

## "Inducing Angiogenesis" A Hallmark too Far

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### Editorial

The term angiogenesis was coined in 1787 [1] and the role of vessels in cancer has been studied since. In 1971 Folkman [2] introduced the hypothesis, until now widely accepted, that tumour growth is angiogenesis dependent [3,4]. However, the discovery that tumours can also grow without angiogenesis, by co-opting pre-existing vessels in humans [5-8] and in mice [9], has demonstrated that this is not always the case. This observation provides a new aspect of the interaction between vessels and tumours, sheds new light on the biology of the latter and has implications for resistance to antiangiogenic drugs and development of new vascular targeting strategies. Eventually the relationship between cancer and blood vessels is emerging as much more complex than was recently thought to be the case.

However, as the scientific community has been investigating the relationship between blood vessels and cancer for more than a century, it is surprising that such complexity has been so far overlooked. However, as a matter of fact, it has actually been discovered and then forgotten.

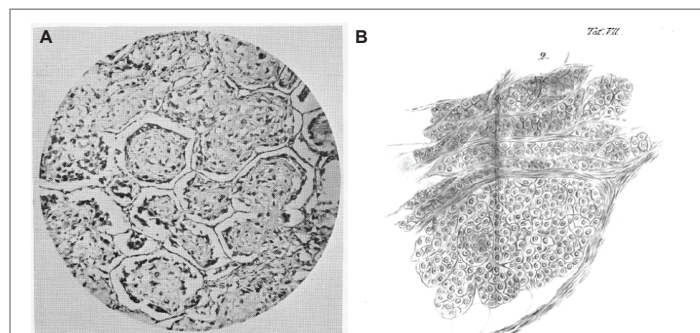
The research line of Folkman [4] has sprouted from the work of Ide [10] as in 1939 he described that tumour implants in the ears of rabbits were accompanied by formation of new capillaries leading him to the idea that angiogenesis is essential to support tumours. In 1971 Folkman published a seminal paper [2] in which the idea that "the growth of solid neoplasms is always accompanied by neovascularization" was put forward. This hypothesis relied mostly on "in vitro" and animal models [3] with experiments conducted in avascular sites, such as the cornea of a rabbit [11], regarded as a classic proof of concept. Subsequent work on mice has not only confirmed the need for angiogenesis but also shown that its induction is an early event [12]. Immunohistochemical studies of human "in situ" breast [13] and cervical [14] carcinomas have demonstrated the enhanced presence of microvessels in the underlying basal membranes at this early stage inferring that angiogenesis may represent an intermediate phase between *in situ* and infiltrating carcinomas [12]. A formal classification of intratumour vessels in human tumours maintained that they were all newly formed [15]. The direct correlation between microvessel density and outcome [16] further strengthened the idea of a link between angiogenesis and tumour growth although such an association has been subsequently strongly questioned [17]. Recently it has been concluded that induction of angiogenesis is a hallmark of cancer as it is necessary to address the needs of tumour cells for oxygen, nutrients and clearance of catabolic products [18].

However many other investigators addressed the issue of cancer and blood vessels in the past and many observations have been published in the past which contrast with the angiogenesis only hypothesis. Reading back into the literature proved to be a very enlightening experience!

In 1988 Kolin et al. [19] described some primary lung carcinomas "often growing mainly in air spaces and preserving the pulmonary framework as their stroma". In 1962 Ritchie [20] writes, in the General Pathology textbook edited by Florey that "One of the principal functions of the stroma is to provide a blood supply within the tumour mass". But "sometimes a tumour will supplement or replace the stroma by making use of pre-existing structures. For example occasional tumours in the lung grow round the alveoli using the alveolar walls in place of stroma".

Further evidence in support of this statement were provided by Willis in 1934 [21] in his classic book "The spread of tumours in the human body". Here he writes that "Intra alveolar growth of tumours in the lung is a characteristic and frequent mode of extension" in which "the plugs of growth occupying the air sacs are themselves avascular, the septal walls constituting the only stroma of the tumours". Alongside providing iconography (Figure 1A) he also quotes several papers, the oldest one from 1861. In this study, entitled "Zwei fälle von carcinosis acuta miliaris" (Two cases of acute miliary carcinomatosis), Erichsen [22] described how in patients with tumours in the lung the neoplastic cells occupy the alveolar spaces but no new vessels can be seen and he illustrates his point with a remarkable "Camera Lucida" drawing (Figure 1B).

In conclusion the blood supply of a tumour can be provided not only by neovascularization, but also by the ability of tumours to co-opt the pre-existing host vasculature growing into non-angiogenic primary and



**Figure 1: A)** A microphotograph of "intra alveolar" tumours by Willis. The original legend [21] reads: "Case 133 of osteosarcoma. Sections of a pulmonary metastasis show alveoli occupied by plugs of growth resembling osteoid tissue. Note the strands of growth connecting the alveolar plugs through the septal pores ( $\times 100$ ).

**B)** The original camera lucida drawing from Erichson paper [22]. The legend the author provides reads: "Cross section through a node carcinoma of the lungs: the alveoli are shaped by with cancerous masses confined between the elastic fibers of the lung tissue, 300 times magnification".

metastatic tumours. Alongside pure non-angiogenic tumours, a mixed pattern of pre existing and newly formed vessels is also commonly seen. Therefore, contrary to the theory of Folkman [3], still regarded as one of Hallmarks of Cancer [18], it is now well established that some tumours can grow and metastasize in absence of angiogenesis [6].

The biological implications are that the triggering of hypoxia related pathways does not necessarily lead to angiogenesis, and that to target tumour blood supply directly may fail because of co-option. Following the initial modest results obtained so far with anti angiogenic drugs [23], understanding the mechanisms driving this behaviour is likely to generate new therapy approaches for these resistant tumours. The reason for the delay in reaching this more global view of the role of blood vessels in cancer can be found in a communication gap between bedside and benchtop research [24] which caused two different lines of work, mostly on animal and “*in vitro*” models on one side and on histopathology on the other, to keep going for years ignoring each other. Eventually, when one line has become predominant, the other had been forgotten for a long time only to be re-emerged when the limitations of a partial approach to the problem emerge.

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