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# A siren song from tumor cells.

W K Cavenee

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Editorial



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Much of the excitement in contemporary cancer research derives from the stunning successes achieved through analyzing the genomes of tumor cells through cytogenetics, molecular genetic mapping, and molecular cloning and sequencing. A vast and intensely interesting array of mutations and other genetic alterations have been uncovered (1) which in concert with hard-core biochemistry, have led to startling insights into the roles and interactions of the products of oncogenes, tumor suppressor genes, and other cellular genes in the regulation of cellular normality. Defects in these processes can be sorted into specific functional categories and into classes with temporal specificity in the process of tumor evolution. This view of the neoplastic process is focused on the cancer cells themselves and pays scant attention to the influence they have on their neighbors or vice versa.

One such influence is manifest in that many cancers, especially brain tumors, have increased densities of tumor-associated and peritumoral blood vessels. The endothelia of these vessels have many ultrastructural features such as widened or discontinuous intercellular junctions, alterations of the basement membrane, and a paucity of mitochondria that distinguish them from normal vessel architecture (2). This suggests that tumors may impinge on the process of angiogenesis and, in fact, may be dependent on the process for their survival (3). Several factors, notably acidic and basic fibroblast growth factor (FGF) and platelet-derived endothelial cell growth factor have been shown to stimulate the growth of endothelial cells and to be angiogenic. However, each lacks a signal sequence for their active export from the cell and so may be only accessible to target cells upon cell death or (in the case of FGF) degradation of storehouses in the extracellular matrix.

In the case of peritumoral vessels it is more difficult to visualize the role of these cell-associated factors; one might expect the involvement of secreted angiogenic factors. One such activity is called vascular endothelial growth factor or vascular permeability factor (VEGPF) which results from a class of protein mitogens of molecular weight ~ 46 kD which have been purified from a variety of sources. Analysis of their cDNAs (4–6) showed: (*a*) the proteins are homodimeric secretory glycoproteins; (*b*) size variants of the protein which arise through differential splicing of the same VEGPF mRNA; and (*c*) that the coding sequence has limited homology to platelet-derived growth factor-B.

In this issue of *The Journal of Clinical Investigation,* two of the leading groups in this area report complementary features of VEGPF biology. In the first, Berkman et al. (7) examine the expression of the mitogen in brain and human central nervous system tumors. They find that glioblastoma multiforme secretes VEGPF in sufficient amounts to induce vascular alterations. Further, normal brain as well as tumor tissues express the three major forms of the mitogen with the same relative distribution among isoforms. However, the expression of the gene is elevated in central nervous system tumors associated with increased vascularization and edema but in only a few of those without these characteristics. Finally, in situ hybridization showed that VEGPF mRNA was present in the tumor cells themselves. These observations are very nearly the "smoking gun" of evidence needed to indict VEGPF in the pathology associated with brain tumors.

The second paper, by Ferrara et al. (8), underscores the point that it takes several lesions to cause a tumor. Here, Chinese hamster ovary cells were transfected with the gene for VEGPF which caused them to secrete bioactive mitogen into their medium. This ability, however, conferred no in vitro growth advantage on the cells; growth rates, final growth density, or growth in soft agar were not enhanced over controls. However, when the clones were innoculated into immunodeficient mice they were able to grow, in sharp contrast to the controls. Importantly, the tumors were self limited in size, did not metastasize, and were histologically well circumscribed despite their demonstrated high level of VEGPF expression in situ.

These very interesting studies point out clearly that the discovery of mutations in tumor cells must be considered within the context of interactions with neighboring normal cells and that one such critical interaction is the recruitment and formation of blood vessels. The multiplex nature of cancer promises many new and surprising interactions for investigation.

W. K. Cavenee
Ludwig Institute for Cancer Research,
Department of Medicine and Center for Molecular Genetics,
University of California, San Diego

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