Inhibitors of Lactate Dehydrogenase Isoforms and their Therapeutic Potentials.

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In many different species, lactate dehydrogenase (LDH) constitutes a major checkpoint of anaerobic glycolysis, by catalyzing the reduction of pyruvate into lactate. This enzyme has recently received a great deal of attention since it may constitute a valid therapeutic target for diseases so different as malaria and cancer. In fact, the isoform expressed by Plasmodium falciparum (pfLDH) is a key enzyme for energy generation of malarial parasites. These species mostly depend on anaerobic glycolysis for energy production, since they lack a citric acid cycle for ATP formation. Therefore, inhibition of pfLDH would potentially cause mortality of P. falciparum and, to this purpose, several small organic molecules have been recently designed and developed for this purpose. Moreover, most invasive tumour phenotypes show a metabolic switch (Warburg effect) from oxidative phosphorylation to an increased anaerobic glycolysis, by promoting an upregulation of the human isoform-5 of lactate dehydrogenase (hLDH-5 or LDH-A), which is normally present in muscles and in the liver. Hence, inhibition of hLDH-5 may constitute an efficient way to interfere with tumour growth and invasiveness. This review provides an overview of the LDH inhibitors that have been developed up to now, an analysis of their possible isoform-selectivity, and their therapeutic potentials.

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