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Inhibitors of lactate dehydrogenase overcome the resistance towards gemcitabine in hypoxic mesothelioma cells, and modulate the expression of the human equilibrative transporter-1 (hENT1)

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Outline

1. Introduction
   • Mesothelioma
   • LDH inhibitors
   • Gemcitabine
2. Effect of gemcitabine and LDH inhibitor NHI-1
3. Role of hypoxia
4. Effect of hypoxia on gemcitabine metabolizing enzymes
5. Effect of LDH inhibition
Pleural Mesothelioma; asbestos related

- 5 years survival of advanced stages between 5 and 15%
- Relatively insensitive to any therapy (usually platinum based with pemetrexed or 2nd line with gemcitabine)
Role of glycolysis in nucleotide supply

Jason R. Cantor, and David M. Sabatini Cancer Discovery 2012;2:881-898
The glycolytic switch

- Glucose → P-enolpyruvate
- P-enolpyruvate → Pyruvate
  - Pyruvate → Acetyl-CoA
  - Pyruvate → Lactate

Cytoplasm

Mitochondria

PDH

Krebs cycle

Normal cell

Cancer cell
In most cancer cells:

- Oxidation of NADH to NAD$^+$ for the production of ATP through glycolysis
- High consumption of glucose and production of lactate
- LDH plays a pivotal role for the energy supply
Aim: evaluate drugs inhibiting LDH in pancreatic cancer cells
LDH is a tetrameric enzyme with 5 isoforms, mostly located in the cytosol

- LDH-M, Muscle (isoforms A or B)
- LDH-H, Heart (isoforms A or B)

Only two types of subunits

- LDH1
  - Prevalent in heart
- LDH2
  - Prevalent in liver and skeletal muscle
- LDH3
- LDH4
- LDH5

- LDH5 overexpressed in highly invasive and hypoxic carcinomas
- LDH5 associated with Hypoxia Inducible Factor HIF-1α
Optimization of LDH inhibitors
Exciting times!

Laboratory Medical Oncology

Gemcitabine (dFdC)

- nucleoside transporters

- dFdU
  - CDA
  - dFdUMP
  - DCTD

- dFdC
  - DCK
  - 5’-NT
  - dFdCDP
  - dFdCTP
  - ribonucleotide reductase
  - Inhibition of DNA Synthesis
Hypoxia decreases gemcitabine sensitivity

* P<0.05 normoxic vs. hypoxic conditions
LDH inhibition synergizes with gemcitabine under hypoxia

Combination index:
- CI > 1.2: antagonism
- 0.8 < CI < 1.2: additive
- CI < 0.8: synergism
NHI-1 enhances gemcitabine induced cell death in H28 cells under hypoxia
LDH inhibition restores hENT1 expression

![Bar chart showing hENT1 mRNA expression under normoxia and hypoxia conditions with control and NHI-1 treatments.](chart.png)

- **Normoxia**
  - Control: *
  - NHI-1: *

- **Hypoxia**
  - Control: 
  - NHI-1: *

Significance: *P<0.05 vs. control*
Conclusions

✓ The new LDH inhibitor NHI-1

1) Blocked cell proliferation under hypoxic conditions
2) Interacted synergistically with gemcitabine
3) Induced apoptosis
4) Rescued hENT1 mRNA expression in hypoxic conditions

LDH-A inhibition synergism with gemcitabine forms a novel strategy targeting hypoxic alterations of glucose metabolism for mesothelioma
Acknowledgements