PI3K/Akt pathway in arsenic-induced liver cancer

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ABSTRACT
International Agency for Research on Cancer defined Arsenic as a carcinogen for human (class 1) for liver, lung, urinary, bladder, skin, kidney and prostate. The present paper focuses on the role of PI3K/Akt cellular signaling pathway in As-induced liver cancer. Current studies suggest that Arsenic can manipulate the PI3K/Akt pathway to induce cell proliferation as well as apoptosis, two different mechanisms.

KEYWORDS: heavy metals, hepatic cancer, hepatocellular carcinoma, occupational exposure, workers, environmental exposure.

1. Introduction
Arsenic (As), an extensively disseminated semimetallic element occurring in diverse compounds in the crust of the earth, is considered one of the most considerable hazardous chemicals in the environment [1]. The exposure to the trivalent inorganic form iAs(III) and its mono- and dimethylated derivatives MMA(III) and DMA(III), correspondingly, are associated with cancers of skin, lung, urinary bladder, kidney and liver [2-7]. In addition, exposure to As is correlated with numerous non-cancer diseases for instance diabetes mellitus, hypertension, cardiovascular and cerebrovascular diseases [8-12]. Intake of contaminated water with inorganic As (iAs) is the primary route of exposure [1, 2]. The next route is the diet [1, 2]. Nevertheless, in food, in particular, seafood, As is generally present in its organic forms, for instance, arsenocholine, arsenobetain or arsenosugars, not currently recognized to be toxic. Inhalation of iAs-contaminated dust is a common health concern in tin, gold and uranium mines [12-18] and copper smelters [19, 20]. As compounds can furthermore be emitted to the air by coal combustion [21]. Occupational sources of As exposure include glass smelters [22] and its use in semiconductors, pesticides, wood preservatives and fireworks [12, 23]. In contradiction, As administered in its trioxide form appear to be a helpful therapeutic device in cancer cure [24]. High concentration of As can elicit rapid toxic effects resulting in death; As is infamously known as the “poison of the kings” [25].

International Agency for Research on Cancer defined As as a carcinogen for human (class 1) for liver, lung, urinary, bladder, skin, kidney and prostate [26]. The latency time in humans of As-related carcinogenesis is about 30-50 yrs [26]. Over the years, scientific efforts have been made to study the mechanism of As-induced toxicity and carcinogenicity; the present review focuses on Phosphatidylinositol 3-kinase (PI3K)/Protein Kinase B (Akt) cellular signaling pathway in As-induced liver cancer.

2. PI3K/Akt cellular signaling
PI3Ks in mammalian cells are classified into Classes I, II, and III. Class I PI3Ks have two subfamilies: class IA, which is activated by receptor tyrosine kinases
(RTKs), and class IB, which is activated by G-protein-coupled receptors.

Class IA PI3Ks are well known for regulating cell activity: proliferation, growth, and survival [27-28]. PI3Ks consist of heterodimers of a catalytic subunit, p110, and a regulatory subunit, p85. PI3K catalyzes the adaptation of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3). Such phosphates can negatively regulate signaling. PIP3 formed from PI3K action recruits Akt, a serine/threonine kinase, and phosphoinositide-dependent kinase 1 (PDK1) to the plasma membrane through binding pleckstrin homology (PH) domains. Given the involvement of PDK1 and Akt to the membrane, PDK1 phosphorylates Akt in its kinase domain (Thr308). Complete activation of Akt comes by phosphorylation of its carboxy-terminal hydrophobic pattern (Ser473) by PDK2 [29-31]. After creation, Akt is released from the plasma membrane and transferred to the cytoplasm and nucleus to phosphorylate numerous molecules that regulate numerous cell functions measured by PI3K signaling.

The major effect of Akt activation connected to cancer cells is survival, proliferation, and growth [32]. Activated RTKs, including epidermal grow factor receptor (EGFR), can interact with the p85 regulatory subunit to increase the catalytic activity of the p110 subunit [33-35]. The p85 regulatory subunit can, also, connect to intracellular proteins as well as protein kinase C, protein tyrosine phosphatase 1 (SHP1), Rac, Rho, Ras, and Src to control PI3K activity [36]. Akt can activate mammalian target of rapamycin complex 1 (mTORC1) indirectly through inhibiting Tuberous Sclerosis Complex 2 (TSC2), thus allowing Ras homolog enriched in brain guanine nucleotide-binding proteins (Rheb-GTP) to trigger mTORC1 signaling [37].

3. PI3K/Akt pathway in arsenic exposure

As exposure leads to PI3K signaling activation. In particular, As has been revealed to amplify enzyme action of PI3K [38-40]. Downstream, As exposure also leads toward augmented phosphorylation of Akt [41-44] that is dependent on PI3K action [45-48]. Then, As could activate PI3K signaling. As alters cell behavior and the PI3K-Akt pathway synchronizes several of these changes. Chronic As exposure can amplify cell proliferation and anchorage-independent growth and both can lead to PI3K-Akt pathway disruption [49]. Several investigations highlighted that As exposure increases cell proliferation [43-49] correlated with PI3K signaling [48]. As moreover increases the aptitude of cells to proliferate autonomously in a PI3K-dependent manner [50, 51]. Chronic exposure of cells to As can lead to the improved capacity for migration and invasion, which is dependent on PI3K signaling [43]. As-induced proliferation is dependent on cyclin D1 [42-44]. Additionally, As increases cyclin D1 levels [42-44] via mechanisms dependent on PI3K-Akt signaling [42-44]. Numerous signaling molecules may contribute to As-induced cell growth and proliferation. As exposure augments β-catenin attributable to As-induced phosphorylation of Glycogen synthase kinase-3β (GSK-3β) [49-51], which is PI3K dependent [46-47, 52]. As induces NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling as IκB kinase (IKK) α and β decreased with As action [51]. As also augments the levels of cyclooxygenase-2 (COX-2), an oncogenic enzyme [53] that is regulated by PI3K [39]. As furthermore augments the phosphorylation of Ribosomal protein S6 kinase beta-1 (p70S6K1), which is PI3K-dependent [40]. In addition to p70S6K1 signaling, As activates the mitogen-activated protein kinase (MAPK) pathway c-Jun N-terminal kinases (JNK)1/2, thus allowing Ras homolog enriched in brain guanine nucleotide-binding proteins (Rheb-GTP) to trigger mTORC1 signaling [37].

Moreover, As exposure can encourage the phosphorylation of EZH2, [56], the catalytic subunit of polycomb-repressive complex 2 (PRC2) that alters methylation of histone H3 leading to extensive changes in the expression of tumor suppressors and oncogenes. As-induced phosphorylation of Enhancer of zeste homolog 2 (EZH2) requires the expression of signal transducer and activator of transcription (STAT)3, JNK, and Akt [56]. As also promotes tumor growth
such an extensive activation of the PI3K/Akt pathway in liver cancer is not entirely understood [65]. Nevertheless, activation by upstream receptor kinases is supposed to be one key mechanism that might comprise overexpression of c-Met, EGFR, and insulin-like growth factor 1 receptor (IGF1-R). Hepatitis virus infections contribute to the activation of the PI3K pathway as well. The HBx protein can activate PI3K/Akt cascade, thus blocking apoptosis through a p53-independent way [66]. Additionally, the PI3K pathway is probably concerned in the development of cirrhosis [67]. Genomic alteration of the PI3K pathway, as revealed by recent genome sequencing efforts in hepatocellular carcinoma (HCC), also indicates its involvement in HCC. Somatic failure of Phosphatase and tensin homolog (PTEN) by gene mutation or deletion is found to occur in 5% of HCC, which might induce Akt activation in HCC [65]. This evidence suggests that various events induce the activation of the PI3K/Akt pathway in liver cancer development.

5. Conclusion

Future studies should look for to understanding how As activates PI3K/Akt and how this pathway regulates a lot of cellular behaviors in liver carcinogenesis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

REFERENCES