EDITORIALS

What Is the Role of Thymidine Phosphorylase in Tumor Angiogenesis?

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In this issue of the Journal, two groups, one from The University of Texas M. D. Anderson Cancer Center, Houston, and the other from Kagoshima University, Japan, report that the expression of thymidine phosphorylase (dThdPase) is up-regulated in human colon cancer and that this overexpression correlates with increased tumor microvessel density (1,2). Takahashi et al. (1) show that, in 96 cancers, dThdPase is predominantly expressed in tumor-infiltrating macrophages but only in a minority of carcinoma cells. Furthermore, in those tumors with high microvessel density, dThdPase expression is higher when vascular endothelial growth factor (VEGF) expression is low in contrast to when VEGF expression is high. While microvessel count correlates with Dukes' stage, dThdPase intensity does not distinguish between metastatic and nonmetastatic tumors. Takebayashi et al. (2) show that in, 163 colon cancers, dThdPase expression is also significantly increased in carcinoma cells as well as in tumor stromal cells (although the percentage of macrophages was not determined). dThdPase expression in the tumors correlates with local tumor invasion, lymphatic and venous invasion, lymph node metastasis, and Dukes' stage. Most interestingly, only Dukes' stage and dThdPase expression are statistically significant prognostic factors for mortality; dThdPase positivity is a prognostic factor, even after adjustment for Dukes' stage and microvessel count by multivariate survival analysis.

The recognition that dThdPase plays a role in angiogenesis originated in 1987 with the purification of an endothelial growth factor from platelets (3). The factor was found to be chemotactic for endothelial cells in vitro and angiogenic for endothelial cells in vivo (4) and was named platelet-derived endothelial cell growth factor (PD-ECGF). However, in these initial reports, PD-ECGF stimulation of endothelial cells was measured by increased uptake of [3H]thymidine. Subsequently, it was learned that PD-ECGF does not induce endothelial cell proliferation (5) and thus could not be considered as an endothelial mitogen. By 1992, PD-ECGF was reported to be identical to dThdPase (5-7). This helped to explain the original experiments (3) on the basis that dThdPase could have exhausted cold thymidine in the medium, resulting in nonspecific accumulation of [3H]thymidine in cells. Recently, it was shown that dThdPase itself is chemotactic to endothelial cells and is angiogenic in vivo (8) and that one of its degradation products, 2-deoxy-D-ribose (a dephosphorylated product of 2-deoxy-D-ribose-1-phosphate) is also angiogenic (9). Increased dThdPase expression in human breast cancer cells was then shown to correlate with microvessel density in the tumor (10), and the enzyme was also found to be up-regulated in breast cancer epithelium and endothelium (11). The two studies in this issue (1,2) now make it clear that increased expression of dThdPase correlates with intensity of angiogenesis in colon carcinoma.

The identification of high expression of dThdPase in tumor stromal cells, and especially in macrophages, taken together with recent observations that dThdPase in macrophages can be up-regulated by tumor necrosis factor-α, interleukin 1, and interferon gamma (12), suggests that this enzyme is perhaps a mediator of angiogenesis in chronic inflammation and that the tumor cells can amplify their own angiogenic activity by recruiting or activating macrophages. This concept of "macrophage potentiation of tumor angiogenesis" was first proposed by Pollverini and Leibovich as discussed in (1).

This pair of papers illustrates the complexity of the interaction between positive and negative mediators of angiogenesis. For any given tumor, it is difficult to determine which angiogenic stimulators govern the final outcome of angiogenic intensity (as quantified by microvessel count in the papers published in this issue (1,2)). During the past 15 years, investigators in the field of angiogenic research have uncovered an impressive array of angiogenic mediators; before the early 1980s, there were no known angiogenic mediators that had been characterized [for review see (13)]. However, despite this accumulated knowledge of proteins and their genes that regulate angiogenesis, we do not understand the logic of growth control in the vascular endothelial cell, i.e., we have, as yet, not come close to a model or a wiring diagram. Investigators in angiogenesis research are still trying to sort out which angiogenic factors act indirectly and which act directly. dThdPase may be an example of the former, and VEGF may be an example of the latter. It has, in fact, been suggested that VEGF may be a proximate angiogenic factor through which others act (14-16),

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and this idea is strengthened by VEGF knockout mice in which the absence of only one allele leads to failure of development of the vascular system and death of the early embryo (17,18). It is too early to say how this will turn out. A final caveat is that we do not yet know for sure whether the dThdPase levels detected by immunostaining in the published reports represent enzyme activity of dThdPase (Ishitsuka H: personal communication). However, if degradative products of thymidine do turn out to play a critical role in triggering angiogenesis in certain tumors, this would open the way for synthesis of low molecular weight antagonists as a therapeutic approach.

Furthermore, the existence of such a variety of angiogenic mediators in tumors suggests that for anticancer therapy, it may be prudent to develop angiogenesis inhibitors that prevent endothelial cells from responding to more than one angiogenic stimulus. Examples would be prolactin 16 kD (19); peptides that block the alpha2beta3 integrin on endothelial cells (20); or angiotatin (21).

The high expression of dThdPase may also be important for the metabolism of certain prodrugs into active agents, e.g., 5'-deoxy-5-fluorouridine (Furtulon) is converted to fluorouracil by dThdPase (22,23).

Finally, the studies by Takahashi et al. (1) and by Takebayashi et al. (2) also illustrate how an important protein can sometimes be discovered from an apparent experimental artifact. Nine years since the first report of PD-ECGF, this angiogenic factor, now known to be dThdPase, is being found to be overexpressed in several different human tumors, has become a potential prognostic indicator, and may play a role in anticancer therapy. From a biological perspective, dThdPase activity is reminiscent of another enzymatic system in which a vasoactive metabolite is derived from a degradative product of nucleotides, i.e., adenosine. Various phosphatases or membrane-bound 5' nucleotidases can convert adenosine monophosphate to adenosine, which, in turn, leads to relaxation of vascular smooth muscle (24).

The heuristic value of dThdPase is that the search to understand how it stimulates angiogenesis may well lead to a new mechanism of regulation of endothelial cell growth. An effort to understand how this enzyme interacts with other angiogenic mediators may lead to a more fundamental comprehension of the logic of capillary blood vessel formation.

References


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