9

Angiogenesis and Ocular Tumorigenesis

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CONTENTS

INTRODUCTION
ANGIOGENESIS
LIMITATIONS AND FUTURE DIRECTIONS
REFERENCES

INTRODUCTION

The development of a tumor is dependent on a number of genetic and epigenetic changes. An important step for the propagation and progression of many solid tumors is the induction of a tumor vasculature, i.e., “the angiogenic switch” (1,2). This ensures an adequate supply of oxygen and metabolites for tumor growth and metastasis. This switch is activated when the angiogenic balance tips in favor of proangiogenesis; this results in the increased production of proangiogenic factors and/or downregulation of antiangiogenic factors. The angiogenic switch may occur at any stage of tumor progression, depending on the nature of the tumor and the microenvironment. However, tumor angiogenesis differs from physiological angiogenesis in several respects: the vascular structure, the endothelial cell and pericyte interactions, blood flow, increased permeability, and delayed maturation (3–6; Table 1).

Tumor blood vessels are typically irregularly shaped, dilated, and tortuous, and can have closed ends. They are not organized into definitive venules, arterioles, or capillaries, and the smooth muscle cells/pericytes are more loosely arranged as compared with normal tissue. This vascular network is consequently often “leaky” and hemorrhagic. These abnormal features are the result of the disproportionate expression of angiogenesis cytokines and inhibitors, which are tumor-dependent and reflect the pathological nature of this process. Therefore, successful targeting of the tumor vasculature in cancer therapy can best be achieved if the phenotypic characteristics of these vessels are adequately addressed. There is a great need for developing reliable methods that would allow for recognition of a tumor’s vascular qualities and thus guide antiangiogenic therapies. The potential contribution of the altered expression of anti- and/or proangiogenic factors during the development and progression of ocular tumors remains largely unexplored.
Table 1
Abnormalities Associated With Tumor Vasculature

<table>
<thead>
<tr>
<th>Abnormality</th>
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<tbody>
<tr>
<td>Excessive proliferation</td>
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<tr>
<td>Defective structure</td>
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<td>Lack of lymphatic system</td>
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<td>Lack of local control mechanisms</td>
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<td>Aberrant perfusion</td>
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ANGIOGENESIS

Angiogenesis, the process of the formation of new blood vessels from preexisting capillaries, is tightly regulated and normally does not occur except during development, wound healing, and the formation of the corpus luteum in the female reproductive cycle. This strict regulation is manifested by a balanced production of positive and negative factors, which keeps angiogenesis in check (1). However, this balance becomes abrogated under various pathological conditions, such as cancer development, resulting in the growth of new vessels. It is now well accepted that the progressive growth and metastasis of many solid tumors are dependent on the growth of new vessels. Therefore, there has been great interest in understanding the molecular and cellular mechanisms that go awry during tumorigenesis, resulting in the acquisition of an angiogenic phenotype. In addition, this knowledge has been exploited in the development of agents that can inhibit angiogenesis as a means of stopping tumorigenesis dead in its tracks.

There has been great progress in understanding the process of angiogenesis and the identification of many factors that have pro- or antiangiogenic activity. Although proangiogenic factors were believed to be involved in promoting angiogenesis for quite some time, it was not until the early 1990s that the potential contribution of antiangiogenic factors to this process began to be appreciated (7). There is now a growing list of naturally occurring inhibitors of angiogenesis whose altered expression is shown to contribute to the angiogenic phenotypes of a variety of tumors (Table 2). One of the first of these to be identified was thrombospondin-1 (TSP1), whose expression was downregulated during malignant transformation (7,8). TSP1 expression was subsequently demonstrated to be downregulated in a variety of tumors, perhaps through inactivation of tumor suppressor genes such as p53. In addition, reexpression of TSP1 in these tumors suppresses their aggressive growth and metastasis (7,8). This is believed to be mediated through the antiangiogenic activity of TSP1.

TSP1 inhibits angiogenesis in vivo and endothelial cell proliferation and migration in vitro (7,8). These activities of TSP1 are mediated through its interaction with CD36, a scavenger receptor expressed on the surface of microvascular endothelial cells (8). TSP1 promotes apoptosis of endothelial cells through the activation of caspases and Jun N-terminal kinase (JNK) signaling pathways, as well as downregulation of bcl-2 expression in vivo and in vitro (8). TSP1 has been shown to be an important regulator of the endothelial cell phenotype, and its expression promotes the quiescent, differentiated phenotype of the endothelium (7). In fact, TSP1-deficient mice exhibit increased retinal vascular density from a defect in vascular pruning and remodeling during later stages of vascular development (9). The regression of hyaloid vessels is also delayed in