Arsenic is a carcinogen and chronic arsenic exposure may cause lung cancer. The tumorigenic action of arsenic is complicated and varied among different cell type (e.g. non-immune vs. immune cells) and durations of arsenic exposure. Here, we explore a possible role of STAT3 in mediating intrinsic and extrinsic pathways that contribute to arsenic lung carcinogenicity.

In our previous study, we have shown sub-chronic arsenic exposure induced lung epithelial cells transformation which was accompanied with oxidative stress and autophagy activation. Our data further indicate that autophagy acts as a cell self-protective mechanism against oxidative-stress-promoted cell transformation. Arsenic exposure causes sustained oxidative stress. But the activation of autophagy, after an initial boost by acute arsenic administration, decreased in response to prolonged arsenic exposure. Forced upregulation of autophagy ameliorates cell transformation. Our interpretation is that with the adequate protection of autophagy, short-term arsenic exposure does not cause cell transformation. Upon prolonged arsenic exposure, however, with decreased protection of autophagy, sustained oxidative stress induces gene mutation/genomic instability and eventually leads to cell transformation. Recently, we further uncovered the involvement of a STAT3-mediated autophagy and inflammation responses in this process.

Chronic sterile inflammation caused by continuous carcinogen exposure has been linked to various steps of tumorigenesis. A pathogenic effect of pulmonary inflammation has been shown in several murine models of lung cancer. Over production of specific cytokines and abnormal activation of transcription factors are underlying the oncogenic action of chronic inflammation. Autophagy, on the other hand, has been proposed as a new immunological paradigm acting as a negative mediator of chronic inflammation. Defects in autophagy under the condition of chronic inflammation are generally in favor of oncogenesis since autophagy functions in cellular homeostasis. Failure to remove cellular garbage in autophagy-defective cells/tissues results in cell injury/death which certainly is an inflammatory stimulus and creates a cancer-prone microenvironment. However, previous work only shows an incomplete picture for the interaction between acute inflammation and autophagy. For instance, IL1β from acute inflammation activates autophagy while TH2 cell-associated cytokines, such as IL4 and IL13, inhibit autophagy. Conversely, autophagy has been shown to inhibit acute inflammatory response. So far little is known regarding the interaction between chronic inflammation and autophagy as well as how it is related to arsenic lung carcinogenesis.

Our recent work uncovers that arsenic enhances interleukin 6 (IL6) secretion from lung epithelial cells. The level of IL6 is increased upon prolonged arsenic exposure which inhibits autophagy activation and thus enhances arsenic-induced cell transformation. Our data further indicate STAT3 as a critical mediator of autophagy and inflammatory response. Acute arsenic treatment inhibits mTOR which then inhibits STAT3 and downregulates Mcl1 expression. Mcl 1, a member of the Bcl 2 family, not only functions in promoting cell survival/proliferation but binds to Beclin 1 and sequesters it from participating in autophagoosome formation. Hence, downregulation of Mcl 1 releases Beclin 1 from the binding of Mcl 1/Beclin 1 and enhances autophagy activity. In contrast, upon long-term arsenic exposure while mTOR is no longer inhibited, the increased secretion of IL6 activates STAT3 and upregulates Mcl1 expression and thus inhibits autophagy. Importantly, one of the target genes of STAT3 is IL6 and activation of STAT3 may further increase IL6 secretion. Moreover, the IL6 in the extracellular milieu secreted not only from epithelial cells but, more importantly, from immune cells, can further activate STAT3 in both epithelial and immune cells through autocrine or paracrine mechanisms. Thus, a feedforward loop is established within an epithelial cell and an interaction is set up between epithelial cells and surrounding immune cells. Together, STAT3 may control not only the intrinsic pathways that regulate survival/proliferation and autophagy but also extrinsic pathways that mediate the crosstalk between cells and their microenvironment, including the immune system (Figure 1). Indeed, inhibition of STAT3 in lung tumor cells has been shown to enhance NK-cell-mediated cancer killing. Therefore, activation of STAT3 in epithelial cells upon chronic inflammation may be carcinogenic and immunosuppressive as well.
while in immune cells STAT3 may function as an orchestrator mediating immune stimulation/suppressive response in response to short- or long-term arsenic exposure, respectively.

Cell transformation caused by environmental factors is not rare even in healthy individuals, but the chance of forming a tumor is much lower due to the existence of immunosurveillance. Namely, although genomic alterations are essential for tumorigenesis, compromised immunomonitoring is equally indispensable since intact host immune system is capable of eliminating/controlling transformed cells. Therefore, arsenic tumorigenicity implicates immunosuppressive actions of arsenic.

The effects of acute arsenic treatment on the immune system appear to be mostly immunotoxic. It decreases the abundance of lymphocytes and inhibits the proliferation of human peripheral blood T cells. However, chronic arsenic exposure more likely causes functional alterations of the immune system. It alters the expression of immune response genes in mouse lung and impairs gene expression and functions of human macrophages, dendritic cells and T cells. Although the molecular mechanism underlying arsenic immunosuppressive effects remains to be provided, STAT3 in immune cells can be a major target of arsenic immunosuppressive actions. STAT3 has been shown to regulate immunosurveillance functions of immune cells. Activation of STAT3 in hematopoietic cells interrupts the antitumor functions of dendritic cells, T cells, and natural killer cells. Furthermore, autophagy functions both in innate and adaptive immunity. Autophagy regulates pathogen and damage-associated molecular patterns of innate immunity and participates in antigen presentation of adaptive immunity. Therefore, the role of STAT3/autophagy in the crosstalk between epithelial cells and their microenvironment including the immune system in the course of arsenic lung carcinogenesis is worth further investigating.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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