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Abstract

Arsenic is a metalloid to which millions of individuals are exposed worldwide, primarily through the consumption of contaminated drinking water or food items. Chronic arsenic exposure is associated with an increased incidence of several diseases, including lung infections and skin cancers. Epidemiological and experimental evidence demonstrates that the metalloid impairs the activity of both the innate and adaptive immune systems. Arsenic alters the differentiation, activation and/or proliferation of human macrophages, dendritic cells and T lymphocytes. Arsenic immunotoxicity results from intracellular oxidative lesions modulating basal gene expression or leading to DNA damage. Arsenic also induces epigenetic effects by modulating DNA methylation and post-translational histone modifications. In addition, the metalloid has recently been found to inhibit *in vitro* and *in vivo* inflammasome activities. Arsenic immunotoxicity likely contributes to the systemic effects associated with arsenic exposure by limiting immune surveillance and/or promoting inflammation. Experimental studies also suggest that the immunosuppressive effects of arsenic efficiently prevent or treat severe immune-related diseases. The purpose of this review is to summarize the current knowledge of the impact of arsenic on the immune system.

Keywords: arsenic, immunity, cell stress, DNA damages, epigenetic, immunosuppression

1. Introduction

Arsenic is a toxic metalloid naturally present at high levels in the earth's crust in many countries worldwide. Arsenic is complexed to a sulphur atom in various mineral ores, such as arsenopyrite, orpiment and realgar. Physical, chemical and/or microbial changes in the soil can promote arsenic mobilization from minerals and its accumulation in groundwater. The consumption of contaminated drinking water is the first source of arsenic exposure for millions of individuals in several Asian and American countries [1]. Since contaminated groundwater can be used to irrigate and cook cereal crops and other food items, humans can also be exposed to arsenic though the ingestion of vegetables, fruits, grains and rice [2]. In addition, arsenic is used for various industrial activities, including the production of wood preservatives, electronics and pesticides, which can induce occupational exposures [3].

Arsenic speciation includes several inorganic and organic species in different oxidation states. Contaminated drinking water, for example, contains inorganic pentavalent and trivalent forms of arsenic, which are largely absorbed from the human gastrointestinal tract, likely through glucose, phosphate or organic anion transporters and aquaporins. In contrast to mercury or cadmium, arsenic is a metalloid that does not chronically accumulate in specific organs. This compound is rapidly metabolized in the liver through biological methylation, oxidation/reduction and glutathione conjugation. Arsenic biotransformation generates reactive mono- and -dimethylated metabolites that likely contribute to its systemic effects [2].

Arsenic toxicity has been extensively reviewed in several recent articles [1–3]. Chronic ingestion of low concentrations of arsenic initially induces skin lesions but can be toxic to many other organs [4]. Long terms effects primarily include cutaneous, respiratory, neurodevelopmental, hepatic, endocrine and cardiovascular disorders [4]. This metalloid is classified by the IARC as a carcinogenic compound for humans (group 1), and epidemiological studies have clearly demonstrated that arsenic significantly increases the incidence of skin, bladder and lung cancers [3]. In addition, arsenic modulates the activity of both innate and adaptive immunity by various cellular and molecular mechanisms.

Immunomodulation likely promotes arsenic systemic toxicity, which results from environmental or occupational exposure. However, specific immunosuppressive effects of arsenic may also be beneficial for the treatment of certain immune-related diseases. Thus, the purpose of this review is to summarize our current knowledge on arsenic immunotoxicity.

2. Effects of arsenic on immune cells

2.1 Macrophages and dendritic cells (DCs)

Macrophages and DCs are professional phagocytes that control innate immunity and regulate immune surveillance against infections and cancers. Monocytes constitute major precursors of both macrophages and DCs, especially during inflammatory states. Monocytes migrate in tissues where they differentiate into mature phagocytes. A primary function of macrophages is to engulf and digest microbes, cellular debris and cancer cells by phagocytosis. In response to infection or tissue damage, macrophages secrete a large spectrum of cytokines according to their local environment. Chronic exposure to arsenic significantly impairs the *ex-vivo* differentiation of peripheral blood monocytes into mature macrophages. Banerjee et al. [5] reported that monocyte-derived macrophages from arsenic-exposed individuals with skin lesions exhibited reduced cell adhesion capacity, F-actin expression, nitric oxide production and phagocytic activity. *In vitro*, 0.5 to 2 µM arsenic trioxide (ATO) was shown to block the differentiation of human peripheral blood monocytes into functional macrophages by repressing NF-κB-related survival pathways [6]. Short treatments of human mature macrophages with non-cytotoxic arsenic concentrations (1 to 5 µM, 6 h) was shown to inhibit the transcriptional activity of the liver X receptor, resulting in the decreased expression of its target genes, ABCA1 and SREBP-1c, and impaired cholesterol efflux [7]. Prolonged treatment (3 to 6 days) with ATO was shown to de-differentiate macrophages into CD14-expressing monocytic-like cells, notably through the reorganization of the actin cytoskeleton [8]. Metalloid-exposed macrophages display increased secretion of the pro-inflammatory chemokines CXCL2 and CCL18 and a decreased expression of several macrophage markers, including metalloproteinase 7, 9 and

12 [8,9]. Moreover, these macrophages exhibit an enhanced pro-inflammatory response to the lipopolysaccharide (LPS) endotoxin. Increased exposure to arsenic through contaminated drinking water is also positively correlated with high CD14 expression on monocytes and with elevated plasma levels of pro-inflammatory cytokines, including TNFα, and IL-8 [10,11].

Recent studies have shown that arsenic alters the functions of microglia, which are the resident macrophages found in the central nervous system [12,13]. The metalloid notably increased *ex-vivo* secretion of IL-6 and TNF-α from microglia isolated from mice exposed for 7 days to 0.38 mg/kg arsenite [12]. *In vitro*, the supernatant of arsenic-exposed-microglial cultures induced murine neuronal cell death [14]. The death process did not result from inflammation but was, rather, caused by a critical cystine/glutamate imbalance induced by arsenic in the microglia. These specific effects may contribute to the increased incidence of developmental neurotoxicity in children chronically exposed to arsenic [15].

DCs are primary antigen-presenting cells that link innate immunity to adaptive immunity. Once activated by infectious agents or tumor cell antigens, DCs migrate in the peripheral lymph nodes where they activate T cells and promote their polarization. At low concentrations (0.1 to 0.5 µm), arsenite does not block the ability of mature DCs to activate the proliferation of human T cells *in vitro*, but it significantly inhibits the secretion of IL-12p70 and IL-23, two interleukins that enhance T cell polarization [16]. At concentrations higher than 1 µM, arsenic blocks myeloid DC differentiation by inducing monocyte necrosis [16], and it decreases the phagocytic activity of immature DCs [17]. These *in vitro* experimental results need to be confirmed by investigating DC functions in chronically exposed individuals. Nevertheless, various reports have shown that quantitative losses and structural lesions of Langherans cells, which are rather similar to dermal DCs, are specifically detected in the skin lesions of exposed individuals [18,19]. Although arsenic can clearly alter DC-induced T cell activation, a specific effect of the metalloid on antigen presentation by DCs remains to be demonstrated.

2.2 Lymphocytes

T and B lymphocytes mediate the cellular and humoral responses of adaptive immunity, respectively. The activation of T lymphocytes by DCs stimulates their proliferation and differentiation into various CD4+ T helper cell subtypes and CD8+ T cytotoxic cells. Numerous studies have demonstrated that arsenic markedly alters both the number and function of human T lymphocytes. Specifically, chronic arsenic exposure is correlated with decreased percentages of peripheral blood CD4+ T cells and CD4/CD8 ratios in children and adults and with reduced *ex-vivo* proliferation of activated T lymphocytes [20–22]. Wu et al. [10] reported that the expression of various pro-inflammatory cytokines, growth factors and chemokines were upregulated in non-stimulated blood lymphocytes isolated from high arsenic-exposed individuals. The transcript levels of IL-1β, IL-6, chemokine C-C motif 2/monocyte chemotactic protein-1 (CCL2/MCP-1), chemokine C-X-C motif ligand 1/growth-related oncogene alpha (CXCL1/GRO1), CXCL2/GRO2 and matrix metalloproteinase 1 (interstitial collagenase) were significantly increased in lymphocytes from individuals with the highest arsenic blood concentrations (9.6 to 46.5 µg/L). Nevertheless, the *ex-vivo* secretion of IL-2 from lymphocytes activated with phytohemaglutinin or concanavalin-A was negatively correlated with urinary arsenic levels [20,21]. *In vitro* experiments have confirmed that low and non-cytotoxic arsenite concentrations significantly repress both the proliferation and IL-2 secretion of human activated T cells [23,24]. Moreover, studies have revealed that the metalloid selectively inhibits the differentiation of T helper 17 lymphocytes by specifically repressing IL-17 expression, a cytokine that increases anti-infectious defenses but also promotes inflammation in several auto-immune diseases [25]. The *In vitro* inhibition of T cell proliferation is sex-dependent, i.e*.,* the inhibition is more potent in peripheral blood lymphocytes isolated from females [26]. *In utero,* arsenic exposure also decreases the percentage of CD4+ T cells in the cord blood [27] and alters the thymic function in newborns [28]. In fact, recent studies carried out on murine models showed that chronic arsenic exposure affects the differentiation of T cell precursors in the thymus. Exposure to low doses of arsenite (< 0.1 mL/L) in drinking water for 30 days increases the numbers of CD4+ CD25+

FoxP3-expressing cells, also known as natural regulatory T (nTreg) cells, in the thymus of male Swiss albinos mice [29]. Oral arsenite gavage (0.038 to 3.8 ppm) of male Balb/c mice for 30 days specifically promotes the CD4 lineage in the thymus without affecting the tissue ultrastructure [30]. However, this treatment also triggers the differentiation of splenic CD4+ T cells into nTreg cells and induces immunosuppression. Further research is thus required to determine the role of nTreg cells in the immunotoxic effects of arsenic in humans.

B lymphocytes, or B cells, mediate humoral immunity by producing and secreting antibodies. In contrast to T cells, the impact of arsenic on human B cells remains to be fully characterized. At low concentrations (0.1 to 2 µM), arsenite has either no effect or modest effects on the *in vitro* CD40L-dependent Immunoglobulin M antibody-forming cell response of human isolated naïve B lymphocytes, whereas this concentration of arsenite markedly reduces the same response of murine B cells [31]. Arsenite and its monomethylated trivalent metabolite, monomethylarsonous acid, have also been demonstrated to reduce *in vivo* and *in vitro* murine pre-B cell development from hematopoietic stem cells, likely by interfering with IL-7 signaling, and to repress murine humoral immunity [32,33]. It will be interesting to confirm these results with human B cells.

3. Molecular basis of arsenic immunotoxicity

3.1 Oxidative stress and DNA damage

Arsenic is a pro-oxidant metalloid that forms stable complexes with vicinal thiol residues in several proteins and increases the levels of reactive oxygen (ROS) in several cell types, including macrophages and lymphocytes [8,34]. Previous reports suggest that the effects of arsenic on the viability and functions of macrophages, DCs or lymphocytes can result from oxidative stress and related DNA damage. In this context, at non cytotoxic concentrations (< 1 µM), ATO produces ROS in human monocyte-derived macrophages by directly activating NADPH oxidase at the plasma membrane [8]. To stimulate this superoxide-generating enzymatic complex, the metalloid induces the phosphorylation and subsequent membrane translocation of the $p47^{phox}$ NADPH oxidase partner through a Rho-kinase/p38-kinase-

dependent signaling pathway. Arsenic may also produce ROS and disrupt macrophage functions by inducing the unfolded protein response [35]. At a higher concentration (5 μM), ATO significantly reduces the mitochondrial transmembrane potential, increases ROS levels and triggers caspase-dependent apoptosis in human CD4+ and CD8+ T cells [36]. ROS likely contribute to the DNA damage detected in peripheral blood lymphocytes either isolated from arsenic-exposed individuals or treated *in vitro* with arsenical compounds, by eliciting 8-hydroxy-2'-deoxyguanosine adducts and/or repressing DNA repair [34,37,38]. In addition to inducing DNA damage, arsenic impairs gene expression in human immune cells by modulating redox-sensitive signaling pathways. Notably, prevention of oxidative stress by an NADPH oxidase inhibitor or an antioxidant blocks CCL18 and CXCL2 gene expression in arsenic-exposed macrophages [8,39]. In addition, in response to cell stress, the transcription factor NRF2 not only regulates the induction of several antioxidant genes but also mediates the arsenic-dependent inhibition of IL12 gene expression in human mature DCs [40].

3.2. Epigenetic effects

Molecular epidemiological studies have suggested that arsenic can regulate gene expression in white blood cells by modifying the epigenome. Increased arsenic exposure through consumption of contaminated drinking water has been positively associated with global DNA methylation in the peripheral blood mononuclear cells of Bangladeshi adults [41,42]. Niedzwiecki et al. (2013) notably reported that the highest DNA methylation levels are measured in individuals with the highest arsenic exposure [42]. However, subtle modifications of DNA methylation can also be detected at the gene level. Indeed, in chronically exposed individuals, increased arsenic exposure either reduces or enhances the methylation levels of various genes involved in major cell functions, such as lipid metabolism, intracellular pH regulation or the nuclear factor κB signaling pathway [43]. Similarly, Engström et al. [44] reported that increased arsenic exposure was associated with significant alterations of the CD4+ T cell methylome in Argentinean women. Both hypo- and hyper-methylated regions were detected in genes regulating T cell activation and differentiation.

Interestingly, among these genes, Engström et al. found that the interferon regulatory factor 1 (IRF1) gene was hyper-methylated and its expression was decreased. In contrast, the ras homolog family member H (RHOH) gene was hypo-methylated and its expression was upregulated. Although these results suggest that arsenic exposure may alter gene expressions by differentially modulating gene methylation levels, additional studies are warranted to assess the causality and clinical significance of this phenomenon. In addition to DNA methylation, other post-translational histone modifications have also been identified in peripheral blood mononuclear cells of adults exposed to arsenic [45,46]. Notably, Chervona et al. (2012) reported that in Bangladeshi adults exposed to water containing up to containing 500 µg/L arsenic, total urinary arsenic concentration was positively correlated with the level of histone 3 lysine 9 di-methylation (H3K9me2) and inversely correlated with H3K9 acetylation [45]. Other post-translational histone modifications associated with arsenic exposure differed in a sex-dependent manner. For example, arsenic concentration in water was positively associated with H3K4me3 and H3K27me3 among females but negatively correlated with the same modifications among males. Finally, Pournara et al. (2016) reported that the impacts of arsenic on histone residues could also differ between CD4+ and CD8+ T cells [46]. Increased arsenic exposure in drinking water was negatively correlated with H3K9me3 in CD4+ T cells but not in CD8+ T cells. Metalloid effects on histone residues are thus complex, depending on the cell types and sex, and these effects need to be further explored for a better understanding of their biological significance.

3.3. Inhibition of inflammasomes

Inflammasomes are cytoplasmic multiprotein complexes that specifically control the activation of the caspase 1-dependent cleavage of the pro-inflammatory cytokines IL-1β and IL-18 into their active forms. These complexes are primarily generated in macrophages exposed to pathogen-derived stimuli (bacterial toxins), self-derived molecules (uric acid, ATP) and environmental contaminants (silica, asbestos) [47]. They are composed of nucleotide-binding oligomerization domain-like receptor (NLR) proteins that act as stimuli

sensors. *In vitro*, arsenite and ATO inhibit the NLRP1, NLRP3 and NAIP5/NLRC4 inflammasomes in murine bone marrow-derived macrophages exposed to their respective activating stimuli [48]. Maier et al. [48] demonstrated that, *in vivo*, arsenite delays the NLRP1-mediated death of mice exposed to anthrax lethal toxin and reduces NLRP3-dependent inflammation in mice treated with monosodium urate crystals. Arsenic blocks the maturation of pro-IL-1β by preventing the autoproteolytic and substrate cleavage activities of caspase-1 in murine macrophages [48]. Low concentrations of ATO (0.1 to 1 μM), which fail to repress the upregulation of IL-1β mRNA caused by LPS in human monocyte-derived macrophages (Figure 1A), inhibit the silica-induced secretion of active IL-1β in the macrophage supernatant (Figure 1B). These results suggest that ATO directly impairs the inflammasome activity of human macrophages, i.e., it suppresses the cleavage of pro-IL-1β. Inflammasome complexes may thus constitute important molecular targets of arsenic in humans.

4. Consequences of arsenic immunotoxicity in humans

4.1 Contribution to diseases associated with chronic environmental exposure

As described above, arsenic exerts pleiotropic effects on immune cells, which may initially result in the suppression of major immune functions. Notably, arsenic decreases bacterial phagocytosis by macrophages, reduces T cell proliferation and markedly represses the secretion of pro-inflammatory cytokines by activated DC and T cells. These inhibitions can increase the susceptibility to infection by limiting pathogen eradication. Arsenic-induced immunosuppression likely increases the incidence of lower respiratory tract infections and diarrhea, which frequently develop in young exposed children from low-income countries [49,50]. Particularly, increased arsenic exposure was found to promote pulmonary tuberculosis in Chile [50] and visceral leishmaniosis in India [51]. In a murine model, chronic exposure to low doses of arsenic also increased morbidity of influenza A infection by repressing DC-mediated immune responses in mice [52]. In addition, immunosuppression impairs the surveillance and killing of tumorigenic cells, which may promote lung and skin

cancer associated with arsenic exposure [53]. Conversely, arsenic may induce a basal inflammatory state by increasing the secretion of molecules such as TNF-α and IL-8 from monocytes/macrophages and lymphocytes. Chronic inflammation and secretion of growth factors, such as IL-8, can also establish microenvironments supportive of tumor development [54]. Epidemiological studies carried out in various countries demonstrate that arsenic significantly increases the risk of atherosclerosis [55,56]. Several mechanisms may contribute to the development of atherosclerosis, including general pro-inflammatory cytokine secretion [10], increased ROS production [8], enhanced monocyte adhesion to vascular endothelium [57] and reduced cholesterol efflux from macrophages [7]. In murine models, at least, methylated metabolites and arsenic-3-methyltransferase play major roles in these pro-atherogenic effects of arsenic [58].

4.2. Potential beneficial effects of arsenic-induced immunosuppression

Recently, various experimental studies have suggested that the immunosuppressive properties of arsenic may reduce or treat severe immune-related diseases. Indeed, ATO prevents the development of a lupus-like syndrome in MRL/lpr mice by eliminating activated T cells that cause lymphoproliferation and skin, lung and kidney damage [59]. ATO also abrogates chronic sclerodermatous graft-versus-host disease that follows allogenic hematopoietic stem cell transplantation in a murine model [60]. The metalloid inhibits the alloreactive process by selectively killing activated DCs and CD4-positive T cells. In addition, ATO prolongs cardiac and islet allograft survival in acute rejection murine models through the repression of alloreactive CD4+ and CD8+ memory T cells [61–63]. Finally, the fact that arsenic blocks inflammasome activity and the subsequent IL-1β production in human macrophages suggests that arsenic may limit chronic inflammation in severe inflammasome-mediated disease [47].

5. Conclusions

Many human population-based and/or experimental studies strongly suggest that arsenic exerts potent immunotoxic effects towards key human immune cells, such as macrophages,

DCs and T lymphocytes (Figure 2). Multiple molecular and cellular mechanisms can mediate arsenic immunotoxicity, including ROS production, alteration of redox-sensitive signaling pathways, DNA damage, epigenetic effects and inflammasome inhibition. Arsenic immunotoxicity likely contributes to the systemic deleterious effects associated with chronic environmental exposure. Notably, arsenic-induced immunosuppression may favor the development of infectious diseases and cancers. On the other hand, data derived from experimental studies using various mouse models support the hypothesis that the immunosuppressive effects of arsenic may be beneficial for limiting the exacerbation of the immune system in severe immune-related diseases. However, further research is still required to determine the role of arsenic immunotoxicity in the systemic effects of arsenic exposure and to investigate the potential use of this metalloid in medical immunosuppressive therapy.

Acknowledgements

This research was supported by grants from Institut National de la Santé et de la Recherche Médicale (INSERM) and from University of Rennes-1. We thank Dr Valérie Lecureur for her helpful comments and critical reading of the manuscript.

References

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

[1] M.B. Shakoor, R. Nawaz, F. Hussain, M. Raza, S. Ali, M. Rizwan, S.-E. Oh, S. Ahmad, Human health implications, risk assessment and remediation of As-contaminated water: A critical review, Sci. Total Environ. 601–602 (2017) 756–769. doi:10.1016/j.scitotenv.2017.05.223.

[2] D.J. Carlin, M.F. Naujokas, K.D. Bradham, J. Cowden, M. Heacock, H.F. Henry, J.S. Lee, D.J. Thomas, C. Thompson, E.J. Tokar, M.P. Waalkes, L.S. Birnbaum, W.A. Suk, Arsenic and Environmental Health: State of the Science and Future Research Opportunities, Environ. Health Perspect. 124 (2016) 890–899. doi:10.1289/ehp.1510209.

[3] K.M. Hunt, R.K. Srivastava, C.A. Elmets, M. Athar, The mechanistic basis of arsenicosis: pathogenesis of skin cancer, Cancer Lett. 354 (2014) 211–219. doi:10.1016/j.canlet.2014.08.016.

[4] M.F. Naujokas, B. Anderson, H. Ahsan, H.V. Aposhian, J.H. Graziano, C. Thompson, W.A. Suk, The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem, Environ. Health Perspect. 121 (2013) 295–302. doi:10.1289/ehp.1205875.

[5] N. Banerjee, S. Banerjee, R. Sen, A. Bandyopadhyay, N. Sarma, P. Majumder, J.K. Das, M. Chatterjee, S.N. Kabir, A.K. Giri, Chronic arsenic exposure impairs macrophage functions in the exposed individuals, J. Clin. Immunol. 29 (2009) 582–594. doi:10.1007/s10875-009-9304-x.

[6] A. Lemarie, C. Morzadec, D. Mérino, O. Micheau, O. Fardel, L. Vernhet, Arsenic trioxide induces apoptosis of human monocytes during macrophagic differentiation through nuclear factor-kappaB-related survival pathway down-regulation, J. Pharmacol. Exp. Ther. 316 (2006) 304–314. doi:10.1124/jpet.105.092874.

[7] A.M.S. Padovani, M.F. Molina, K.K. Mann, Inhibition of liver x receptor/retinoid X receptor-mediated transcription contributes to the proatherogenic effects of arsenic in macrophages in vitro, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 1228–1236. doi:10.1161/ATVBAHA.110.205500.

[8] A. Lemarie, E. Bourdonnay, C. Morzadec, O. Fardel, L. Vernhet, Inorganic arsenic activates reduced NADPH oxidase in human primary macrophages through a Rho kinase/p38 kinase pathway, J. Immunol. 180 (2008) 6010–6017.

[9] E. Bourdonnay, C. Morzadec, L. Sparfel, M.-D. Galibert, S. Jouneau, C. Martin-Chouly, O. Fardel, L. Vernhet, Global effects of inorganic arsenic on gene expression profile in

human macrophages, Mol. Immunol. 46 (2009) 649–656. doi:10.1016/j.molimm.2008.08.268.

[10] M.-M. Wu, H.-Y. Chiou, I.-C. Ho, C.-J. Chen, T.-C. Lee, Gene expression of inflammatory molecules in circulating lymphocytes from arsenic-exposed human subjects, Environ. Health Perspect. 111 (2003) 1429–1438.

[11] K. Dutta, P. Prasad, D. Sinha, Chronic low level arsenic exposure evokes inflammatory responses and DNA damage, Int. J. Hyg. Environ. Health. 218 (2015) 564–574. doi:10.1016/j.ijheh.2015.06.003.

[12] V. Singh, S. Mitra, A.K. Sharma, R. Gera, D. Ghosh, Isolation and characterization of microglia from adult mouse brain: selected applications for ex vivo evaluation of immunotoxicological alterations following in vivo xenobiotic exposure, Chem. Res. Toxicol. 27 (2014) 895–903. doi:10.1021/tx500046k.

[13] G. Chen, J. Mao, J. Zhao, Y. Zhang, T. Li, C. Wang, L. Xu, Q. Hu, X. Wang, S. Jiang, X. Nie, Q. Wu, Arsenic trioxide mediates HAPI microglia inflammatory response and the secretion of inflammatory cytokine IL-6 via Akt/NF-κB signaling pathway, Regul. Toxicol. Pharmacol. RTP. 81 (2016) 480–488. doi:10.1016/j.yrtph.2016.09.027.

[14] V. Singh, R. Gera, R. Kushwaha, A.K. Sharma, S. Patnaik, D. Ghosh, Hijacking microglial glutathione by inorganic arsenic impels bystander death of immature neurons through extracellular cystine/glutamate imbalance, Sci. Rep. 6 (2016) 30601. doi:10.1038/srep30601.

[15] J.S. Tsuji, M.R. Garry, V. Perez, E.T. Chang, Low-level arsenic exposure and developmental neurotoxicity in children: A systematic review and risk assessment, Toxicology. 337 (2015) 91–107. doi:10.1016/j.tox.2015.09.002.

[16] M. Macoch, C. Morzadec, O. Fardel, L. Vernhet, Inorganic arsenic impairs differentiation and functions of human dendritic cells, Toxicol. Appl. Pharmacol. 266 (2013) 204–213. doi:10.1016/j.taap.2012.11.008.

[17] A. Bahari, V. Salmani, Environmentally relevant dose of arsenic interferes in functions of human monocytes derived dendritic cells, Toxicol. Lett. 275 (2017) 118–122. doi:10.1016/j.toxlet.2017.05.005.

[18] B.J. Wang, Y.Y. Lee, C.P. Mak, H.F. Kao, M.L. Hsu, J.R. Hsien, Quantitative and morphological changes of Langerhans cells in Bowen's disease from patients with chronic arsenicism, J. Formos. Med. Assoc. Taiwan Yi Zhi. 90 (1991) 1093–1098.

[19] C.-H. Lee, C.-H. Hong, C.-L. Yu, L.-F. Wang, B.E. Clausen, W.-T. Liao, S.-K. Huang, G.-S. Chen, H.-S. Yu, Arsenic mobilizes Langerhans cell migration and induces Th1 response in epicutaneous protein sensitization via CCL21: a plausible cause of decreased Langerhans cells in arsenic-induced intraepithelial carcinoma, Biochem. Pharmacol. 83 (2012) 1290–1299. doi:10.1016/j.bcp.2012.01.028.

[20] G.A. Soto-Peña, A.L. Luna, L. Acosta-Saavedra, P. Conde, L. López-Carrillo, M.E. Cebrián, M. Bastida, E.S. Calderón-Aranda, L. Vega, Assessment of lymphocyte subpopulations and cytokine secretion in children exposed to arsenic, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 20 (2006) 779–781. doi:10.1096/fj.05-4860fje.

[21] R. Biswas, P. Ghosh, N. Banerjee, J.K. Das, T. Sau, A. Banerjee, S. Roy, S. Ganguly, M. Chatterjee, A. Mukherjee, A.K. Giri, Analysis of T-cell proliferation and cytokine secretion in the individuals exposed to arsenic, Hum. Exp. Toxicol. 27 (2008) 381–386. doi:10.1177/0960327108094607.

[22] W.-T. Liao, C.-L. Yu, C.-C.E. Lan, C.-H. Lee, C.-H. Chang, L.W. Chang, H.-L. You, H.-S. Yu, Differential effects of arsenic on cutaneous and systemic immunity: focusing on CD4+ cell apoptosis in patients with arsenic-induced Bowen's disease, Carcinogenesis. 30 (2009) 1064–1072. doi:10.1093/carcin/bgp095.

[23] C. Morzadec, F. Bouezzedine, M. Macoch, O. Fardel, L. Vernhet, Inorganic arsenic impairs proliferation and cytokine expression in human primary T lymphocytes, Toxicology. 300 (2012) 46–56. doi:10.1016/j.tox.2012.05.025.

[24] S.W. Burchiel, F.T. Lauer, E.J. Beswick, A.J. Gandolfi, F. Parvez, K.J. Liu, L.G. Hudson, Differential susceptibility of human peripheral blood T cells to suppression by

environmental levels of sodium arsenite and monomethylarsonous acid, PloS One. 9 (2014) e109192. doi:10.1371/journal.pone.0109192.

- [25] C. Morzadec, M. Macoch, M. Robineau, L. Sparfel, O. Fardel, L. Vernhet, Inorganic arsenic represses interleukin-17A expression in human activated Th17 lymphocytes, Toxicol. Appl. Pharmacol. 262 (2012) 217–222. doi:10.1016/j.taap.2012.05.004.

  The investigators demonstrate that trivalent inorganic arsenic (As_2O_3, 0.25-2 µM) totally inhibits expression and secretion of IL-17A from naive and memory human CD4+ T lymphocytes differentiated into Th17 cells, notably by impairing JNK/C-jun-dependent signalling and RORC-γt expression. IL-17A, which plays a key role in anti-infectious defenses but also in the development of various chronic inflammatory diseases, may thus constitute a major target of the arsenic in humans.

[26] L. Vega, P. Montes de Oca, R. Saavedra, P. Ostrosky-Wegman, Helper T cell subpopulations from women are more susceptible to the toxic effect of sodium arsenite in vitro, Toxicology. 199 (2004) 121–128. doi:10.1016/j.tox.2004.02.012.

[27] M.L. Kile, E.A. Houseman, A.A. Baccarelli, Q. Quamruzzaman, M. Rahman, G. Mostofa, A. Cardenas, R.O. Wright, D.C. Christiani, Effect of prenatal arsenic exposure on DNA methylation and leukocyte subpopulations in cord blood, Epigenetics. 9 (2014) 774–782. doi:10.4161/epi.28153.

[28] S. Ahmed, K.B. Ahsan, M. Kippler, A. Mily, Y. Wagatsuma, A.M.W. Hoque, P.T. Ngom, S. El Arifeen, R. Raqib, M. Vahter, In utero arsenic exposure is associated with impaired thymic function in newborns possibly via oxidative stress and apoptosis, Toxicol. Sci. Off. J. Soc. Toxicol. 129 (2012) 305–314. doi:10.1093/toxsci/kfs202.

[29] S. Choudhury, P. Gupta, S. Ghosh, S. Mukherjee, P. Chakraborty, U. Chatterji, S. Chattopadhyay, Arsenic-induced dose-dependent modulation of the NF-κB/IL-6 axis in thymocytes triggers differential immune responses, Toxicology. 357–358 (2016) 85–96. doi:10.1016/j.tox.2016.06.005.

[30] R. Gera, V. Singh, S. Mitra, A.K. Sharma, A. Singh, A. Dasgupta, D. Singh, M. Kumar, P. Jagdale, S. Patnaik, D. Ghosh, Arsenic exposure impels CD4 commitment in thymus and suppress T cell cytokine secretion by increasing regulatory T cells, Sci. Rep. 7 (2017) 7140. doi:10.1038/s41598-017-07271-z.

[31] H. Lu, R.B. Crawford, C.M. North, B.L.F. Kaplan, N.E. Kaminski, Establishment of an immunoglobulin m antibody-forming cell response model for characterizing immunotoxicity in primary human B cells, Toxicol. Sci. Off. J. Soc. Toxicol. 112 (2009) 363–373. doi:10.1093/toxsci/kfp224.

- [32] P.C. Ezeh, F.T. Lauer, D. MacKenzie, S. McClain, K.J. Liu, L.G. Hudson, A.J. Gandolfi, S.W. Burchiel, Arsenite selectively inhibits mouse bone marrow lymphoid progenitor cell development in vivo and in vitro and suppresses humoral immunity in vivo, PloS One. 9 (2014) e93920. doi:10.1371/journal.pone.0093920.

The investigators demonstrate for the first time that, at low environmentally relevant levels, arsenite selectively inhibits CFU-B colony formation in femur and T-dependent antibody response in spleen of mice exposed through contaminated drinking water. *In vitro*, its monomethylated metabolite, monomethylarsonous acid, selectively suppresses the differentiation of murine CFU-B formation, at low nM concentrations, in the absence of apparent cytotoxicity. These finding support a marked sensitivity of murine lymphoid progenitor to inorganic arsenic and its methylated metabolite.

[33] P.C. Ezeh, H. Xu, F.T. Lauer, K.J. Liu, L.G. Hudson, S.W. Burchiel, Monomethylarsonous acid (MMA+3) Inhibits IL-7 Signaling in Mouse Pre-B Cells, Toxicol. Sci. Off. J. Soc. Toxicol. 149 (2016) 289–299. doi:10.1093/toxsci/kfv233.

[34] J. Biswas, D. Sinha, S. Mukherjee, S. Roy, M. Siddiqi, M. Roy, Curcumin protects DNA damage in a chronically arsenic-exposed population of West Bengal, Hum. Exp. Toxicol. 29 (2010) 513–524. doi:10.1177/0960327109359020.

[35] R.K. Srivastava, C. Li, S.C. Chaudhary, M.E. Ballestas, C.A. Elmets, D.J. Robbins, S. Matalon, J.S. Deshane, F. Afaq, D.R. Bickers, M. Athar, Unfolded protein response (UPR) signaling regulates arsenic trioxide-mediated macrophage innate immune function disruption, Toxicol. Appl. Pharmacol. 272 (2013) 879–887. doi:10.1016/j.taap.2013.08.004.

[36] S. Gupta, L. Yel, D. Kim, C. Kim, S. Chiplunkar, S. Gollapudi, Arsenic trioxide induces apoptosis in peripheral blood T lymphocyte subsets by inducing oxidative stress: a role of Bcl-2, Mol. Cancer Ther. 2 (2003) 711–719.

[37] A.D. Kligerman, C.L. Doerr, A.H. Tennant, K. Harrington-Brock, J.W. Allen, E. Winkfield, P. Poorman-Allen, B. Kundu, K. Funasaka, B.C. Roop, M.J. Mass, D.M.

DeMarini, Methylated trivalent arsenicals as candidate ultimate genotoxic forms of arsenic: induction of chromosomal mutations but not gene mutations, Environ. Mol. Mutagen. 42 (2003) 192–205. doi:10.1002/em.10192.

[38] A.S. Andrew, J.L. Burgess, M.M. Meza, E. Demidenko, M.G. Waugh, J.W. Hamilton, M.R. Karagas, Arsenic exposure is associated with decreased DNA repair in vitro and in individuals exposed to drinking water arsenic, Environ. Health Perspect. 114 (2006) 1193–1198.

[39] E. Bourdonnay, C. Morzadec, O. Fardel, L. Vernhet, Redox-sensitive regulation of gene expression in human primary macrophages exposed to inorganic arsenic, J. Cell. Biochem. 107 (2009) 537–547. doi:10.1002/jcb.22155.

[40] M. Macoch, C. Morzadec, R. Génard, M. Pallardy, S. Kerdine-Römer, O. Fardel, L. Vernhet, Nrf2-dependent repression of interleukin-12 expression in human dendritic cells exposed to inorganic arsenic, Free Radic. Biol. Med. 88 (2015) 381–390. doi:10.1016/j.freeradbiomed.2015.02.003.

[41] M.L. Kile, A. Baccarelli, E. Hoffman, L. Tarantini, Q. Quamruzzaman, M. Rahman, G. Mahiuddin, G. Mostofa, Y.-M. Hsueh, R.O. Wright, D.C. Christiani, Prenatal arsenic exposure and DNA methylation in maternal and umbilical cord blood leukocytes, Environ. Health Perspect. 120 (2012) 1061–1066. doi:10.1289/ehp.1104173.

[42] M.M. Niedzwiecki, M.N. Hall, X. Liu, J. Oka, K.N. Harper, V. Slavkovich, V. Ilievski, D. Levy, A. van Geen, J.L. Mey, S. Alam, A.B. Siddique, F. Parvez, J.H. Graziano, M.V. Gamble, A dose-response study of arsenic exposure and global methylation of peripheral blood mononuclear cell DNA in Bangladeshi adults, Environ. Health Perspect. 121 (2013) 1306–1312. doi:10.1289/ehp.1206421.

[43] M. Argos, L. Chen, F. Jasmine, L. Tong, B.L. Pierce, S. Roy, R. Paul-Brutus, M.V. Gamble, K.N. Harper, F. Parvez, M. Rahman, M. Rakibuz-Zaman, V. Slavkovich, J.A. Baron, J.H. Graziano, M.G. Kibriya, H. Ahsan, Gene-specific differential DNA methylation and chronic arsenic exposure in an epigenome-wide association study of adults in Bangladesh, Environ. Health Perspect. 123 (2015) 64–71. doi:10.1289/ehp.1307884.

• [44] K. Engström, T.K. Wojdacz, F. Marabita, P. Ewels, M. Käller, F. Vezzi, N. Prezza, J. Gruselius, M. Vahter, K. Broberg, Transcriptomics and methylomics of CD4-positive T cells in arsenic-exposed women, Arch. Toxicol. 91 (2017) 2067–2078. doi:10.1007/s00204-016-1879-4.

By analysing methylomics (target-enrichment next-generation sequencing) of human blood CD4+ T lymphocytes from arsenic-exposed Argentinean women, the investigators demonstrate that high arsenic exposure is associated with increased DNA methylation and that hyper-methylated regions showed enrichment for immune-related gene ontologies associated with the basic functions of T lymphocytes. This finding shows that the metalloid can be immunotoxic by altering epigenetic regulation of gene expression in human T lymphocytes

[45] Y. Chervona, M.N. Hall, A. Arita, F. Wu, H. Sun, H.-C. Tseng, E. Ali, M.N. Uddin, X. Liu, M.A. Zoroddu, M.V. Gamble, M. Costa, Associations between arsenic exposure and global posttranslational histone modifications among adults in Bangladesh, Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 21 (2012) 2252–2260. doi:10.1158/1055-9965.EPI-12-0833.

[46] A. Pournara, M. Kippler, T. Holmlund, R. Ceder, R. Grafström, M. Vahter, K. Broberg, A.E. Wallberg, Arsenic alters global histone modifications in lymphocytes in vitro and in vivo, Cell Biol. Toxicol. 32 (2016) 275–284. doi:10.1007/s10565-016-9334-0.

[47] J.A. Howrylak, K. Nakahira, Inflammasomes: Key Mediators of Lung Immunity, Annu. Rev. Physiol. 79 (2017) 471–494. doi:10.1146/annurev-physiol-021115-105229.

• [48] N.K. Maier, D. Crown, J. Liu, S.H. Leppla, M. Moayeri, Arsenic trioxide and other arsenical compounds inhibit the NLRP1, NLRP3, and NAIP5/NLRC4 inflammasomes, J. Immunol. Baltim. Md 1950. 192 (2014) 763–770. doi:10.4049/jimmunol.1301434.

The investigators show that trivalent inorganic arsenic inhibits *in vitro* activation of NLRP1, NLRP3 and NAIP5/NLRC4 inflammasomes in murine bone marrow-derived macrophages by preventing autoproteolytic activation of caspase-1 and subsequent processing and secretion of IL-1β. Arsenic also prevents NLRP3-dependent inflammation in a murine peritonis model induced by monosodium urate crystals. These results demonstrate time that inflammasomes constitute molecular targets of the metalloid.

[49] A. Rahman, M. Vahter, E.-C. Ekström, L.-Å. Persson, Arsenic exposure in pregnancy increases the risk of lower respiratory tract infection and diarrhea during infancy in Bangladesh, Environ. Health Perspect. 119 (2011) 719–724. doi:10.1289/ehp.1002265.

[50] A.H. Smith, G. Marshall, Y. Yuan, J. Liaw, C. Ferreccio, C. Steinmaus, Evidence from Chile that arsenic in drinking water may increase mortality from pulmonary tuberculosis, Am. J. Epidemiol. 173 (2011) 414–420. doi:10.1093/aje/kwq383.

[51] M.R. Perry, V.K. Prajapati, J. Menten, A. Raab, J. Feldmann, D. Chakraborti, S. Sundar, A.H. Fairlamb, M. Boelaert, A. Picado, Arsenic exposure and outcomes of antimonial treatment in visceral leishmaniasis patients in Bihar, India: a retrospective cohort study, PLoS Negl. Trop. Dis. 9 (2015) e0003518. doi:10.1371/journal.pntd.0003518.

[52] C.D. Kozul, K.H. Ely, R.I. Enelow, J.W. Hamilton, Low-dose arsenic compromises the immune response to influenza A infection in vivo, Environ. Health Perspect. 117 (2009) 1441–1447. doi:10.1289/ehp.0900911.

[53] N.L. Dangleben, C.F. Skibola, M.T. Smith, Arsenic immunotoxicity: a review, Environ. Health Glob. Access Sci. Source. 12 (2013) 73. doi:10.1186/1476-069X-12-73.

[54] A. Yuan, J.J.W. Chen, P.-L. Yao, P.-C. Yang, The role of interleukin-8 in cancer cells and microenvironment interaction, Front. Biosci. J. Virtual Libr. 10 (2005) 853–865.

[55] Y. Chen, F. Wu, J.H. Graziano, F. Parvez, M. Liu, R.R. Paul, I. Shaheen, G. Sarwar, A. Ahmed, T. Islam, V. Slavkovich, T. Rundek, R.T. Demmer, M. Desvarieux, H. Ahsan, Arsenic exposure from drinking water, arsenic methylation capacity, and carotid intima-media thickness in Bangladesh, Am. J. Epidemiol. 178 (2013) 372–381. doi:10.1093/aje/kwt001.

[56] F.J. Mateen, M. Grau-Perez, J.S. Pollak, K.A. Moon, B.V. Howard, J.G. Umans, L.G. Best, K.A. Francesconi, W. Goessler, C. Crainiceanu, E. Guallar, R.B. Devereux, M.J. Roman, A. Navas-Acien, Chronic arsenic exposure and risk of carotid artery disease: The Strong Heart Study, Environ. Res. 157 (2017) 127–134. doi:10.1016/j.envres.2017.05.020.

[57] M. Lemaire, L.F. Negro Silva, C.A. Lemarié, A.M. Bolt, M. Flores Molina, R.M. Krohn, J.E. Smits, S. Lehoux, K.K. Mann, Arsenic Exposure Increases Monocyte Adhesion to the

Vascular Endothelium, a Pro-Atherogenic Mechanism, PloS One. 10 (2015) e0136592. doi:10.1371/journal.pone.0136592.

[58] L.F. Negro Silva, M. Lemaire, C.A. Lemarié, D. Plourde, A.M. Bolt, C. Chiavatti, D.S. Bohle, V. Slavkovich, J.H. Graziano, S. Lehoux, K.K. Mann, Effects of Inorganic Arsenic, Methylated Arsenicals, and Arsenobetaine on Atherosclerosis in the Mouse Model and the Role of As3mt-Mediated Methylation, Environ. Health Perspect. 125 (2017) 077001. doi:10.1289/EHP806.

[59] P. Bobé, D. Bonardelle, K. Benihoud, P. Opolon, M.K. Chelbi-Alix, Arsenic trioxide: A promising novel therapeutic agent for lymphoproliferative and autoimmune syndromes in MRL/lpr mice, Blood. 108 (2006) 3967–3975. doi:10.1182/blood-2006-04-020610.

• [60] N. Kavian, W. Marut, A. Servettaz, H. Laude, C. Nicco, C. Chéreau, B. Weill, F. Batteux, Arsenic trioxide prevents murine sclerodermatous graft-versus-host disease, J. Immunol. Baltim. Md 1950. 188 (2012) 5142–5149. doi:10.4049/jimmunol.1103538.

Using a murine model of sclerodermatous graft-versus-host disease, the investigators report that arsenic trioxide markedly abrogates severe clinical syndromes developed by transplanted mice, through depletion of glutathione and production of reactive oxygen species that selectively kill activated CD4+ T cells and plasmacytoid dendritic cells. These results support the hypothesis that inorganic arsenic may display beneficial effects in the management of chronic graft-versus-host disease in humans.

[61] G. Yan, Y. Xi, S. Xu, Y. Lin, J. Chen, H. Dai, J. Xia, C. Li, Q. Li, Z. Li, Z. Qi, Inhibition of accelerated rejection mediated by alloreactive $CD4^+$ memory T cells and prolonged allograft survival by arsenic trioxide, Immunol. Invest. 42 (2013) 438–454. doi:10.3109/08820139.2013.801986.

[62] C. Gao, J. Jiang, P. Ma, P. Cheng, Y. Lian, B. Zhao, C. Li, Y. Peng, F. Wang, Y. Lin, N. Jin, J. Li, L. Wang, Q. Li, Y. Leng, J. Xia, Z. Qi, Arsenic Trioxide Induces T Cell Apoptosis and Prolongs Islet Allograft Survival in Mice, Transplantation. 99 (2015) 1796–1806. doi:10.1097/TP.0000000000000735.

[63] C. Li, T. Guan, C. Gao, Y. Lin, G. Yan, M. Zhu, C. Lv, J. Xia, Z. Qi, Arsenic trioxide inhibits accelerated allograft rejection mediated by alloreactive CD8(+) memory T cells

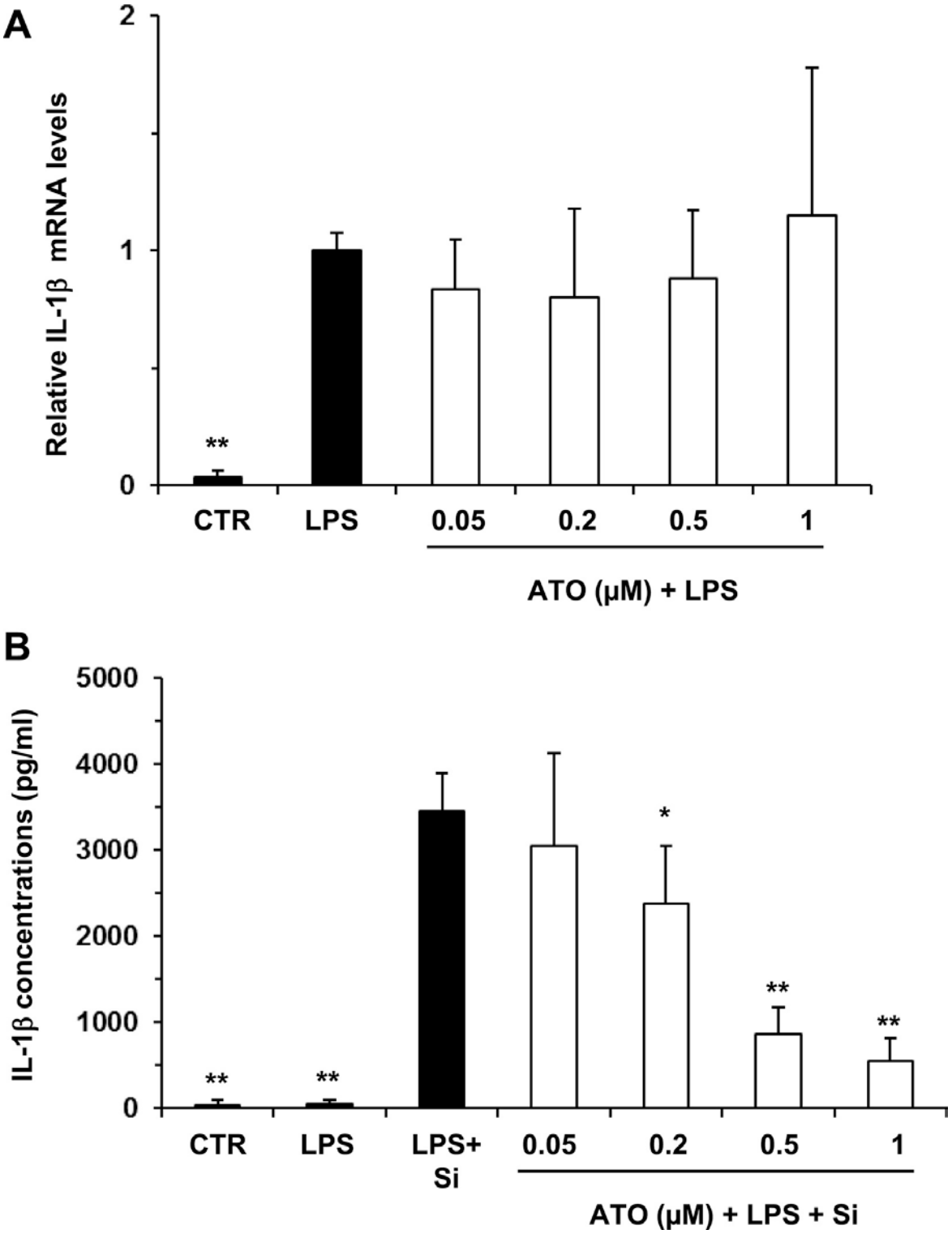
and prolongs allograft survival time, Transpl. Immunol. 33 (2015) 30–36. doi:10.1016/j.trim.2015.05.004.

Legends

Figure 1. Arsenic trioxide (ATO) inhibits IL-1β secretion from human macrophages without impairing IL-1β mRNA levels. Following the isolation of peripheral blood mononuclear cells by Ficoll gradient centrifugation, human monocytes were selected by an adhesion step and then differentiated into macrophages in RPMI medium containing 50 ng/mL macrophage-colony stimulating factor for 6 days. Macrophages were left untreated (CTR) or pre-treated with ATO for 2 h before stimulation with 20 ng/mL LPS (*Escherichia coli* 055:B5, Sigma Aldrich, France) for 4 h to increase IL-1β mRNA expression. Next, cells were harvested (A) or cultured with 0 or 100 µg/mL silica (Si) (DQ12 mineral dust silica, DMT GMBH, Germany) for 16 h (B) to activate NLRP3 inflammasome and produce active IL-1β protein. At the end of the treatment, the culture media were collected and the levels of active IL-1β secreted in the supernatant were quantified by ELISA (Duoset ELISA development system kits, R and D system, France) (B). In (A), mRNA levels were determined by RT-qPCR using the fluorescent dye SYBR Green methodology and a CFX384 real-time PCR system (Bio-Rad). Data are presented relative to mRNA levels found in macrophages treated with LPS and arbitrarily set at the value of 1. Results in (A) and (B) are expressed as the means ± SD of 6 independent experiments. Significant differences were evaluated using ANOVA followed by the multi-range Dunett's t test for multiple comparisons. The criterion for significance of the difference between means was *$p < 0.05$ or **$p<0.01$, versus LPS (A) or LPS+Si (B).

Figure 2. Effects of arsenic on immune cells and their potential consequences for humans. Environmental or occupational exposure to arsenic can impact the differentiation and activation of macrophages, dendritic cells and T lymphocytes. Arsenic impairs immune cell functions by several molecular mechanisms, including the production of reactive oxygen (ROS), modulation of redox-sensitive signaling pathways controlling gene expression, induction of DNA damage, epigenetic effects (DNA methylation and histone modifications), and the inhibition of the inflammasome. Arsenic immunotoxicity may contribute to the increased incidence of respiratory infections, diarrhea, lung and skin cancers, and

atherosclerosis in environmentally exposed individuals. In contrast, experimental studies have demonstrated that the immunosuppressive effects of arsenic may counteract hyperactivity of the immune system in murine models of lupus, chronic sclerodermatous graft-versus-host disease and acute allograft rejection. Moreover, these effects may prevent NLRP3-dependent inflammation from developing in mice exposed to monosodium urate crystals. These results support the idea that arsenic may have beneficial therapeutic immunosuppressive effects for the treatment of certain human diseases.


A
Relative IL-1β mRNA levels
2
1
0
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CTR
LPS
0.05
0.2
0.5
1
ATO (μM) + LPS
B
IL-1β concentrations (pg/ml)
5000
4000
3000
2000
1000
0
**
**
*
**
**
CTR
LPS
LPS+ Si
0.05
0.2
0.5
1
ATO (μM) + LPS + Si

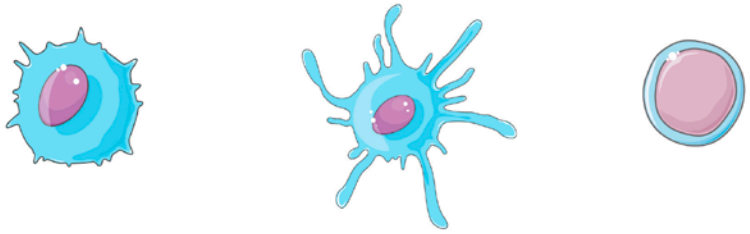
Exposure to arsenic

ROS, signaling, DNA damages

Epigenetic effects

Inhibition of Inflammasome

Alteration of the differentiation and activation of macrophages, dendritic cells and/or T lymphocytes



Potential consequences of

Environmental exposure to arsenic

Infection
Cancer
Atherosclerosis
Other diseases (?)

Medical treatment with ATO

Immunosuppression