COMMENTARY

Search of antilactate dehydrogenase-A molecules - A promising anticancer agent

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Abstract

The aim of this commentary is to summarize some of the recent articles on biology of human lactate dehydrogenase A (hLDH-A) in normal and cancer cells that support the anticancer therapeutic approach based on hLDH-5 inhibition. Up till now, no suitable drug is known that selectively inhibits hLDH-A and can be used for tumor therapies in the clinics throughout the world. This review thus encourages the academic institutions and pharmaceutical industries in search of specific inhibitors for hLDH-A.

Keywords: Anticancer agents, human lactate dehydrogenase-A, literature search

Introduction and Discussion

It is known that most of the energy in the form of adenosine triphosphate (ATP) required for cellular functions is released from dietary molecules (glucose, fatty acids, and amino acids) is by oxidative (aerobic) metabolism.[1] However, when there is hypoxia, energy released from glucose (and glycogen) is shifted to anaerobic pathway where pyruvate of glycolysis is converted into lactic acid.[1,2] In this pathway, overall although the energy production is quite less than aerobic metabolism but due to regeneration of nicotinamide adenine dinucleotide (NAD^+), the anaerobic glycolysis continue for a long time without oxygen.[3] In this way, the cells continue to obtain energy, although less but "something is better than nothing" and is a temporary compensatory mechanism. In the case of cancer cells, although there is no hypoxia in the body but probably due to microhypoxia (the so-called diffusion-limited hypoxia) in specific tumor tissues, cells prefer anaerobic glycolysis for energy production.[2,4] This is called as Warburg effect as suggested by the Warburg[5] and catalyzed by an enzyme known as lactate dehydrogenase (LDH; EC 1.1.1.27).[6] This is a tetrameric enzyme made up of two different protein subunits (LDH-A or LDH-M or LDH-5 and LDH-B or LDH-H or LDH-1), each one is encoded by separate genes. Here, LDH-M isoenzyme means that mostly synthesized in skeletal muscle and LDH-H means that mostly synthesized in heart muscle. This enzyme is necessary for interconversion of pyruvate, and NAD hydrogen (NADH) generated during glycolysis to lactate and NAD^+, respectively, (for details read reviews written by Ahmed and Dingding[7] and Valvona *et al.*[8]). The isoenzyme-A favors the formation of lactate from pyruvate (anaerobic metabolism) and the isoenzyme-B favors the reverse reaction (aerobic metabolism).[9] The direction of catalytic reaction depends on the proportion of LDH-A and LDH-B isoenzymes in the LDH complex. It is proposed that the uptake of pyruvate by mitochondria is suppressed during anaerobic metabolism. This pyruvate is then converted to lactate by cytosolic LDH-A isoenzyme and thus reduces the growing pyruvate pool and thereby regenerating NAD^+ that allows energy production to continue, especially in cancer cells/tissues. The regenerated NAD^+ is required to use more and more glucose/glycogen for anaerobic glycolysis to produce enough ATP for the survival of cells. Thus, LDH-A is the main regulatory enzyme involved in sustaining cancer's glycolytic energy and phenotype[7,10] as most

of the tumor cells are reliant on lactate production for their survival.[11]

Therefore, it has been suggested that human LDH-A (hLDH-A) could be a good molecular target for the drugs that can thus inhibit the anaerobic glycolysis. Thus, this specific inhibition then could be a good step to inhibit the growth and proliferation of cancer cells.[7] Some researchers have already reported the inhibition of hLDH-A by small molecules that showed antiproliferative activity.[7,12,13] Another related observation has also supported this view. In that, when there is a complete genetic deficiency of LDH-A isoenzyme, there are no observed signs and symptoms of cancer in those humans under normal circumstances.[14,15] Recently, it has been shown by Allison *et al*.[10] that knockdown of the LDH-A by RNA interference (RNAi) results in death of HCT116 cancer cells. Similarly by upregulation of LDH-A isoenzyme, some studies indicated that proliferation of tumor cells in enhanced. This was particularly seen in those cancers that have high malignant potential.[7,16] According to Zhou *et al*.,[17] the breast cancer cells become resistant to taxol and in these patients the hLDH-A was shown to be elevated. They also observed that these taxol-resistant cells are quite sensitive to inhibitory effect of oxamate (an analog of pyruvate). The upregulation of LDH-A gene in cancer cells by oncogenic signals (such as hypoxia-inducible factor [HIF] and Myc) is believed to be due to phosphorylation of LDH-A via the oncogenic receptor tyrosine kinase.[11] It has been shown by Fan *et al*.[11] that phosphorylation at Y10 and Y83 potentiates LDH-A activity by many folds. The promotion, cancer cell metabolism and tumor growth is then achieved by the regulation of NADH/NAD^+ ratio. This represents an acute molecular mechanism underlying lactate production and the Warburg effect, while the chronic mechanism is thought to be regulated by Myc and HIF.[11] When the LDH-A was down-regulated by specific hLDH-A RNAi, LDH-A activity was also decreased in the cells and these cells then become more sensitivity to the treatment of taxol (re-sensitization mechanism).

However, LDH-A inhibition does not only inhibit anaerobic glycolysis but also alters the balance between NAD^+/NADH ratio in the cells. This could disturb the homeostasis of other cellular processes and enzymes dependent on the ratio of NAD^+/NADH. Some of these enzymes have critical physiological and therapeutic functions. An example for this is the oxidoreductase NAD(P)H quinone oxidoreductase 1 that uses NADH to reduce the quinone-based anticancer prodrug Apaziquone (EO9) to cytotoxic metabolites.[18]

These findings and observations suggest that selective hLDH-A inhibitors could be very useful in the treatment of cancer.[7,19] However, the ratio of NAD^+/NADH is also required for functions of normal (noncancer) cells, and this approach carries a risk of toxicity to normal cells.[20] Thus, strategies designed to modulate NAD^+/NADH ratio selectively in cancer cells are required, and one potential approach is targeting hLDH-A in cancer cells. Therefore, hLDH-A is considered an attractive molecular target for the development of novel anticancer agents.[7]

Conclusion

According to Valvona *et al*.,[8] "currently there is no suitable hLDH-A inhibitors available for tumor therapies in the clinic." Thus, it is concluded that although many research institutions including some Pharma companies are involved in this task, the discovery of specific hLDH inhibitors that can be used as drugs looks very difficult to resolve this scientific burning challenge.

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