Newer Vascular Targets

Beverly A. Teicher, PhD

Summary

The identification of cell-surface markers expressed selectively by tumor vasculature is challenging. To get as close to the human disease as possible, investigators have isolated endothelial cells from fresh human tumor specimens and subjected them to RNA-based gene-expression analysis. The data indicate that there are few proteins that distinguish tumor vasculature from normal vasculature and reinforce the notion that the endothelium is a tissue specialized cell type. Endosialin and tumor endothelial marker 7 (TEM 7) were identified as a cell-surface TEMs. The selective expression of endosialin and TEM 7 by tumor vasculature and stroma has been confirmed. Although the function of endosialin and TEM 7 remains to be elucidated, the expression pattern for this protein may be favorable for cancer therapy. PRL-3 was also identified by SAGE (serial analysis of gene expression) as a TEM. PRL-3 is an intracellular phosphatase that is expressed not only in tumor vasculature but in aggressive disease. SAGE analysis of subpopulations of tumors has provided useful leads for new vascular targets. It remains to the basic scientists to elucidate the function of these proteins and to the “drug hunters” to determine whether these targets can be used in therapeutically meaningful ways.

Key Words: SAGE; endosialin; TEM; antiangiogenesis; vascular targets; gene-expression analysis.

The field of antiangiogenic therapies has moved very quickly from laboratory discoveries into the clinic. As with other areas of science, the rapidity of the development of the antiangiogenic field was fueled by the availability of models and the identification of therapeutic targets. The field was also fueled by the early hypothesis which held that angiogenesis was the same no matter where it occurred. Therefore, angiogenesis during embryo development or wound healing was the same as angiogenesis during the growth of malignant disease (Fig. 1) (1–4). The corollary to this hypothesis was that models of normal embryo development and models working with mature well-differentiated endothelial cells in culture would be sufficient and satisfactory models for tumor endothelial cells. This hypothesis also held that because endothelial cells involved in malignant disease were normal, these cells would be less susceptible to developing drug resistance because they were genetically stable (5,6).
Angiogenesis as an anticancer target

<table>
<thead>
<tr>
<th>Early hypothesis</th>
<th>Current hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiogenesis is a normal process, wherever it occurs</td>
<td>Angiogenesis during malignant disease is abnormal</td>
</tr>
<tr>
<td>Angiogenesis during wound healing or embryo development is the same as angiogenesis in malignant disease. Targets identified by studying normal or neoangiogenesis will apply to malignant disease</td>
<td>Targets identified by studying endothelial cells isolated from fresh samples of human cancers will be most relevant for developing therapeutic agents to treat human malignant disease</td>
</tr>
</tbody>
</table>

Fig. 1. Hypotheses supporting angiogenesis as a target for cancer therapy are shown.

The current hypothesis is that angiogenesis occurring during malignant disease is abnormal and that therapeutic targets identified by studying endothelial cells isolated from fresh samples of human cancers will be most relevant for developing therapeutic agents to treat human malignant disease (7–10).

1. NEW TARGET DISCOVERY

Early studies of gene expression were carried out primarily with cell lines. As the importance of the tissue microenvironment and the easy plasticity with which cells alter gene expression in response to the microenvironment became evident, the severe limitations, indeed, inaccuracies in disease representation by monolayer cell culture, were recognized. “Drug-target hunters” realized the need to get as close to the human disease as possible to identify disease critical molecular targets. To accomplish this, fresh samples of human malignant tumors and corresponding normal tissues were used as starting materials (11–25). Gene-expression profiling techniques such as microarray analysis (11–20) and SAGE (serial analysis of gene expression) (21–25) have provided global views of the levels of mRNAs in malignant tissues compared with normal tissues and allowed identification of genes and pathways involved in the malignant process. Specific diseases including ovarian cancer, breast cancer, gastric cancer, multiple myeloma, lung adenocarcinoma, Wilms’s tumor, and neuroblastoma have been analyzed for diagnostic and prognostic gene-expression characteristics and for identification of potential drug targets (14–20). Chief among the issues being faced by these studies is developing data analysis methods that allow investigators to draw biologically meaningful conclusions from very large datasets (12,13).

The one of the challenges for gene-expression studies is to translate research findings of multigene-expression signature classifiers/genomic signatures of disease into applications in diagnostics and therapeutics (26–30). Integrative computational and analytical data analysis approaches including meta-analysis, functional enrichment analysis, interactome analysis, transcriptional network analysis, and integrative model system analysis are being applied to gene-expression data. Some studies focus on the expression of mRNAs that code for enzymes as potential drug targets, some search for functional regulators driving large-scale transcriptional signatures, and others focus on epigenetic alterations that regulate gene expression (27–32).