The sole or key enzymes of purine and pyrimidine metabolisms might direct the organisms to the cell proliferation

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ABSTRACT

Cancer development and regenerative cells proliferation are two apposite and self-excluded processes in the organism. However, the classical biochemical pathways of purine and pyrimidine metabolism basically are the same. We presented over years results, evidencing, inhibition of the cells purine and pyrimidine catabolism via influence on the key regulative enzymes and activation of their synthesis might consequently trigger cell proliferation.

Key Words: *Purine; Pyrimidine; Metabolism; Cancer; Regeneration; Cells proliferation*

Two processes – cells regenerative division, including neurogenesis or fast generation of epithelial, dermal and other types of the tissues cells and proliferation of the cancer cells are two different processes. However, both in the basis have the same classical mechanism of purine and pyrimidine biosynthesis as well as their catabolism.

In accordance to the rules of biochemical pathways, every chain of the metabolic interchanges and formations has the regulative components-enzymes, conducting the entire process or pathway.

The scope of our interest during the last decade was devoted to the investigations of 3 key regulative enzymes: Phosphoribosyl Pyrophosphate Synthase-1 (PRPS-1; EC 2.7.6.1), Xanthine Oxidoreductase (XOR; 1.17.3.2) and Dihydopyrimidine Dehydrogenase (DPD; EC 1.3.1.2).

Xanthine Oxidase (XO) as well as the Xanthine Dehydrogenase (XDH) are the two enzymes responsible for the last steps of purines metabolism, hydroxylation of a wide variety of pyrimidine, pterin, and aldehyde substrate. They are the modifications of XOR enzyme.

The mammalian enzymes, which catalyze the hydroxylation of hypoxanthine and xanthine, the last two steps in the formation of urate, are synthesized as the dehydrogenase form and exist mostly as such in the cell but can be readily converted to the oxidase form – XO, by oxidation of sulfhydryl residues or by proteolysis. XDH shows a preference for NAD+ reduction at the flavin adenine dinucleotide (FAD) reaction site, whereas XO fails to react with NAD^+ and exclusively uses dioxygen as its substrate, leading to the formation of superoxide anion and hydrogen peroxide (1).

PRPSs (ATP: D-ribose-5-phosphate pyrophosphotransferase) are a family of the enzymes that catalyse the synthesis of PRPP from ATP and R5P (ribose 5-phosphate) by transferring the β,γ-diphos-phoryl moiety of ATP to the C1-hydroxy group of R5P figure (2-4). PRPP is a key intermediate of metabolism that is required for synthesis of the purine and pyrimidine nucleotides, the pyridine nu-cleotide cofactors NAD and NADP, and the amino acids histidine and tryptophan (5,6).

The gene DPYD, which encodes DPD (EC 1.3.1.2), is the initial and rate-limiting enzyme in the catabolism of the pyrimidine bases uracil and thymine (7).

Our investigations are highlighting one side of the coin: regenerative processes.

Regenerative processes and regulative enzymes

Based on our own investigations we concluded, in pathological as well as in normal conditions inhibition of purine but not pyrimidine catabolism by the inhibitors of the regulative enzymes – XOR and DPD (8-11) along with the activation of purine and pyrimidine synthesis via triggering with phosphates PRPS-1 (results are in the process of publication), which is dominating type of PRPS-1 in mammalian organism, it is possible to initiate cells proliferation as the regenerative mechanism after experimental stroke. The other face of the cells proliferation is the cancer development.

Cancer and regulative enzymes of purine, pyrimidine metabolism

Recent data are evidencing, 5-aminoimidazole-4-carboxamide-1-β-riboside (AICAr) inhibits pyrimidine catabolism and induces multiple myeloma cell death, apoptosis via deprivation of phosphoribosyl pyrophosphate in contrast to the impact on the purine metabolism (12).

XOR activity is associated with the numerous diseases and expression of pathological processes including: inflammation, endothelial dysfunction, cytotoxicity. The negative correlation of XOR activity was associated with the high malignity grade and a worse prognosis in neoplasms of the breast, liver, gastrointestinal tract and kidney cancers, which normally express high level of XOR protein. The explanation for this phenomenon is linked to the metabolic activation of carcinogenic substances or formation of the oxygen as well as nitrogen free radicals (13,14). Additionally, obesity, Type 2 Diabetes Mellitus (T2DM), and the metabolic syndrome (MetS) linked to the cancer, might be triggered by the hyperuricemia associated with excess cancer (15). Decreased expression of XOR was also reported is associated with ovarian cancer (16). Data are evidencing, XOR takes part also in the processes of cells differentiation and its diminished expression contributes to gastric (17) as well as breast cancer aggressiveness, which makes this enzyme the biomarker for the breast cancer detection (18,19). In one of the studies it was investigated along with the other enzymes the mRNA level of the DPD. The authors state, that DPD mRNA protein expression levels were significantly lower in ovarian cancer cells (20). The other groups presents results, evidencing, DPD activity is up regulated in pancreatic tissue as well as prostate cancer (21) compared to normal tissue (22). Other publication states, the patients with high DPD expression had significantly higher levels of recurrence compared with those with low DPD expression in oral squamous cell carcinoma (23). Interestingly, in accordance to our investigations in human embryo brain derived cell culture in normal conditions inhibition of purine catabolism was moderately elevating activity of pyrimidine catabolism (8). Thus, in both, so differently directed processes – cancer and regenerative proliferation, activation of PRPS-1 and inhibition of XOR triggers cells proliferation, whereas DPD activity is moderately regulative for above mentioned conception or not fully investigated.

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