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Mini-Review

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 semi-metallic 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

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(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 in a PI3K-dependent manner [54]. As also induces carcinogenesis through epigenetic mechanisms. An investigation demonstrates that As can induce phosphorylation of histone H3 that is dependent on PI3K and Extracellular signal-regulated kinases (ERK) signaling [55].

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

via promoting angiogenesis with low concentration exposure [57-60].

In vivo studies showed that As can induce angiogenesis [58], activate Hypoxia-inducible factors (HIF)-1 signaling [58] and upregulate vascular endothelial growth factor (VEGF) expression [38, 58, 60] in a PI3K-dependent mode [38, 58]. Besides, disruption of PI3K-Akt signaling decreased *in vivo* angiogenesis, consequential of As exposure [58]. As has wide-ranging effects and PI3K-Akt is an essential signaling pathway mediating numerous cellular modification with As exposure. The mechanism through which As activates PI3K is not well stated. As-induced activation of PI3K-Akt signaling may be mediated by reactive oxygen species (ROS) as the ROS scavengers N-acetyl-L-cysteine (NAC) and catalase do not permit As-induced Akt activation [38, 58, 60] even if one report showed ROS inhibitors could not stop As-induced phosphorylation of Akt [48]. ROS-mediated activation of Akt appears to be significant for As-induced carcinogenesis as inhibition of ROS prevents As-induced cell transformation [49] and *in vivo* angiogenesis [58]. Additional factors might, also, play a role in PI3K activation, for instance, MAPK signaling, as a p38 inhibitor, prohibited the As-induced Akt phosphorylation [48], but this mechanism is not well understood.

Inhibition of JNK or STAT3 also prevents As-induced activation of Akt [61] by multiple mechanisms. Therefore, As activated EGFR, probably because As-induced activation of PI3K-Akt signaling is mediated by EGFR [62].

Finally, inhibition of tyrosine-protein kinase Met (c-Met), which is the receptor for the hepatocyte growth factor, also reduces As-induced activation of Akt [45]. PI3K and Akt are activated upon As exposure and are critical for many of the carcinogenic effects.

4. PI3K/Akt pathway activation in liver cancer

Liver cancer, as well identified as hepatic cancer, is one of the deadliest cancers and gravely threatens the health of people [63-64].

Several investigations point to atypical activation of the PI3K/Akt signaling pathway often occurring in liver cancer. The cellular mechanisms underlying 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

1. Mandal, B. K. and Suzuki, K. T. 2002, Talanta, 58(1), 201-235.
2. Tapio, S. and Grosche, B. 2006, Mutat. Res., 612(3), 215-246.
3. Chen, C., Chen, C. W., Wu, M. and Kuo, T. 1992, Br. J. Cancer, 66(5), 888-892.
4. Chiou, H., Hsueh, Y., Liaw, K., Horng, S., Chiang, M., Chen, C., Chiou, H., Hsueh, Y., Pu, Y., Lin, J. S., Huang, C. and Chen, C. 1995, Cancer Res., 55(6), 1296-1300.
5. Liu, Y. and Chen, Z. 1996, Lung Cancer, 14(Suppl. 1), S137-48.

6. Chen, C. and Wang, C. 1900, Cancer Res., 50(17), 5470-5474.
7. Tsai, S., Wang, T. and Ko, Y. 1999, Arch. Environ. Health, 54(3), 186-193.
8. Tseng, C., Tseng, C., Chiou, H., Hsueh, Y., Chong, C. and Chen, C. 2002, Toxicol. Lett., 133(1), 69-76.
9. Chen, C., Hsueh, Y., Lai, M., Shyu, M., Chen, S., Wu, M., Kuo, T. L. and Tai, T. 1995, Hypertension, 25(1), 53-60.
10. Tseng, C., Chong, C., Tseng, C., Hsueh, Y., Chiou, H., Tseng, C. and Chen, C. 2003, Toxicol. Lett., 137(1-2), 15-21.
11. Chiou, H., Huang, W., Su, C., Chang, S., Hsu, Y. and Chen, C. 1997, Stroke, 28(9), 1717-1723.
12. Ledda, C., Iavicoli, I., Bracci, M., Avola, R., Senia, P., Santarelli, L., Pomara, C. and Rapisarda, V. 2018, Toxicol. Lett., 282, 49-56.
13. Tomasek, L. and Darby, S. C. 1995, Environ. Health Perspect., 103(Suppl. 2), 55-57.
14. Chen, W. and Chen, J. 2002, Occup. Environ. Med., 59(2), 113-118.
15. Qiao, Y., Taylor, P. R., Yao, S., Erozan, Y. S., Luo, X., Barrett, M. J., Yan, Q., Giffen, C. A., Huang, S., Maher, M. M., Forman, M. R. and Tockman, M. S. 1997, Ann. Epidemiol., 7(8), 533-541.
16. Taylor, P. R., Qiao, Y., Schatzkin, A., Yao, S., Lubin, J., Mao, B., Rao, J., McAdams, M., Xuan, X. and Li, J. 1989, Br. J. Ind. Med., 46(12), 881-886.
17. Kusiak, R. A., Springer, J., Ritchie, A. C. and Muller, J. 1991, Br. J. Ind. Med., 48(12), 808-817.
18. Simonato, L., Moulin, J. J., Javelaud, B., Ferro, G., Wild, P., Winkelmann, R. and Saracci, R. 1994, Am. J. Ind. Med., 25(5), 625-633.
19. Viren, J. R. and Silvers, A. 1994, Regul. Toxicol. Pharmacol., 20(2), 125-138.
20. Lubin, J. H., Pottern, L. M., Stone, B. J. and Fraumeni, Jr. J. F. 2000, Am. J. Epidemiol., 151(6), 554-565.
21. Liu, J., Zheng, B., Aposhian, H. V., Zhou, Y., Chen, M., Zhang, A. and Waalkes, M. P. 2002, Environ. Health Perspect., 110(2), 119-122.
22. Rahman, M., Wingren, G. and Axelson, O. 1996, Scand. J. Work Environ. Health, 22(2), 146-149.
23. Abernathy, C. O., Liu, Y., Longfellow, D., Aposhian, H. V., Beck, B., Fowler, B., Goyer, R., Menzer, R., Rossman, T., Thompson, C. and Waalkes, M. 1999, Environ. Health Perspect., 107(7), 593-597.
24. Abernathy, C. O., Thomas, D. J. and Calderon, R. L. 2003, J. Nutr., 133(5 Suppl. 2), 1536S-8S.
25. Chen, Q. Y. and Costa, M. 2018, Mol. Pharmacol., 94(1), 784-792.
26. Straif, K., Benbrahim-Tallaa, L., Baan, R., Grosse, Y., Secretan, B., El Ghissassi, F., Bouvard, V., Guha, N., Freeman, C., Galichet, L. and Cogliano, V. 2009, Lancet Oncol., 10(5), 453-454.
27. Jiang, B. and Liu, L. 2009, Adv. Cancer Res., 102, 19-65.
28. Jiang, B. and Liu, L. 2008, Biochim. Biophys. Acta Proteins Proteomics, 1784(1), 150-158.
29. Hresko, R. C., Murata, H. and Mueckler, M. 2003, J. Biol. Chem., 278(24), 21615-21622.
30. Sarbassov, D. D., Guertin, D. A., Ali, S. M. and Sabatini, D. M. 2005, Science, 307(5712), 1098-1101.
31. Stokoe, D., Stephens, L. R., Copeland, T., Gaffney, P. R. J., Reese, C. B., Painter, G. F., Holmes, A. B., McCormick, F. and Hawkins, P. T. 1997, Science, 277(5325), 567-570.
32. Vivanco, I. and Sawyers, C. L. 2002, Nat. Rev. Cancer, 2(7), 489-501.
33. Zhu, G., Decker, S. J. and Saltiel, A. R. 1992, Proc. Natl. Acad. Sci. USA, 89(20), 9559-9563.
34. McGlade, C. J., Ellis, C., Reedijk, M., Anderson, D., Mbamalu, G., Reith, A. D., Panayotou, G., End, P., Bernstein, A., Kazlauskas, A., Waterfield, M. D. and Pawson, T. 1992, Mol. Cell. Biol., 12(3), 991-997.
35. Hu, P., Margolis, B., Skolnik, E. Y., Lammers, R., Ullrich, A. and Schlessinger, J. 1992, Mol. Cell. Biol., 12(3), 981-990.
36. Hennessy, B. T., Smith, D. L., Ram, P. T., Lu, Y. and Mills, G. B. 2005, Nat. Rev. Drug Discov., 4(12), 988-1004.
37. Carnero A. 2010, Curr. Pharm. Des., 16(1), 34-44.

38. Gao, N., Shen, L., Zhang, Z., Leonard, S. S., He, H., Zhang, X., Shi, X. and Jiang, B. 2004, Mol. Cell. Biochem., 255(1-2), 33-45.
39. Lee, K. M., Hwang, M. K., Lee, D. E., Lee, K. W. and Lee, H. J. 2010, J. Agric. Food Chem., 58(9), 5815-5820.
40. Ouyang, W., Li, J., Ma, Q. and Huang, C. 2006, Carcinogenesis, 27(4), 864-873.
41. Ouyang, W., Luo, W., Zhang, D., Jian, J., Ma, Q., Li, J., Shi, X., Chen, J., Gao, J. and Huang, C. 2008, Environ. Health Perspect., 116(1), 1-6.
42. Ouyang, W., Li, J., Zhang, D., Jiang, B., Huang, C. 2007, J. Cell. Biochem., 101(4), 969-978.
43. Wang, Z., Yang, J., Fisher, T., Xiao, H., Jiang, Y. and Yang, C. 2012, Environ. Health Perspect., 120(1), 92-97.
44. Liu, Y., Hock, J. M., Sullivan, C., Fang, G., Cox, A. J., Davis, K. T., Davis, B. H. and Li, X. 2010, J. Cell. Biochem., 111(6), 1546-1555.
45. Kim, S., Lee, S. H., Kang, S., Lee, L., Park, J. and Ryu, D. 2011, Biol. Pharm. Bull., 34(11), 1748-1752.
46. Hossain, K., Akhand, A. A., Kawamoto, Y., Du, J., Takeda, K., Wu, J., Yoshihara, M., Tsuboi, H., Kato, M., Suzuki, H. and Nakashima, I. 2003, Free Radic. Biol. Med., 34(5), 598-606.
47. Sandoval, M., Morales, M., Tapia, R., Alarcón, L. C., Sordo, M., Ostrosky-Wegman, P., Ortega, A. and López-Bayghen, E. 2007, Toxicol. Sci., 99(1), 126-140.
48. Souza, K., Maddock, D. A., Zhang, Q., Chen, J., Chiu, C., Mehta, S. and Wan, Y. 2001, Mol. Med., 7(11), 767-772.
49. Carpenter, R. L., Jiang. Y., Jing, Y., He, J., Rojanasakul, Y., Liu, L. and Jiang, B. 2011, Biochem. Biophys. Res. Commun., 414(3), 533-538.
50. Skinner, H. D., Zhong, X., Gao, N., Shi, X. and Jiang, B. 2004, Mol. Cell. Biochem., 255(1-2), 19-23.
51. Ouyang, W., Li, J., Shi, X., Costa, M. and Huang, C. 2005, Mol. Cell. Biochem., 279(1-2), 35-43.
52. Watcharasit, P., Suntararuks, S., Visitnonthachai, D., Thiantanawat, A. and Satayavivad, J. 2012, Environ. Toxicol., 26, 280-287.
53. Ghosh, N., Chaki, R., Mandal, V. and Mandal, S. C. 2010, Pharmacol. Rep., 62(2), 233-244.
54. Ding, J., Ning, B., Huang, Y., Zhang, D., Li, J., Chen, C. and Huang, C. 2009, Curr. Cancer Drug Targets, 9(4), 500-509.
55. He, Z., Ma, W., Liu, G., Zhang, Y., Bode, A. M. and Dong, Z. 2003, J. Biol. Chem., 278(12), 10588-10593.
56. Chen, B., Liu, J., Chang, Q., Beezhold, K., Lu, Y. and Chen, F. 2013, Cell Cycle, 12(1), 112-121.
57. Kao, Y., Yu, C., Chang, L. W. and Yu, H. 2003, Chem. Res. Toxicol., 16(4), 460-468.
58. Liu, L., Jiang, Y., Carpenter, R. L., Jing, Y., Peiper, S. C. and Jiang, B. 2011, PLoS One, 6(6), e20858.
59. Soucy, N. V., Ihnat, M. A., Kamat, C. D., Hess, L., Post, M. J., Klei, L. R., Clark, C. and Barchowsky, A. 2003, Toxicol. Sci., 76(2), 271-279.
60. Watcharasit, P., Visitnonthachai, D., Suntararuks, S., Thiantanawat, A. and Satayavivad, J. 2012, Environ. Toxicol. Pharmacol., 33(1), 53-59.
61. Liu, J., Chen, B., Lu, Y., Guan, Y. and Chen, F. 2012, Toxicol. Sci., 129(2), 363-371.
62. Ferrante, M., Ledda, C., Conti, G. O., Fiore, M., Rapisarda, V., Copat. C., Sole. G., Terzo, N. and Travali, S. 2017, Mol. Med. Rep., 15(5), 3361-3365.
63. Ledda, C., Cannizzaro, E., Lovreglio, P., Vitale, E., Stufano, A., Montana, A., Li Volti, G. and Rapisarda, V. 2020, Antioxidants, 9(1), 30.
64. Ledda, C., Loreto, C., Zammit, C., Marconi, A., Fago, L., Matera, S., Costanzo, V., Sanzà, G. F., Palmucci, S., Ferrante, M., Costa, C., Fenga, C., Biondi, A., Pomara, C. and Rapisarda, V. 2017, Mol. Med. Rep., 15(2), 511-533.
65. Zhou, Q., Lui, V. W. Y. and Yeo, W. 2011, Future Oncol., 7(10), 1149-1167.
66. Lee, Y. I., Kang-Park, S., Do, S. and Lee, Y. I. 2011, J. Biol. Chem., 276(20), 16969-16977.
67. Neef, M., Ledermann, M., Saegesser, H., Schneider, V. and Reichen, J. 2006, J. Hepatol., 45(6), 786-796.