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Review Article

Role of Thymidine Phosphorylase/Platelet-Derived Endothelial Cell Growth Factor in Health and Cancer Growth

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Abstract

The intensity of cellular DNA synthesis and, thus, cell division, depends on the level of deoxythymidine triphosphate (dTTP, the key precursor for DNA synthesis). Thymidine phosphorylase – the enzyme of the «salvage pathway» of thymidilate synthesis. It is similar to the platelet-derived endothelial cell growth factor (PD-ECGF) and hence plays dual role in cell biology. On the one side, TP plays a key role in maintaining the balance of the nucleoside pool and controlling nucleic acid homeostasis, by ensuring the correct supply of deoxyribonucleoside triphosphates (dNTPs) for DNA replication and repair. From the other, it has the angiogenic effect. It has been observed that TP strongly induces revascularization and plays an important role in angiogenesis, tumor growth, invasion and metastasis. Overall a higher level of PD-ECGF/TP expression is correlated with more metastasis and it appears to be a poor prognostic factor. The various complex interactions of TP/PD-ECGF give it an essential role in cellular functioning, and hence it is an ideal target in cancer chemotherapy.

Keywords: Thymidine Phosphorylase; Platelet–Derived Endothelial Cell Growth Factor; Angiogenesis; Proliferation; Chemotherapy

Thymidine phosporylase (TP) an enzyme involved in pyrimidine catabolism. TP is overexpressed in various tumors and plays an important role in angiogenesis, tumor grows, invasion and metastasis. Thymidine phosphorylase (TP, EC 2.42.4.) is one from the key regulatory enzymes of pyrimidines "salvage pathway" synthesis. TP first described in mammalian tissue in 1953 and then purified of plant, animal and bacterial sources [1, 2]. This enzyme catalyses phosphorolysis of the nucleosidic linkage of pyrimidine-2-deoxynucleosides with the formation of the thymine and deoxyribose.

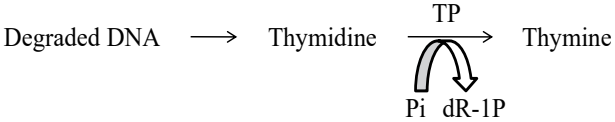

Figure 1. Numerous immunohistochemical and TP-enzyme activity studies have shown that TP participates in many pathological and non-pathological processes.

In main metabolic function appears to be catabolic, although some bacteria and tumors utilize the reverse reaction ana-

bolicaly under stress of certain genetic or dietary deficiency. The catabolic function of TP is also suggested that the enzymatic activity is inhibited by thymine and enhanced by thymidine. The biochemical characterization of TP demonstrated that the enzyme has a low substrate specificity being able to recognize not only thymidine but also deoxypyrimidine and some pyrimidine analogs [1,3]. A recent study reports that TP is strictly enantioselective, since, contrary to some human and viral enzymes involved in nucleotide metabolism, accepts in its active site and acts only on the naturally occurring D-thymidine and D-thymidine analogs, but not on their L-counterparts.

Besides, resent studies have suggested, that TP plays a key role in maintaining the balance of the nucleoside pool and controlling nucleic acid homeostasis, by ensuring the correct supply of deoxyribonucleoside triphosphates (dNTPs) for DNA replication and repair [4].

Concerning the amino acid residues and the molecular interactions responsible for the catalysis recent crystallographic and theoretical studies on E. coli TP suggest that the movement of two protein domains produces a cleft which, by generating a functional active site, can be critical for enzymatic activity. This model explains observed kinetic results and satisfied requirement for efficient enzyme catalysis, most notably through the exclusion of water from the enzymes active site.

Various kinds of solid tumors express TP and high TP-activity is correlated with microvessel density. A recent study has reported that TP enhances interleukin-8 (IL-8) expression [5] and various inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin 1α (IL-1α) and interferon γ (IFN-γ). IFN-γ most effectively increased the expression of TP in cultured human monocytic cells [5]. Nevertheless, how TP expression is up-regulated in human tumors is still unclear.

In 1987 a novel angiogenic factor was investigated in platelet lysate [6], which was thought to be a classic growth factor that binds its cell receptor to exert angiogenetic activity. This factor was named platelet–derived endothelial cell growth factor (PD-ECGF). In 1992, during the characterization of different variants of PD-ECGF transcripts, Usaka and colleagues observed that the amino acid sequence of human PD-ECGF is homologues to that of E. coli thymidine physphorylase and reported, that PD-ECGF had additional structural and biochemical similarities with TP among which is TP activity [7]. Sequence analysis of the gene revealed a stretch of 120 amino acid to be identical to TP. Spraggon G. based upon the already published three-dimensional-structure of TP and the biochemical and biophysical similarities between PD-ECGF and TP suggested that human PD-ECGF was be same as human TP [8].

How does TP induce angiogenesis?

There are a lot of facts and a lot of hypothesis. It has been observed that TP strongly induces revascularization and plays an important role in angiogenesis, tumor growth, invasion and metastasis. Deoxy-D-ribose (DR) one of the degradation products of thymidine generated by TP activity has both angiogenic and chemotactic activity [3]. Both DR and TP inhibit a hypoxia-induced apoptotic pathway. These findings suggest that DR is a downstream mediator of TP function. 2-deoxy-D-ribose, a stereoisomer of DR inhibits the promotion of angiogenesis, tumor growth and metastasis by TP [3,4,6,7].

The possible relationship between 2 deoxy-d-ribose and angiogenesis has been reviewed in detail by Brawn et. Al. They observed that: contrary to the majority of known endothelial-cell polypeptide chemo attractants that bind to endothelial-cell-surface receptor 2-deoxy-D-ribose appears to lack such a cell-surface receptor.

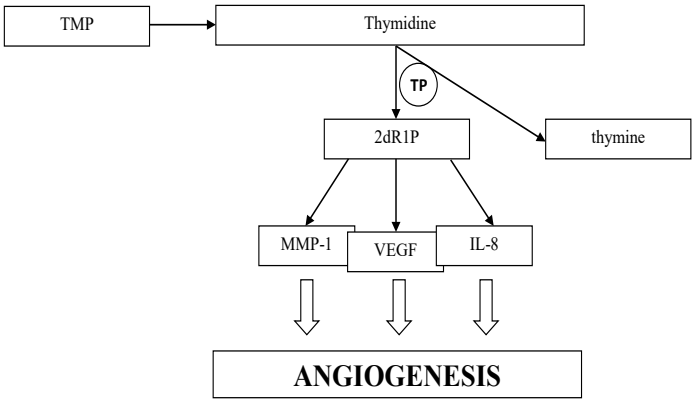

Figure 2. A simplified representation of the mechanism for TP-induced angiogenesis proposed by Brown. The degradation of TMP in tumor cell into thymine and 2-deoxy-D-ribose-1-phosphate. The phosphorylated sugar is a potent protein-glycating agent that generates oxygen radicals. In tumor cells, free radical stress activates the production of IL-8, VEGF and MMP-1, thymidine phosphorylase (TP) and deoxy-D-ribose-1-phosphate.

Recent evidence suggests that DR effects endothelial cell migration though activation of the integrin downstream signaling pathway. It was known that DR may be an important energy source under hypoxic conditions. Many reports suggest that TP pivotal for tumor progression [5, 6]. They suggested, that thymidine upregulated hydroxide anion in a dose-dependent manner in tumor cells with high TP expression. Since cellular oxidative stress is responsible for hydroxide anion induction and, TP induced cellular oxidative stress.

In conclusion, PD-ECGF/TP has been found to have higher expression in tumor tissue compared to normal tissues in a variety of human malignancies and its expression is not only found in cancer cells but also in the stromal macrophages, lymphocytes and fibroblasts. Overall a higher level of PD-ECGF/TP

expression is correlated with more metastasis and it appears to be a poor prognostic factor [7, 8, 9].

The disease in which an elevated level of PD-ECGF/TP has been described thus far are immune system related and have features of chronic inflammation. Elevated levels of PD-ECGF/TP were found in rheumatoid arthritis patients. In another study it was shown that the expression of thymidine kinase (TK) and thymidine phosphorylase as they relate to proliferation (Ki-67 labeling index) and angiogenesis (CD-31-stained blood vessels) in a series of 110-small cell lung cancer (NSCLC) tumors. Tumor size was not found to be associated with TK, TP, Ki-67. These findings provide additional evidence for the role of thimidine metabolism in the complex interaction of proliferation and angiogenesis [10].

Recent studies have suggested that direct 5-Fluorouracil (FUra) anabolism to active FUra/UMP through the DNA pathway could result in high drug efficacy and demonstrated that TP was the limiting step of FUra tumoral activation following the DNA pathway yielding tumoral TP activity could therefore enhance drug response by augmenting the direct formation of the active metabolite FU/UMP [11, 12, 13]. Since last century the 5-FU with other anticancer agents and prodrugs from group of fluoropyrimidine are widely used. These drugs provide the basis for neoadjuvant chemotherapy in combination with various types of surgical procedures and different methods of polychemotherapy (endolymphatic and intra-arterial chemotherapy). Although our results [14] and many reports from other laboratories suggest that TP is pivotal for tumor progression and may be used for diagnosis and treatment of oncology patients.

We have also provided that TP activity changes in the blood serum of patients with gastric cancer demonstrate their activity peculiarities in tissues. Thus far, we have not direct proof of the presence of isoenzyme forms of TP, but different localization in the cytosol and in the nucleus is known to be capable of isoenzymes. Our results raise the possibility that the control of individual dynamics of TP activity in blood serum of gastric cancer patients may be useful as information tool for monitoring of patients and treatment optimization [14].

Conclusion

This review describes TP, its activity, it`s possible mechanism of action and its role in angiogenesis. We try to show, that the enzymatic activity of TP is required for the enhanced IL-8 expression and ROS generation.

Further study of the molecular mechanism for the generation of ROS by TP and for the enhanced IL-8 expression by ROS will contribute to our understanding of TP roles in the malignant progression of tumors. Thus TP activity was thought as potential target for controlling tumor – dependent angiogenesis and could be used as enzymatic test to anticancer chemotherapy.

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