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Effect of Environmental Concentrations of Arsenic on Dendritic Cells Derived from Human Monocytes

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ABSTRACT

Arsenic is an environmental pollutant and an extremely dangerous toxin to human health that has been known as a carcinogen and a weakening of the immune system.Dendritic cells play a key role in cellular immunity for T-cell activation and antigen secretion. In this paper, the expression of some key and functional genes, cell viability and phagocytosis ability of dendritic cell monocytes (MDDC) after 12 and 24 h exposure to very low doses of arsenic were investigated. Arsenic decreased the phagocytic ability of MDDCs. In addition, the decrease in expression of CD40 molecules on the cell surface at 24 h after arsenic treatment indicates that arsenic is involved in the phagocytosis process. Also, higher arsenic concentrations decrease the ability of dendritic T cells to activate. IL-1B and TNF-a pro-inflammatory cytokines increased expression in these arsenic-treated MDDCs, whereas IL-6 temporarily decreased expression. Overall, new findings from this study suggest that low levels of arsenic disrupt the four main processes of the dendritic cells immune system. Mechanistically, these results could explain the observed immunodeficiency resulting from arsenic and further enhance the understanding of the spread of infections due to prolonged use of arsenic.

KEYWORDS: *arsenic, monocytes derived from dendritic cells, phagocytosis, T cell activation, pro-inflammatory cytokines*

I. INTRODUCTION

Arsenic contamination of water and soil resources is one of the major human health concerns around the world. Arsenic causes damage to many organs including the liver, kidney, lung and immune system. Arsenic prooxidant specificity leads to ATP deficiency in the cell, thereby reducing cell replication, transcription, and translocation resulting in cell division [2, 1]. Many studies have shown that long-term consumption of arsenic in drinking water increases susceptibility to infections. In addition, immunosuppressive activities such as altering the ratio of interfering T cells to respiratory immunity, altering the pattern of microRNAs associated with innate and acquired immune pathways, and reducing the number of dendritic cells in lymph nodes have been reported. Dendritic cells are a bridge between the innate and acquired immune systems and play an important role in initiating immune responses including phagocytosis, antigen presentation, activation of T cells, and eventually the release of cytokines. Therefore, DCs can detect, devour, process, and provide antigens to regulate

immune responses [3-5]. Many DCs responses are reduced in the presence of low and non-toxic doses of arsenic by reducing the secretion of some cytokines such as IL12. This decrease reduces the maturation of DCs as well as decreases cellular immune responses. Since innate and acquired innate immune responses are completely dependent on DCs, any change in the key roles of arsenic DCs reduces phagocytosis, cell viability, and cytokine secretion [6-9].

This study sought to determine whether too low doses of arsenic reduced the expression of key immune molecules at the protein and mRNA levels, and whether these changes correlated with arsenic dose and challenge time.

II. Methodology

Twenty male volunteers 18-21 years after blood sampling were obtained and according to a previous report by Spring et al., PBMC cells were isolated. MDDCs were also prepared and challenged with arsenic according to the report of Mohammadi et al. [10] Trypan blue rejection assay was performed according to previous reports by Bahari et al. [12, 11]. Annexin-PI staining for arsenic effects on the apoptosis process after 12 and 24 h was also performed according to the method of Bahari et al., 2013. [12, 11] RNA purification was performed by Denaziz Iranian RNA Extraction Kit. 2 µg of the resulting RNA was reverse transcribed using the Fermentase Co. kit using 10 picomol of Oligo DT primer. Realtimepcr reaction was performed in a total volume of 20 microliters on a Rotorgene 6000 (QLAgen USA) machine using a SolxBioDyne 5x evagreen kit.

III. RESULTS AND DISCUSSION

Phagocytic DCs are professional. In this study, we evaluated the effect of arsenic on the ability of MDDCs to swallow polyester sterile microparticles coated with FITC probe as an indicator of their phagocytic ability. MDDCs were challenged with six concentrations of arsenic including 1.0, 1.0, 5.5, 10 µM at 12 and 24 h.

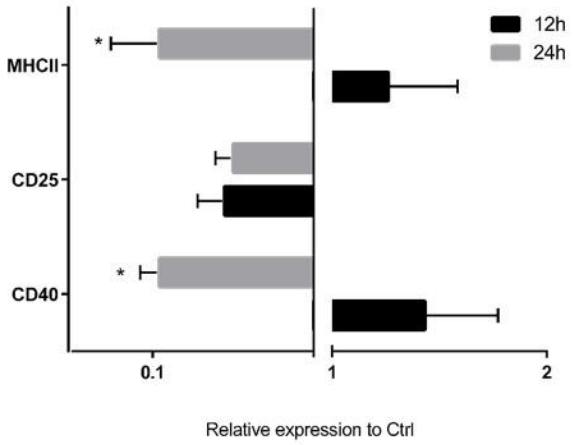

Figure 1
Effect of arsenic on expression of activation markers: MDDCs One micromolar of arsenic was challenged with MDDCs for 12 to 24 hours and CD25, CDE40 and MHCII changes were measured by flow cytometry. The bar graphs represent the mean of cells containing each of these markers; standard deviation. * Indicates p≤0.05.

At concentrations of less than 1 mM arsenic did not change phagocytosis and after 12 to 24 h challenge reduced the number of microparticles entering MDDC in a dose-dependent manner. The percentage of MDDCs that had significantly lost phagocytic ability at concentrations above 100 mM was very high at concentrations above 100 µM arsenic. This finding indicates that arsenic at high concentrations has toxic effects on this process. To evaluate the role of arsenic as an inflammatory factor, it challenged MDDCs with very low doses of arsenic for 12 to 24 hours and measured the expression of four cytokines including IL10, IL6, IL1β, and TNFα.

Table 1.Registration Number, Primer Sequence, and Expected Fragment Size in PCR and Their Melting Rate

Target	Accession number	Fwd& Rev sequences	Amplicon(bp)	Ta (^{0} C)
IL6	NM_000600	CACCTCTTCAGAACGAATTG GGCAAGTCTCCTCATTGA	194	55
IL10	NM_000572	TGGAGGACTTTAAGGGTTAC GATGTCTGGGTCTTGGTT	104	54
IL1β	NM_000576.2	GCTTATTACAGTGGCAATGA GTGGTCGGAGATTCGTAG	129	56
TNFα	NM_000594	CTCAGCCTCTTCTCCTTC GGGTTTGCTACAACATGG	111	58
TLR40.	NM_138554	GAGGCCATTATGCTATGT TTTCTCCCTTCCTCCTTT	143	55
ACTB	NM_001101	TGAAGATCAAGATCATTG TAACGCAACTAAGTCATA	179	56

Arsenic increased TNFα expression at both time points, but miraculously reduced arsenic challenge by 12 hours, but the changes in IL1β and IL10 were not significant.To determine the potential of arsenic in MDDC stability, 10,000 MDDCs were analyzed after 12 and 24 hours of arsenic challenge. As expected, the concentration of 1 µM arsenic did not change in the number of MDDC necrotic cells.

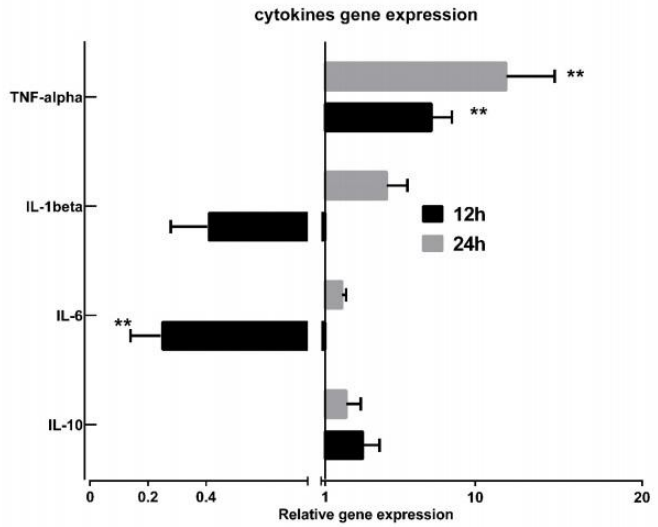

Figure 2

Expression of four key cytokine genes in MDDCs after 12 and 24 h: TNF = alpha at both time points increased expression, whereas IL-6 only decreased at 12 h time. All data were normalized by ACTB as internal control. ** indicates P≤0.01.

24 h arsenic challenge induced CD40 and MHC II expression, however, 1 µM arsenic did not change IL2R (CD25) status at 12 and 24 h compared to controls. Arsenic contamination in water and soil resources today has increased dramatically as a result of human activities such as fossil fuels, metal sources, glass industries, and a wide range of arsenic-related DNA and protein damage has been reported. Arsenic has a debilitating effect on innate and acquired immunity, which also plays a role in the treatment of cancer and Crohn's disease. Since DCs affect innate immune responses at the same time, a small alteration in the viability of these cells may interfere with immune responses. Recent studies have shown that arsenic in the form of arsenic has serious interference with the vital activities of MDDCs in the human immune system.

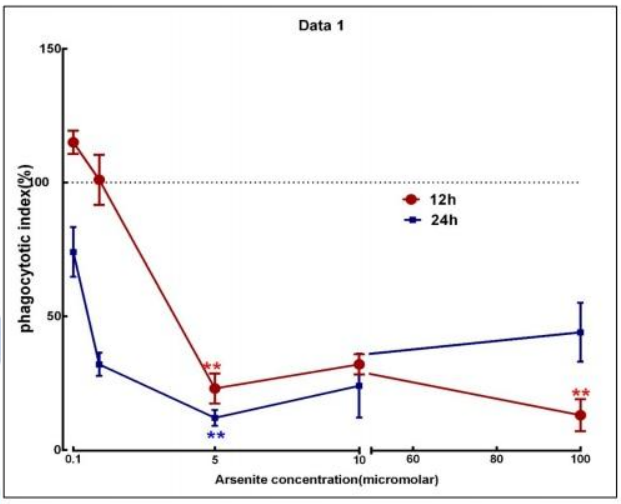

Figure 3

Arsenic inhibition of phagocytosis of MDDCs at different doses: challenge with 5 doses of arsenic with MDDCs at both 12 and 24 h time points and phagocytosis capacity was measured by flow cytometry. The dotted line represents the phagocytosis index for the control group

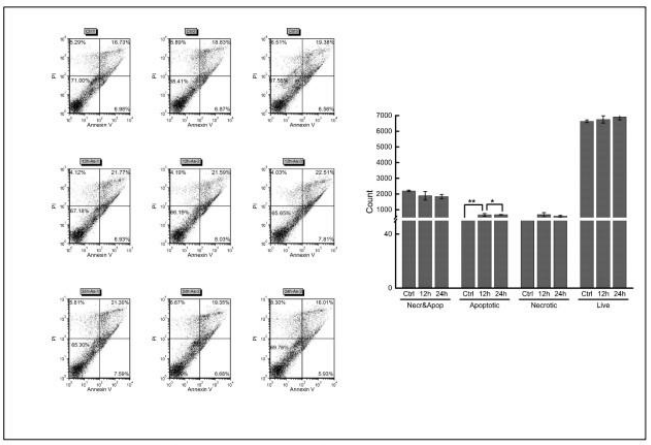

Figure 4

Arsenic effects on apoptosis and necrosis Annexin V. MDDcs and PI were determined by flow cytometry to differentiate apoptotic and necrotic cells from living cells.

IV. CONCLUSION

Previous studies have clearly shown that very low doses of arsenic even for 2 h lead to the expression of NRF2 in MDDCs. The cause of the expression changes observed in this study is likely due to genetic elements on the promoters of these genes that have antioxidant response properties.; it may also be caused by epigenetic alterations in the promoter of certain genes (such as IL8). In this study, we observed an increase in the expression of proinflammatory cytokines in a different pattern, whereas TNFα decreased

expression of IL6 and IL1β at 12 and 24 hours of challenge, and this decrease was compensated at 24 hours, indicating that That NFkB does not play a major role in TNFα expression in arsenic-induced TNFα expression increases. The reason for this is probably due to the greater binding of transcription factors such as AP-1 to the TNF-alpha promoter than to other cytokines. AP-1 enhances the expression of many genes through environmental stimuli. It has been previously reported that AFB1 alters the expression of proinflammatory factors including cytokines through pattern recognition receptors such as TLR4. The decrease in CD40 and MHCII protein levels clearly showed that arsenic ppb1 changes overnight in mature MDDCs. This finding is consistent with other reports showing the role of arsenicera in reducing T = cell proliferation and CD4 + cell count. The present report did not show an increase in necrosis of MDDCs in challenge with a single micromolar of arsenic, whereas in the treatment of leukemia when treated with one to two micromolar of arsenic, DCs led to necrosis. Taken together, this study showed that arsenic-exposed MDDCs were unable to modulate the responses between innate and acquired immunity, which could make one susceptible to a variety of pathogens and infections.

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