Biphasic Effect of Arsenic on Cell Growth and Its Clinical Significance

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ABSTRACT
Arsenic stimulates proliferation at low levels and inhibits cell growth at high concentrations, showing a biphasic effect on biological process. The biphasic effect requires that arsenic concentration has to be maintained at an appropriate threshold during chemotherapy. The apoptosis may be a primary mechanism related to dual properties of the arsenic.

Keywords: Arsenic; Biphasic effect; Endemic arsenism; Carcinogenesis; Chemotherapy

INTRODUCTION
Arsenic element (As) is widely distributed in nature, which is often combined with oxygen or sulfur to form compounds. The arsenic is closely associated with the biological process as well. Its pathophysiological roles are characterized by the following aspects: (a) low-dose arsenic stimulates cell proliferation and carcinogenesis. When sodium arsenite was utilized to treat HepG2 cancer cells or HHI-5 hepatocytes, the percentage of cell death was negative in initial phase, which suggests that the low-dose arsenite promotes cell growth (Figure 1). The arsenic could enhance cell viability at a narrow range of low concentration. As the level of arsenite reached a critical point, it began to inhibit the proliferation and to accelerate cell death. The consistent result had been also reported by other study [1]. In some geological regions, the arsenic concentration in drinking water exceeds the standard content (0.01 mg/L) recommended by World Health Organization. The arsenic-enriched drinking water causes endemic arsenism in local residents [2]. Incidence of various cancers (e.g., skin, lung, kidney, urine bladder, liver and so on) in the endemic areas are significantly higher than those in non-endemic regions [3]. The arsenic had been identified as a human carcinogen by International Agency for Research on Cancer; (b) high concentration of the arsenic inhibits cell growth. In clinical practice, arsenic compounds (i.e. As2O3, As2S2, etc.) are commonly utilized to kill cancer cells during chemotherapy. Moreover, the arsenide has been the first-line medicine for the treatment of certain cancers such as acute promyelocytic leukemia or solid visceral neoplasm [4-6]. Sometimes, the arsenic compounds are combined with other drugs in order to obtain the best therapeutic effect. The arsenide not only induces tumor development, but also kills cancer cells as basic drug in clinical treatment. The arsenic has dual properties of carcinogen and cancer suppressor. Thus, a novel concept “biphasic effect” is proposed to describe its bidirectional role in cell growth.

Figure 1: Schematic diagram of biphasic effect. The arsenic stimulates cell proliferation at low doses, whereas it accelerates cell death at high concentrations.
DISCUSSION

What is exact mechanism that gives rise to dual properties of the arsenic? Currently, there is no clear answer for the question. However, available research results support that apoptosis plays a crucial role. The apoptosis is a gene-controlled, energy-consumed, suicidal process to maintain the tissue structure. A balance between apoptotic and anti-apoptotic competencies not only determines cell viability, but directly affects tissue function as well. So far, the apoptosis has been thought of as primary mechanism to connect carcinogenesis and cancer suppression. Inhibitor of apoptosis proteins (IAPs) has a powerful function in regulating cell survival and controlling apoptosis cascade [7]. Furthermore, the expression of IAPs is modulated by multiple nuclear factors, such as NF-kappa B, FoxA2, C/EBP-beta and so on [7]. Relationship between arsenic and apoptosis is worthy of further investigation. We need additional evidence to demonstrate that (a) low-dose arsenic inhibits apoptosis and stimulates cell proliferation. It is well known that the carcinogenesis has to overcome the resistance of apoptosis; (b) high-dose arsenic triggers apoptosis and kills cancer cells. The core strategy for cancer treatment is to induce apoptosis of cancer cells. A reasonable hypothesis is that the arsenic inhibits apoptosis at low concentrations, whereas promotes apoptosis at high concentrations. It is also speculated that IAPs and their regulatory network may be responsible for the dual properties of arsenide.

An exploration on biphasic effect of arsenic (arsenide) has special significance in clinical treatment of the cancer. When arsenic compound is administered with other medicines together, dosage of the arsenic compounds is often reduced. Owing to dual properties of arsenic, we should evaluate the medicinal value of the arsenic compound while taking drugs in combination. At this moment, the local concentration of arsenide must be maintained at a specific level to induce the apoptosis of cancer cells. Otherwise, the arsenide may promote the proliferation of cancer cells. There is no any therapeutic effect, even an opposite outcome. Hence, we have to consider bidirectional response of the arsenide, especially during combination with other drugs. What is the exact threshold for arsenide to inhibit the tumor? How to administer the arsenide to reach the threshold concentration and keep it constant? What are biomarkers reasonable for monitoring the concentration of arsenide in the blood? Up to now there have been no answers for above questions. Biological characteristics of the arsenic also raise a new topic for the toxicology. In the traditional definition of toxicology, killing cells or increasing death rate is generally thought of as toxicological behavior. However, boosting the proliferation of cancer cells is also toxic to the body. So the behavior of low-dose arsenic is another aspect of toxicology. Perhaps it can be defined as inverse toxicology or reverse toxicology. Presently, we work on molecular markers that can estimate the concentration of arsenide in the blood and evaluate its therapeutic effect. Leukemia and solid tumors may require different concentrations of arsenic drugs [4]. Clinical trials in large samples are needed to test the true role of arsenide in the treatment of various cancers. Moreover, the quantification of functional state of cells is the current focus.

CONCLUSION

In summary, the arsenic has biphasic effect on cell growth, which is manifested by the proliferation at low levels and inhibition at high concentrations. Because of the biphasic effect, a threshold of arsenic concentration must be maintained to kill cancer cells during cancer treatment. Otherwise, the arsenide may stimulate the proliferation of cancer cells, achieving a reverse effect. Preliminary studies reveal that the anti-apoptotic IAP family and its regulatory network play an important role in arsenic biology. The apoptosis may be an essential mechanism related to dual properties of the arsenic.

DECLARATION OF INTERESTS

The authors have nothing to disclose.

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