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Highlights

- Development of the therapeutic combination by an anti-VEGF strategy with angiopoietin 2 targeted agents
- Exploitation of the interactions of bone morphogenic protein (BMP) with the other angiogenic factors for improvement of anti-angiogenic therapy
- Targeting hypoxia for enhancing anti-angiogenic agents in cancer treatment
- Targeting the endothelial barrier function as a potential intervention targets for cancer metastasis
- Exploitation of the cross-link between tumour angiogenesis and the metabolic defects of tumour for new biomarkers and therapeutic targets
- Shedding a new insight on the roles of tumour vascular niches in cancer stem cells including acute myeloid leukaemia
- Systematically reviewing the current anti-angiogenic agent for gastric cancer treatment

Abstract

During tumour progression, the significant variation in the pathological deregulated pathways is responsible for the tumour progression of malignancy. Furthermore, the tumour microenvironment is highly diverse consisting of various cell types, including vascular cells. The availability of vascular niche is crucial for normal and neoplastic cells. Johad Folkman's pioneer work of targeting the tumour vasculature to "starving a tumour to death" was conceived more than three decades ago. However, the approach of eradicating tumour vasculature has not been effective as we expected, with only extending the survival of cancer patients by few months.

The tumorigenic mechanisms that tumour cells employ during tumour development are clearly dependent on pathological deregulation of the multiple pathways of host vasculature, including VEGF-dependent, VEGF-independent, interaction between tumour and stromal cells. Not only these pathways are important in the clinical perspective of their associated targeted therapeutics, but their studies also continue to provide critical information to the fundamental knowledge of tumour-associated vasculature. For this reason, the present Special Issue of the Cancer Letters is dedicated to addressing the critical research issue of this field from the aetiology of tumour angiogenesis, the role of tumour vascular niche, the development of biomarkers for anti-angiogenic therapy. Topics and authors were careful selected to cover challenging issues within the broad field of the tumour microenvironment.

Editorial foreword special issue: "Angiogenesis-Convergent or divergent, that is the question: research toward targeted strategies in oncology"

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There is a plenty of evidence that VEGF-independent angiogenic pathways are associated with increased anti-VEGF escape mechanisms. Some of the key factors involved in the possible compensatory angiogenic signalling. In this regard, **Biel and Siemann** review mechanisms driven by angiopoietin2 (Ang-2)/Tie-2 axis for vessel destabilisation and disruption of vascular endothelial cell-cell contact, well known to be critical step for tumour angiogenesis. The authors then discuss the current development of the therapeutic combination by an anti-VEGF strategy with Ang-2 targeted agents. **Lin and Jiang** approach the same issue for the bone morphogenic protein (BMP) family in the context of solid tumour development. The authors explore the cross-talk within BMP family members as well as their interactions with the other angiogenic factors as an important sample for improvement of anti-angiogenic therapy.

Hypoxia has been identified as a hallmark of solid tumours. It has been suggested that anti-angiogenic agents can cause vascular collapse or regression, which may further lead to an increase in the hypoxia within the tumour microenvironment and selection of more aggressive clones of the cancer cells resisting to therapy including anti-angiogenic therapy. **Broggini and colleagues** experimentally explore targeting hypoxia for overcoming the disappointing performance of anti-angiogenic agents in glioma.

Tumours may progress via local invasion or/and circulation dissemination (haematogenous and lymphatic spread). The circulation dissemination represents a crucial developmental step in most tumour types as they can lead to distant metastasis. In the perspective of presenting up-to-date data on the poor structural integrity of the tumour-associated blood vessels related to the intravasation and extravasation of tumour cells, **Shenoy and Lu** discuss the possible mechanisms of transendothelial migration of cancer cells. A clear take-home message is that cancer cells can remodel themselves and vasculature to breach the endothelial barrier, which might lead to potential intervention targets for cancer metastasis.

Worthy to note, putative associations between tumour angiogenesis and metabolic defects of the tumour must be evaluated in the light of current biology data. **Husain and colleagues** discuss the role of $BRAF^{v600E}$, an oncoprotein, in the crossroad of tumour angiogenesis and cachexia in undifferentiated thyroid carcinoma. The authors proposed the exploitation of the mechanisms of the

microenvironment angiogenic factors involving the metabolic defects of tumour represented a promising candidate for new biomarkers and therapeutic targets.

Within the tumour microenvironment tumour and host cell populations dynamically interact via direct cell-to-cell contact and soluble molecules of paracrine regulation. The microenvironmental components are compartmentalised into different tumour niches, which harbour cancer stem cells (CSCs). CSCs represent a heterogeneous subpopulation of cancer cells that retains the potential of self-renewal, which leads to malignant progeny. A whole new insight on how blood vascular niches support CSCs was achieved with studies on variety types of tumours. Three reviews in the present Special issue deals with the relationship between the vasculature and CSCs: **Ping and colleagues** discuss how CSCs orchestrate their vascular niches to facilitate themselves survival, maintain stemness and escape from radio-chemotherapy. While **Jhaveri and Colleagues** further suggest that the CSCs may sustain the vascular niches by transdifferentiating into endothelial cells directly or through the secretion of angiogenic factors. **Colge** discusses an intriguing and barely explored topic of targeting bone marrow vascular niches for treating the refractory acute myeloid leukaemia (AML) by applying anti-angiogenic agents. Mechanistic insights on how AML can functionally integrate within the vascular niches, become quiescence and resist cytotoxic chemotherapy. The author believes that there is a strong rationale to initiate a combination of anti-angiogenic agents with cytotoxic chemotherapy for AML treatment.

The complexity of angiogenesis process leads to many potential targets for tumour intervention. Till date, more than ten anti-angiogenic agents have been approved by the US Food and Drug Administration (FDA) for tumour treatment. **Shan and colleagues** systematically review the anti-angiogenic trials in gastric cancer. The authors found that most of the current anti-angiogenic settings had improved the response rate but not in overall survive compared to chemotherapy alone. The authors also point out that there is a lack of suitable biomarkers to select patients who may most benefit from the combined treatment of anti-angiogenic agents to chemotherapy, as well as of new biomarkers may lead to more effective anti-angiogenic therapeutic management.

Conflict of Interest Statement

The author does not have conflict interest regarding this manuscript.