Summary

The tumor vasculature is largely induced by secreted VEGF-A and consists of a heterogeneous mixture of highly abnormal blood vessels. Recently, it has been possible to replicate many of these vessel types by introducing an adenovirus expressing VEGF-A<sup>164</sup> (Ad-VEGF-A<sup>164</sup>) into mouse tissues. At least five different microvessels form in sequence from preexisting venules, each with distinctly different structural and functional properties. Mother vessels (MV) from first and evolve into several types of daughter vessels: bridged MV, capillaries, glomeruloid microvascular proliferations (GMP), and vascular malformations (VM). In addition to this angiogenic response, feeder arteries (FA) and draining veins (DV) develop from preexisting arteries and veins, respectively, to supply and drain the tumor microvasculature. This classification has helped to elucidate the steps and mechanisms by which tumors induce new blood vessels and hopefully will lead to the identification of new therapeutic targets that can improve anti-angiogenic tumor therapy.

Key Words: VEGF-A; angiogenesis; tumor blood vessels; arteriogenesis; venogenesis.

1. INTRODUCTION

It has been known for more than a century that tumors have their own blood supply and for the better part of that time that the tumor vasculature is highly abnormal, differing from that of normal tissues with respect to organization, structure, and function. At one time, it was believed that the tumor vasculature was more abundant than that of normal tissues; this misconception arose because tumor vessels are often of large size and were therefore more obvious to the naked eye than the smaller but more numerous and functionally superior vessels supplying normal tissues. By the early 1970s, however, it was clear that tumor blood flow was unevenly distributed and, overall, significantly lower than that of normal tissues. It was also clear that tumor vessels were hyperpermeable to plasma and plasma proteins. Further, it was known that tumor vessels were induced by tumor-secreted products, though the tumor angiogenic factor(s) responsible had not as yet been identified. In the years that followed, much was learned about the molecular basis of angiogenesis and particularly about the central importance of one cytokine/growth factor, vascular permeability factor/vascular endothelial growth factor (VPF/VEGF, VEGF-A). More recent work has elucidated the steps and mechanisms by which VEGF-A induces tumor blood vessels and has demonstrated convincingly that tumor blood vessels are not of a single type but rather exhibit extensive heterogeneity. Further, it has become clear that, in addition to angiogenesis (generation of microvessels), both arteriogenesis and venogenesis contribute importantly to the tumor vasculature. Taken together, tumor blood vessels can now be classified in a manner that has clinical and therapeutic significance. Further, recent successes with agents that block VEGF-A or its receptors provide proof of principle that antiangiogenesis can provide a valuable new adjunct to traditional tumor therapy. This chapter reviews the properties of tumor blood vessels, their differences from normal vessels, and the steps and mechanisms by which they form.

2. THE NORMAL MICROVASCULATURE

Before discussing the tumor vasculature, it will be helpful to review briefly the structure of normal blood vessels as a standard of comparison. In most normal tissues, arterial blood enters arterioles, and, thereafter, capillaries, post-capillary venules, and veins. In some tissues (e.g., skin), blood can bypass capillaries by way of arteriovenous shunts. Though part of a continuum with some degree of overlap, each type of vessel has a characteristic structure and function. Arteries are large vessels lined by endothelium and coated with varying amounts of elastic tissue and several layers of smooth muscle cells. Arterioles have a structure similar to muscular arteries but are smaller in size, typically 10–20 μm in diameter. Arteriolar tone is regulated by autonomic, generally sympathetic, nerves that modulate vascular smooth muscle cell contraction and in this way regulate blood pressure and flow. Smooth muscle relaxation is modulated in part by endothelial cell-secreted nitric oxide.

Capillaries are small vessels, typically 4–9 μm in diameter, which are lined by a thin, flattened but, in most tissues, continuous endothelium and are enveloped by basement membrane and a variable coating of pericytes. In some tissues (e.g., kidneys and endocrine glands), the endothelium is not continuous but fenestrated. Fenestrae are 50–150 nm zones of extreme endothelial cell thinning that in most tissues are closed by diaphragms. Capillaries are normally spaced at intervals of approximately 100–200 μm,