DISODERS OF PURINE AND PYRIMIDINE NUCLEOTIDES METABOLISM IN HUMAN GASTROINTESTINAL TRACT CANCER

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Stomach cancer is the fourth most common cancer in the world, with 989,000 new cases diagnosed in 2008 [WCRF International].
Key enzymes of thymidine metabolism

**Thymidine kinase (TK; EC 2.1.2.1.)**

**Thymidine phosphorylase (TP; EC 2.4.2.4.)**

TP is similar to the platelet-derived endothelial cell growth factor (PD-ECGF) and hence plays dual role in cell biology.

\[
\text{NH}_3 + \text{CO}_2 + \text{ATP} \rightarrow \text{Asp} \rightarrow \cdots \rightarrow \text{UMP} \rightarrow \cdots \rightarrow \text{dUMP} \rightarrow \text{dTMP}
\]

**DE NOVO**

- The activity of the pathway in norm 90-95%
- In tumor ~80% ↓

**SALVAGE**

- The activity of the pathway in norm 5-10%
- In tumor ~20% ↑

**TP**

Thymine \(\rightarrow\) Thymidine

**TK**

Cancer feedback mechanism is absent

Total pool

- dTDP
- dTTP
DNA synthesis

TMP

TK

Thymidine

Thymine

Carcinoma cell

Degraded DNA

Necrotic Area

DNA synthesis

MMP-1

Degradation extracellular matrix

VEGF

Endothelial cell proliferation

IL-8

Endothelial cell migration

P

2dR1P

Oxygen radicals

Proliferation

Angiogenesis
The thymidine salvage pathway enzymes TK and TP compete for thymidine as a substrate and catalyze opposing synthetic and catabolic reactions that have been implicated in the control of proliferation and angiogenesis, respectively.
Key enzymes of adenosine (Ado) metabolism

Ecto-5'-nucleotidase (5'-NT AMP) or CD73 (5'-NT: 3.1.3.5)
Adenosine deaminase (ADA: 3.5.4.4)

- Has Hormone and Neurotransmitter properties
- Regulates energy metabolism by lowering the utilization of ATP as a hormone
- Is involved in many metabolic pathways
The aim of this study is to investigate the DNA precursors metabolism in healthy and patients with gastric cancer $T_{3-4}N_{0-x}M_0$ and to determine the possible role of it`s regulatory enzymes as biomarkers.
PATIENTS AND METHODS

- Seventy-four adult patients, 35–80 year old, with gastric cancer were included in this study.
- Patients were staged in the accordance with TNM classification (the 6th edition) as $T_{3-4}N_{0-x}M_0$.
- Eighty-two non-cancerous patients of the same age without gastroduodenal zone pathology formed control group and also were examined.
- The study protocol was approved by Ethical Committee permission of M. Gorky National Medical University (Donetsk, Ukraine) for studies with human materials.
- The features of enzymes activity were studied in blood serum and tissues. Activity of tissue enzymes was determined in the surgically removed material in thirty tumors (the mucosa margin of resection distant from the carcinoma had being as a control).
PATIENTS AND METHODS

- TK activity was determined by the radioisotope method. Radioactivity of diethyl-amino-ethyl-cellulose paper disks (DEAE-cellulose disks paper "Limbro" (UK) was counted in a liquid scintillation SL-8 on a biological scintillation counter (CBS-2, Russia). TK activity was given in nanomoles of thymidylate formed within an hour per 1 mg of protein.

- TP, ADA [Fritch], 5`NT [Edwards. Clin. Path. Immunology,1980] activity was determined spectrophotometrically.

- Protein concentration in biological material was determined using the method described by Lowry et al.

- Statistical analysis of results was performed using Medstat software package. On significance of differences was analyzed by parametric and nonparametric methods.
TP and TK activity in the serum of control group, patients with gastric cancer and in tissues, nmol/mg•min and nmol/mg•h, respectively


TK and TP activity in blood serum of control group in dependence of age

The thymidine kinase activity

The thymidine phosphorylase activity
The activity of enzymes, which regulates metabolism of adenosine in blood serum of control group and gastric cancer patients


TP and TK activity of gastric cancer patients in different age groups
The activity of enzymes, which regulates metabolism of adenosine in blood serum of control group and gastric cancer patients.
ADA activity in blood cells of gastric cancer patients

Analysis of lymphocytes and erythrocytes functional power

**The blast transformation reactions of lymphocytes**

- Control
- Cancer disease

**Sorption capacity of erythrocyte membrane**

- Control
- Gastric cancer

**The decline of cellular immune function**

**Disorder of transport function of erythrocytes**
Regulatory enzymes of adenosine metabolism in blood serum and lymphocytes of gastric cancer patients

<table>
<thead>
<tr>
<th>Age, years</th>
<th>ADA, nmol/mg*min</th>
<th>5`-NT, nmol/mg*min</th>
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<tbody>
<tr>
<td></td>
<td>Healthy serum</td>
<td>Oncology patients</td>
</tr>
<tr>
<td></td>
<td>lymphocytes</td>
<td>serum lymphocytes</td>
</tr>
<tr>
<td>36-45</td>
<td>1,83 ±0,14</td>
<td>182,4±9</td>
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<tr>
<td></td>
<td>1,74 ±0,22</td>
<td>178,4±2,1</td>
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<tr>
<td></td>
<td>2,18 ±0,45</td>
<td>100,7±7,2</td>
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<td>46-60</td>
<td>5,48 ±0,52</td>
<td>50,3 ±3,1</td>
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<td>5,2±0,33</td>
<td>10±0,5</td>
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<tr>
<td>61-70</td>
<td>5,63 ±0,46</td>
<td>45,1 ±2,1</td>
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</tbody>
</table>
Inhibits:

Higher Ado level

Leads to disorder of erythrocytes

Ino

ADA

NH3

Function of T- and B- lymphocytes

Deficiency of immune system

Platelets aggregation

Thrombosis

Ischemia
The association between serum enzymes activity and volume of surgical intervention

<table>
<thead>
<tr>
<th>Enzymes activity</th>
<th>The type of surgery</th>
<th>radical</th>
<th>before</th>
<th>after 9 days</th>
<th>diagnostic</th>
<th>before</th>
<th>after 9 days</th>
<th>palliative</th>
<th>before</th>
<th>after 9 days</th>
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</thead>
<tbody>
<tr>
<td>TK, nmol/mg·h</td>
<td></td>
<td></td>
<td>6,29 ±</td>
<td>1,47</td>
<td>3,40 ±</td>
<td>0,58*</td>
<td>1,76</td>
<td>4,02 ±</td>
<td>0,45</td>
<td>0,67</td>
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<td></td>
<td>1,47</td>
<td></td>
<td>0,58</td>
<td>1,97 ±</td>
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<td>0,20*</td>
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<td>TP, nmol/mg·min</td>
<td></td>
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<td>15,28 ±</td>
<td>2,1</td>
<td>38,33 ±</td>
<td>1,9**</td>
<td>2,2</td>
<td>10,03 ±</td>
<td>2,4</td>
<td>1,8</td>
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<td></td>
<td></td>
<td>2,1</td>
<td></td>
<td>1,9</td>
<td>10,03 ±</td>
<td></td>
<td>1,7*</td>
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<tr>
<td>ADA, nmol/mg·min</td>
<td></td>
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<td>7,19 ±</td>
<td>2,9</td>
<td>5,95 ±</td>
<td>0,6</td>
<td>2,2</td>
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<td>0,6</td>
<td>7,45 ±</td>
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<td>2,5</td>
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<tr>
<td>5'-NT, nmol/h·mg</td>
<td></td>
<td></td>
<td>63,02 ±</td>
<td>8,1</td>
<td>40,58 ±</td>
<td>6,3*</td>
<td>2,1</td>
<td>51,48 ±</td>
<td>2,1</td>
<td>3,9*</td>
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<td>6,3</td>
<td>51,48 ±</td>
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<td>6,5</td>
</tr>
</tbody>
</table>

Note: authentic differences versus previous value: * - p < 0.05, ** - p < 0.01
Comparative dynamic of thymidine kinase and thymidine phosphorylase activity during treatment

Radical type of surgery

Palliative type of surgery

Enzymes activity vs. time (days) for Radical type of surgery and Palliative type of surgery.
References


Conclusions

An activity of TK, TP, ADA and 5´-NT has an effect on the tumor disorders.

The control of individual dynamics of this enzymes activity in blood serum of gastric cancer patients may be used as informative tool for monitoring of patients and treatment optimization.
Thank for your attention!

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