Neoplastic Non-Angiogenic Growth by Means of Vascular Co-Option

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Summary

The case for angiogenesis dependence

The availability of oxygen and nutrients supplied by the vasculature is critical for cancer growth and the role played by the blood vessels has been a long standing object of many studies. The introduction of the concept of angiogenesis goes back as far as 1787 [1] and the role of vessels in cancer has being studied since. In 1971 Folkman [2] introduced the hypothesis, until now widely accepted, that tumour growth is angiogenesis dependent [3]. However, the discovery that cancer can also grow without angiogenesis, by co-opting pre-existing vessels both in humans [4-7] and in mice [8] has demonstrated that this is not always the case. The observation that cancer cells can exploit pre-existing vessels provides a new aspect of the interaction between host and tumors, sheds new light on the biology of the latter and has implications for resistance to antiangiogenic drugs and development of new vascular targeting strategies.

Introduction

The creation of the term angiogenesis goes back to 1787 [1] and the role of vessels in cancer has being studied since. In 1971 Folkman [2] introduced the hypothesis, until now widely accepted, that tumour growth is angiogenesis dependent [3]. However, the discovery that cancer can also grow without angiogenesis, by co-opting pre-existing vessels both in humans [4-7] and in mice [8] has demonstrated that this is not always the case. The observation that cancer cells can exploit pre-existing vessels provides a new aspect of the interaction between host and tumors, sheds new light on the biology of the latter and has implications for resistance to antiangiogenic drugs and development of new vascular targeting strategies.

The case for angiogenesis dependence

In 1971 Folkman published a seminal paper [12] in which the idea that "the growth of solid neoplasm is always accompanied by neovascularization" was put forward. This hypothesis was mostly based on "in vitro" and animal models [13] with experiments conducted in avascular sites, such as the cornea of a rabbit's [14], regarded as 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 [15].

Immunohistochemical studies of human in situ breast [16] and cervical [17] carcinomas have demonstrated the enhanced presence of micro vessels in the underlying basal membranesat this early stage inferring that angiogenesis may represent an essential intermediate phase between in situ and infiltrating carcinomas [15]. A formal classification of intratumour vessels in human tumours maintained that they were all newly formed [18]. The direct correlation between microvessel density and outcome [19] further strengthened the idea of a link between angiogenesis and tumour growth although such an association has been subsequently strongly questioned [20].

Recently it has been concluded that induction of angiogenesis is not always the case. The observation that some malignant tumours grow in the absence of neo-angiogenesis by co-opting the pre-existing vasculature.

Non-angiogenic tumours

An increasing body of evidences has uncovered an added layer of complexity: the possibility that some malignant tumours grow in the absence of neo-angiogenesis by co-opting the pre-existing vasculature.

This observation was first made in clinically detected non-small cell lung carcinomas where four distinct patterns of growth and vascularization were described [22-24]. Three of these patterns have in common the destruction of normal lung architecture, the recruitment of tumour-associated stroma and new vessel formation as they grow in an organ-like fashion [21]. In the fourth non-angiogenic pattern, the immunostainings for endothelial markers highlight the alveolar vessels, entrapped by the neoplastic cells filling the alveolar spaces and growing by co-opting the existing vessels. Soot in macrophages is commonly seen alongside these vessels indicating that they are pre date the appearance of the tumour. Tumours with both angiogenic and non-angiogenic areas are also commonly seen [5]. Clinico-pathological correlation showed that stage I pT1N0 non-angiogenic tumours actually had a worst overall and disease free survival, compared with the angiogenic, with microvessel density having no prognostic value [25,26]. Furthermore also lung metastases were found to growth in a non-angiogenic fashion [4,27] even when the primary tumour was angiogenic [2000] raising doubts about the idea that angiogenesis is always linked to progression of disease and showing that the angiogenic switch can be reversed during disease progression.

This type of non-angiogenic growth in the lung had been previously described as "intra alveolar" [10] and the first description is accredited to a paper from 1861 [28] although, not surprisingly, the relevance to the problem of angiogenesis was not discussed.

If some neoplastic cells are able to grow in a non-angiogenic way by co-opting pre-existing vessels, this type of tumour growth may be expected to be seen in some other organs, and indeed this is the case in the liver. Vermuelem and colleagues [7,29] described three different patterns of hepatic metastatic growth of colorectal and breast adenocarcinomas. In two types, the desmoplastic and the pushing, the architecture of the liver parenchyma was not preserved and an angiogenic tumour is present. However, in the replacement growth pattern, the metastatic cells infiltrate the liver parenchyma without any disturbance of the pre-existing liver structure. As in the lung, liver...
metastases can have a pure or mixed pattern of growth with some patients who have multiple metastases displaying both “pure” angiogenic and non-angiogenic tumours [30]. The patients with non-angiogenic metastases appeared to have a slower but still aggressive disease as they had a better prognosis at 24 but not at 60 months [31]. The incidence of these liver patterns of metastases depends on the tissue of origin: breast, pancreatic and urothelial secondaries have a chronic inflammation and fibrosis were characteristics of angiogenic are able to co-opt the pre-existing vessels. These finding have been supported by further animal models in which both gliomas [36,37] and metastatic melanoma [28] were growing in the brain by vascular co-option. The evidence so far suggest that the type of vascularization associated with a tumor reflects the biology of the malignant cells on one side and the anatomical structure of the organ on the other. It has been recently started to be demonstrated that blood vessels provide not only oxygen and nutrients, but that they also secrete a large and diverse number of cytokines and growth factors in a paracrine manner [called “angiocrines”], which affect/stimulate tumor growth. It could well be that both angiogenic and non-angiogenic pattern of growth are, at least in part, dictated by the angiocrine activity of the vessels involved. [23]

Finally, whatever the site of non-angiogenic growth, the possibility that antiangiogenic facotors are blocking the triggering of vascular growth should be also investigated.

Blood vessels and anti angiogenic treatment

As predicted when non-angiogenic tumours were first described [5], vascular co-option is now being increasingly considered as one of the likely leading causes of reduced responses or intrinsic resistance to antiangiogenic treatment [45], especially of metastases in organ such as the lungs and liver. Nevertheless, this constitutes only one piece of the response/resistance puzzle, and there are likely many reasons for the limited clinical benefits in prolonging progression free or overall survival outcomes in cancer patients receiving antiangiogenic drug treatments.

One is the underappreciated heterogeneous nature of the tumor vasculature, including the angiogenic vasculature populating tumors, and this especially applies to spontaneous tumors that have existed for a considerable period of time - perhaps years - in patients, as opposed to rapidly growing transplanted tumors in mice.

The work of Dvorak and colleagues has revealed evidence for such extensive tumor blood vessel heterogeneity and the fact that certain types of abnormal tumor blood vessels are not necessarily VEGF-dependent [46]. Moreover, antiangiogenic drug treatments may alter this morphologic and functional tumor blood vessel heterogeneity, and indeed, vessel normalization in tumors as a consequence of antiangiogenic therapy may be an example of this [47]. The nature of this heterogeneity may be strongly influenced by metastatic spread, and this may help explain why in some preclinical studies distant lung metastases are unresponsive to a drug such as sunitinib, in contrast the same tumour cell line is treated as a primary tumor mass [48]. Such results highlight one of the deficiencies of most types of conventional
mouse tumor therapy models, which rarely involve treatment of established visceral metastatic disease [49].

If on one hand the description of non-angiogenic tumours helps to explain why the clinical benefits of anti-angiogenic drugs have been modest so far, on the other hand their understanding can become a tool to better use these drugs and exploit their potential to the full. The identification of how much of vascular co-option and classic angiogenesis is present in tumours will help to distinguish those which are more likely to benefit from anti-angiogenic drugs from those which are less likely. It is therefore conceivable that this approach could lead to obtain better results from drugs targeting classic angiogenesis.

Furthermore by unveiling the pathways dictating the non-angiogenic growth of cancer cells new targets for treatment could be discovered leading to develop a new class of anti-vascular drugs.

Conclusion: “Inducing angiogenesis” a hallmark too far?

The blood supply of a tumour can be provided not only by neoangiogenesis, but also by pre-existing vasculature exploited by cancer cells growing into a non-angiogenic primary or metastatic tumour. A mixed pattern of pre-existing and newly formed vessels is also commonly seen in many types of cancers. Therefore, contrary to the theory of Folkman [3], still regarded as one of Hallmark of Cancer [21], it is now well established that some tumours can grow and metastatize in absence of angiogenesis [4]. The reason for the delay in reaching a more global view of the role of blood vessels in cancer can be found in a gap between bedside and benchtop research [50-54].

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 [45], understanding the mechanisms driving this behaviour is likely to generate new therapy approaches for these resistant tumours.

References


