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Mini-review

Lactate dehydrogenase 5: An old friend and a new hope in the war on cancer

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ABSTRACT

A hallmark of most cancer cells is an altered metabolism involving a shift to aerobic glycolysis with lactate production coupled with a higher uptake of glucose as the main source of energy. Lactate dehydrogenase 5 (LDH-5) catalyzes the reduction of pyruvate by NADH to form lactate, thus determining the availability of NAD^+ to maintain the continuity of glycolysis. It is therefore an important control point in the system of cellular energy release. Its upregulation is common in many malignant tumors. Inhibiting LDH-5 activity has an anti-proliferative effect on cancer cells. It may reverse their resistance to conventional chemo- and radiotherapy. Recent research has renewed interest in LDH-5 as an anticancer drug target. This review summarizes recent studies exploring the role of LDH-5 in cancer growth, its utility as a tumor marker, and developments made in identifying and designing anti-LDH-5 therapeutic agents.

Introduction

From a metabolic standpoint, the most distinctive feature of cancer cells is enhanced lactate production due to increased glycolytic activity that correlates with high glucose uptake, regardless of oxygen availability. This phenomenon, known as the Warburg effect, was first observed and described as a sophisticated adaptability of tumor cells to the energy demand more than 90 years ago [1,2]. The underlying molecular mechanism is still not fully understood, despite the considerable progress that has been made in the field of cancer biology.

It is known that specific changes in the tumor microenvironment and hypoxia can enhance glycolysis, which becomes a major source for the production of ATP in cancer cells, through activation of specific transcriptional factors, such as Myc proto-oncogene proteins or the hypoxia inducible factors HIF-1 and HIF-2, which regulate the transcription of genes involved in glucose metabolism [1–4].

A central player in the Warburg effect is lactate dehydrogenase-5 (LDH-5), which catalyzes the formation of lactate in the final step of the glycolytic pathway. It was confirmed that LDH-5 plays a crucial role in tumor maintenance and that elevated *LDHA* gene expression characterizes many human tumors. Recent studies have shown that inhibiting *LDHA* expression may reduce the invasive and metastatic potential of cancer cells by decreasing their proliferation ability and reversing their resistance to chemotherapy [5]. Therefore, LDH-5 is considered a highly promising target in cancer therapy anew.

In this review, we summarize the state of knowledge about LDH-5 and discuss its significance in the treatment and prognosis of neoplastic diseases.

Lactate dehydrogenase-5: a member of the LDH family

Functional roles of LDH-5

Lactate dehydrogenase (LDH, L-lactate, NAD^+ oxidoreductase, EC1.1.1.27) is a family of NAD^+-dependent enzymes. There are at least six LDH isoenzymes. They catalyze the reversible conversion of pyruvate to lactate with concomitant regeneration of NAD^+, which is needed for the continuous generation of ATP to maintain glycolysis. Active lactate dehydrogenase is a homo- or heterotetramer assembled from two types of subunit with molecular weights of approximately 35,000 Da each: LDHA (M) and LDHB (H). These are encoded by separate genes, *LDHA* and *LDHB*, which are respectively located on chromosomes 11p15.4 and 12p12.2-p12.1. The combinations of LDHA and LDHB proteins into tetramers result in the five major isoforms of LDH, numbered 1–5 (LDH-1 through LDH-5) [6]. A third subunit, encoded by the *LDHC* or *LDHX* gene, which is located on chromosome 11p15.5-p15.3 and is likely a duplicate of *LDHA*, forms testis-specific isoform known as LDH-6 or LDH-X [7]. Each subunit determines the metabolic characteristics of isoforms and predisposes them to act in either an aerobic or anaerobic environment. The LDHB protein kinetically favors the lactate–pyruvate conversion. Therefore, the higher the number of LDHB subunits the tetrameric complex contains, the lower the ability of an enzyme to

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catalyze the forward reaction. The LDH isoenzymes can be separated and identified by differences in their electrophoretic mobility in polyacrylamide gel. LDH-5 forms the slowest-migrating band [6,8].

Lactate dehydrogenase-5 (LDH-5 or LDH-A4) contains only LDHA subunits. Of the LDH isoenzymes, it has the highest efficiency to catalyze the conversion of pyruvate to lactate. LDH-5 is mainly localized to the cytoplasm, where it participates in glucose metabolism (Fig. 1). However, about 0.5% of the total LDH-5 is present in the nucleus, where it acts as a single-stranded DNA-binding protein that affects the DNA-polymerase–alpha-primase complex in a stimulatory fashion, possibly being involved in transcription and/or DNA replication [9]. The subcellular localization of LDH-5 appears to be dependent on the phosphorylation state of Y238 [10]. It is known that LDH-5 can serve as a substrate of the oncogenic viral Src (v-Src) tyrosine kinase and the oncogenic receptor tyrosine kinase FGFR1 [11].

Post-translational modifications of LDH-5

Fan et al. showed that direct phosphorylation of LDHA at Y10 and Y83 strongly enhanced LDH-5 tetramer formation and cofactor binding, resulting in significantly increased LDH enzymatic activity and promoting cancer cell metabolism and tumor growth. They suggested that the LDH-5 tyrosine phosphorylation might be an extra regulatory mechanism underlying the Warburg effect and lactate production [11]. In addition to phosphorylation, lysine acetylation appears as a specific modification of LDH-5. It is involved in the control of its activity. Acetylation at Y5 was found to decrease the LDHA protein level and inhibit LDH-5 activity. Lysine-5 acetylation was shown to reduce and be accompanied with increased LDHA protein levels in both early and late stages of pancreatic cancers [12]. Acetylated LDHA can be recognized by a cytosolic chaperone and it is easily degraded by lysosomal proteolysis [13].

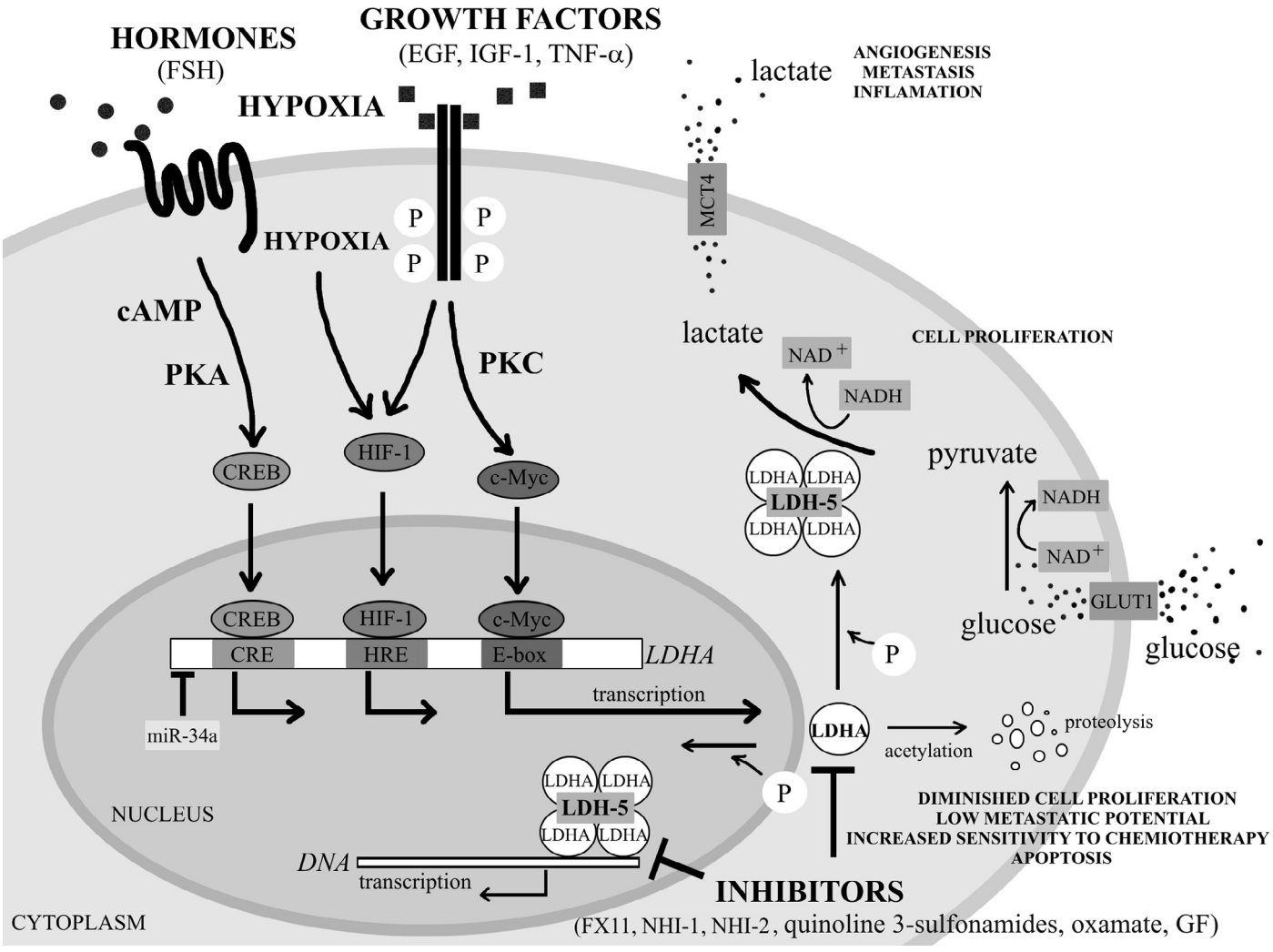

Fig. 1. Schematic illustration of extracellular factor- and hypoxia-mediated LDHA gene regulation and LDH-5 activation pathways. Growth factors and hormones originating from outside the cell or hypoxia stimulate both receptor- and non-receptor-mediated signals, which lead to activation of transcription factors such as CREB, HIF-1 and c-Myc. The activated transcription factors bind to response elements of the LDHA promoter region, leading to increased transcription of the LDHA gene. Post-translational modifications of LDHA protein result in LDHA proteolysis (LDHA acetylation) or enhance the formation of homo-tetrameric active enzyme, LDH-5, which catalyzes the reduction of pyruvate by NADH to form lactate. That determines the availability of NAD^+ to maintain the continuity of the glycolysis (LDHA phosphorylation). LDHA tyrosine phosphorylation also decides about the translocation of LDH-5 to the nucleus, where it acts as a single-stranded DNA-binding protein, stimulating transcription and/or DNA replication. LDH-5 inhibitors decrease mitochondrial membrane potential and elevate intracellular oxidative stress that diminishes the ability of cells to proliferate, reduces their metastatic potential, and increases sensitivity to chemotherapeutic drug(s). Inhibitors can also act as a blocker of the LDH-5–ssDNA interactions to prevent RNA synthesis. Additionally, miR-34a is a direct repressor of LDHA gene expression.