naturally occurring compound in the earth's crust and it is highly toxic in its inorganic form. Exposure to elevated levels of inorganic arsenic (iAs) through contaminated drinking water is a major health threat worldwide. Levels higher than 10µg/L have been associated with carcinogenic effects on the liver, lung, bladder and skin. A prominent sign of arsenic toxicity are skin lesions (hyperkeratosis, melanosis, leukomelanosis, Bowen's) which can be precursor to arsenic induced skin cancer (squamous cell carcinoma and basal cell carcinoma) as well as other arsenic related malignancies. Consumed iAs are methylated using S-Adenosyl Methionine (SAM) producing monomethylarsonic acid (MMA) and then dimethylarsinic acid (DMA). The reaction is catalyzed by methyltransferases, most notably, arsenite methyltransferase (*AS3MT*). In a previous large-scale genome-wide association study (GWAS) we identified genetic variants, rs11191527 and rs9527, in the *AS3MT* gene region, to play a key role in arsenic metabolism and arsenic induced skin lesions (Pierce et al., 2012). Chronic low levels of arsenic exposure can evoke an inflammatory response (Dutta et al., 2015). Here, we evaluate whether plasma levels of inflammatory cytokines are associated with skin lesion risk due to long term arsenic exposure.

Methods

We measured a panel of inflammatory cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, INF-ϒ, GM-CSF and TNF-α) using a Luminex based multiplexed assay among 1596 randomly selected individuals from our GWAS participants (Male= 790, Female= 806) drawn from two population studies in rural Bangladesh: Health Effects of Arsenic Longitudinal study (HEALS) and the Bangladesh Vitamin E Selenium Trial (BEST). All participants were exposed to arsenic. There were 996 skin lesion cases and 600 controls. Genotype data were generated with Illumina Infinium HD SNP array. Using multivariate logistic regression analyses we evaluated the relationships among the inflammatory cytokines, AS3MT variants and skin lesions risk adjusting for age, gender, and BMI.

Results

We observed that males are at higher risk of developing arsenic induced skin lesions than females (OR 1.71, 95% CI 1.40- 2.10). However regardless of gender, individuals with skin lesions had significantly higher levels of all the thirteen inflammatory cytokines tested than the control group (Figure 1). Age also plays a role in skin lesion risk: those under the age of 35 and over the age of 51 were at significantly higher risk (OR 1.92 and 1.79 respectively). Those with variant allele A (GA and AA genotype) compared to wild type (GG) for the SNP rs9527 were genetically predisposed to a higher risk of arsenic induced skin lesions (OR 1.43, 95% CI 1.09-1.88). We calculated the median concentration for each cytokine from individuals without skin lesions and we split the population into 2 groups. We found that the individuals with above median cytokine levels (for any of the tested 13 inflammatory cytokines) were at significantly

higher risk for skin lesions than those who had ≤median levels of corresponding cytokines (OR 1.37-3.79) independent of age, gender, BMI and rs9527 genotype. Males showed independent association with skin lesion when adjusted for any of the 13 cytokines and the SNP rs9527 also showed it for many of the cytokines (IL-1, IL-4, IL-5, Il-6, IL-7, IL-13 and TNF-α, OR 1.33-1.38) but not all.

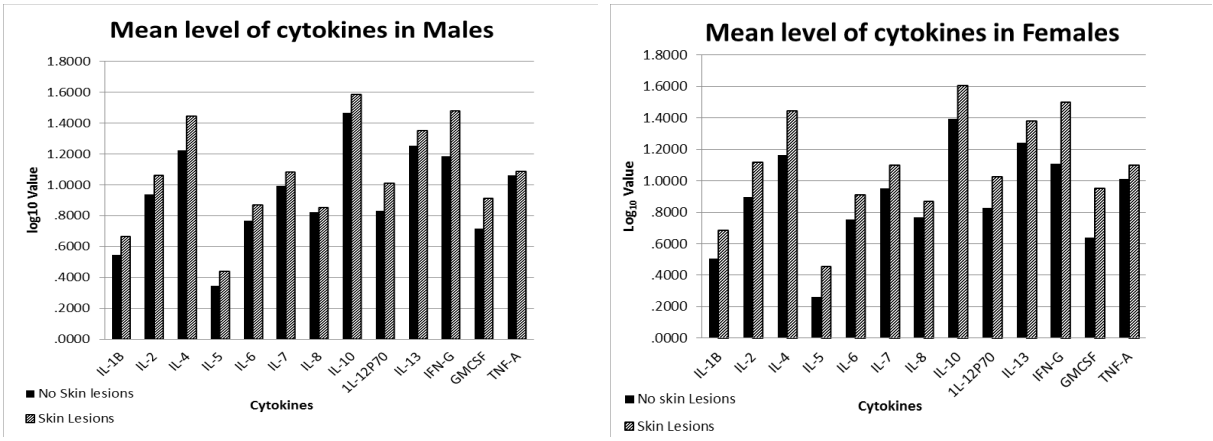

Figure 1. Comparison of mean inflammatory cytokine levels (log_{10} transformed) in male and female in both the control (Black bars) and skin lesion (shaded bars) groups.

Conclusion

Systemic Inflammatory response, male gender and having a variant allele in rs9527 are independently associated with pathogenesis of arsenic induced skin lesion in As-exposed individuals. These results could improve our understanding of the biological basis for development of arsenical skin lesions.

References

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