

An Italian pioneer in the study of tumor angiogenesis

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It is generally accepted that the role of angiogenesis in the progression of human solid tumors was originally postulated by Folkman in 1971.¹ The central component in this revolutionary paradigm was that tumor cells undergo an angiogenic switch and generate vascularization intimate to the tumor.² Prior to this switch, tumors are less than 3 mm³ and thus this new vascularization allows them to grow rapidly, invade and spread. The switch to an angiogenic phenotype is essentially an outcome of a change in the pro- and anti-angiogenic vascular factors produced by tumor cells, such that the micro-environment is altered and tumor-related microvessels proliferate. Research on tumor angiogenesis, however, was really started by Virchow³ who recognized that the stroma of tumors has a distinctive capillary network. Many investigators subsequently showed that vessels induced by tumor are different from normal vessels.⁴ The growth of these vessels is related to that of the tumor and they may thus be targets for therapy.⁵ Tumor vascularization was first studied systematically by Goldmann,⁶ who described the vasoproliferative response of the organ in which a tumor develops as follows: *"The normal blood vessels of the organs in which the tumor is developing are disturbed by chaotic growth, there is a dilatation and spiralling of the affected vessels, marked capillary budding and new vessel formation, particularly at the advancing border"*.

When Clark *et al.*^{7,8} perfected the implantation of transparent chambers in a rabbit's ear, the morphologic characteristics of blood vessels could be studied *in vivo*, including the use of contrast media. In 1939 Ide *et al.*⁹ were the first to suggest that tumors release specific factors that stimulate the growth of blood vessels, while in

1945 Algire and Chalkley¹⁰ used a transparent chamber implanted in the skin of a cat to study the vasoproliferative reaction secondary to a wound or implantation of normal or neoplastic tissues and showed that the vasoproliferative response induced by tumor tissues was more substantial and earlier than that induced by normal tissues or following a wound. They concluded that the growth of a tumor is closely connected to the development of an intrinsic vascular network. In his treatise *Il Cancro*, published by Ambrosiana in 1946,¹¹ Pietro Rondoni, Professor of General Pathology at the University of Milan, and Director of the Milan Cancer Institute, stated with regard to the stroma of tumors that: *"a tumor acts both angioplastically and angiotactically, in other words it promotes the formation of new vessels and attracts vascular outgrowths (capillaries and pluripotent perivascular cells) so as to build up and shape a stroma of its own, a newly formed stroma. It must thus be unreservedly admitted that tumors are partly vascularized by the already existing network of vessels around them. As in other pathological processes, therefore, such neof ormation as takes place is a vascular neof ormation from budding of the existing capillaries"*.

The importance of this passage lies in the fact that Rondoni refers to the ability of a tumor to induce the formation of new blood vessels from those that already surround it. He also asserts that this angiogenic activity occurs in its stroma.

Harold Dvorak in 1986¹² first highlighted the role played by the stromal component in tumor progression and proposed a similarity between tumors and wounds by defining cancer as a *wound that does not heal*. Subsequent research has demonstrated that the tumor microenvironment plays an active role through adhesion molecules, angiogenesis and stromal host cells. The peritumoral inflammatory infiltrate surrounding newly formed

blood vessels consists of fibroblasts, macrophages, mast cells and other leukocytes that may contribute to the induction of an angiogenic response by secreting angiogenic cytokines and proteolytic enzymes which, in turn, mobilize angiogenic factors stored in the extracellular matrix.¹³

The topicality of Rondoni's remarks is evident. More than 50 years ago, he was speaking of both the angiogenic capacity of a tumor and the importance of the stroma in new vessel formation. The concept of a microenvironment within which angiogenesis occurs is particularly topical. This context, indeed, appears to govern the time and space patterns of angiogenesis. It also determines whether it will remain confined within physiologic bounds or progress to a pathologic state, and is thus a therapeutic target through which normality may be restored.

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