Aberrations in Angiogenic Signaling and MYC Amplifications are Distinguishing Features of Angiosarcoma

Vittal Kurisetty and Brad A Bryan

Department of Biomedical Sciences, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas, USA

Abstract

Angiosarcomas are very aggressive, rare malignant tumors that originate from vascular or lymphatic vessels and primarily occur following chemical exposure or radiation therapy. Tumor response to either chemotherapy, radiation, or novel anti-angiogenic therapeutics is very low, and because little is known regarding the aberrant signaling that controls these tumors, personalized treatment options for many of these patients are lacking. In this review, we summarize several recent findings regarding the genomics of angiosarcomas, including new discoveries regarding aberrant angiogenic signaling and Myc amplification as key features of this tumor type.

Keywords

Angiosarcoma; Vascular tumor; Sarcoma; Genomics; MYC; Angiogenesis; Vascular endothelial growth factor; Hemangiosarcoma; Lymphangiosarcoma

Introduction

Angiosarcomas, which represent approximately 2–4% of all sarcomas, are malignant neoplasms characterized by quickly proliferating, extensively infiltrating cells derived from the vascular system (Figure 1). These tumors can be divided into two classifications based on their tissue of origin-lymphangiosarcomas (which display aberrant lymphangiogenesis [i.e., overgrowth of newly formed lymph vessels]) and hemangiosarcomas (which display aberrant angiogenesis [i.e., overgrowth of newly formed blood vessels]). Most angiosarcomas rapidly become metastatic because their vascular origin permits tumor dissemination without the need for initial recruitment of new blood vessels (as is a rate limiting requirement for all other solid tumors) [1–3]. Unlike epithelioid sarcomas which initially disseminate to regional lymph nodes, angiosarcomas generally metastasize directly to the lungs via the vascular system [4,5]. Due to their rapid dissemination and aggression,
the median survival rate of patients with this tumor is very short—generally less than 6 months.

Angiosarcomas manifest in several different locations throughout the body with approximately 50% of the cases occurring in the head and neck region. Human soft-tissue angiosarcomas occur irrespective of the patient’s age whereas bone angiosarcomas occur in the individuals from the age of 25 and above. Like many vascular tumors, gender plays a significant role in the development of these tumors, with dermal angiosarcomas occurring more frequently in males than in females (ratio of 2:1) [6] and head and neck angiosarcomas affecting more females than males (69% and 38%, respectively) [7]. Aside from age and gender, several risk factors are associated with the development of angiosarcomas. Hepatic angiosarcoma, which is the most common sarcoma of the liver, is largely linked to toxic exposure to chemicals such as vinyl chloride, thorium dioxide, or arsenic. While primary angiosarcomas of the breast occur sporadically (0.04% of breast tumors) and usually arise in the 3rd and 4th decade of life [8], secondary angiosarcomas can occur in 0.1 to 0.3% of patients following breast conservation therapy combined with radiation therapy [9].

Secondary angiosarcomas are generally found in older women (usually late 60’s) who have previously undergone treatment for breast cancer and can be divided into two categories—lymphedema-associated cutaneous angiosarcoma and post irradiation angiosarcoma. Lymphedema-associated cutaneous angiosarcoma develops on the chest wall cavity and lymphedematous limbs following mastectomy and axillary lymph node dissection. The incidence of these tumors has decreased following increased use of breast conserving therapy. In contrast, post irradiation angiosarcomas generally affect the dermis or parenchyma of the breast tissue in the area previously treated by radiation. This incidence of this form of angiosarcoma has dramatically increased following breast conservation following tumor treatment [9,10].

Current treatment of angiosarcomas typically involves surgery, radiation, and neoadjuvant and/or adjuvant chemotherapy with doxorubicin or taxanes. Yet even following aggressive therapy, patient outcome is often very poor, with five year survival rates for angiosarcomas at less than 30% [11]. Multiple randomized studies failed to show a survival benefit from chemotherapy in patients with angiosarcomas, and while radiotherapy results in 80% local control of angiosarcomas, irradiation does not improve patient survival with metastatic tumors [12]. Several phase II trials have investigated the therapeutic efficacy of novel anti-angiogenic drugs such as Bevacizumab, Sunitinib, and Sorafenib against angiosarcomas [13,14]. Unfortunately, even with these molecular targeting therapeutics, a minimal to absent response was observed in these patients.

In this review, we will critically analyze recent advances in our understanding of angiosarcomas, specifically dealing with transcriptional signatures associated with aberrant angiogenesis as well as MYC amplifications in secondary angiosarcomas. Furthermore, we will identify specific areas that should be further developed to gain a better understanding of the molecular mechanisms contributing to the progression of this tumor and identify potential treatment options that should be tested to increase patient survival.
Transcriptional Signatures of Angiosarcomas

Though angiosarcomas commonly contain mutations seen in many cancers (p53 [15], Ras [16], BRCA [17], and PTEN [18]), given their unique vascular nature, it is prudent to identify mutations or signaling aberrations unique to this particular solid tumor so that we can exploit this characteristic as a weakness. Though heterogeneous in clinical presentation, transcriptional profiling of angiosarcomas reveals that these tumors form a tight genomic grouping distinct from all other sarcoma types [19]. The top most upregulated genes in angiosarcomas included angiogenic regulators such as TIE1, VEGFR2, SNRK, TEK, and VEGFR1, revealing that aberrant angiogenic signaling is a key feature of this sarcoma. Indeed, compared to other sarcomas, angiosarcoma tumors exhibited higher expression levels of endothelial marker/functional genes including PECAM1, EPHA2, ANGPT2, ENDRB, PGE, FLI1, VWF and reduced expression levels in KIT, VEGFA, and VEGFB [19]. A comprehensive miRNome analysis of a large panel of heterogeneous human sarcomas identified 79 angiosarcoma specific alterations in miRNA expression, out of which 12 miRNAs were downregulated and 67 miRNAs were upregulated [20]. Of the highly upregulated miRNAs identified, miRDB miRNA target prediction (www.mirdb.org) indicated that miR-520c-3p, miR-519a and miR-520h potentially target a number of tumor suppressors and pro-apoptotic genes. On the contrary, highly downregulated miRNAs include miR-483-5p, miR-136 and miR-335 which putatively target oncogenes, the MAPK pathway, sarcoma specific metabolism, and cell adhesion. Comparisons of gene expression changes between primary breast angiosarcomas and secondary radiation-induced breast tumors revealed a unique oxidative stress mRNA signature as a defining characteristic of secondary angiosarcomas, even when histological and pathological features were similar between the two vascular tumor categories [21]. The authors postulated that the chronic oxidative stress could be due to mitochondrial dysfunction, dysregulated lipid oxidation, DNA damage response/repair, or oxidized misfolded proteins.

Aberrant Angiogenic Signaling in Angiosarcoma

Given that angiosarcomas arise from cells of vascular origin, it seems reasonable that alterations in angiogenic signaling may be drivers in the tumor formation and progression specific to this tumor type. Moreover, it may be possible to exploit the unique vascular defects associated (Figure 2) with this tumor to our clinical advantage. In addition to high expression levels of the proliferative proteins Ki67 and cyclins A, D and E [22], angiosarcomas show remarkably variable expression in key angiogenic regulators such as VEGF-A (0–94% of angiosarcomas), VEGF-B (39% of angiosarcomas, though only tested in one report), VEGF-C (12–100% of angiosarcomas, though only tested in one report), VEGF-D (100% of angiosarcomas, though only tested in one report), VEGFR1 (62–79% of angiosarcomas), VEGFR2 (64–94% of angiosarcomas), and VEGFR3 (79–100% of angiosarcomas) [22–29]. This data suggests that angiosarcoma progression may not only be driven by VEGF-A/VEGFR2 signaling (which dominates vascular endothelial signaling), but also by VEGF-C/VEGFR3 which is largely involved in lymphangiogenesis and maintenance of the lymphatic endothelium. Indeed, amplification of VEGFR3 occurs in 25% of secondary angiosarcomas [19,30]. As opposed to targeting the VEGF-A signaling pathway, perhaps VEGFR3 kinase blockers or neutralizing antibodies against VEGF-C may show therapeutic efficacy against specific
subsets of angiosarcomas. Interestingly, the high expression of the VEGF decoy receptor VEGFR1 appears at first paradoxical given the potent angiogenic capacity of angiosarcoma tumors. However, despite its established anti-angiogenic role, VEGFR1 is overexpressed in a number of cancers [31,32] and is a negative prognostic factor for multiple carcinomas [33–38]. Using a canine hemangiosarcoma model which is ontogenetically related to the human disease, Tamburini et al. [39] provided strong evidence that genetic background plays an important role in predisposed susceptibility to angiosarcoma. In addition to altered expression in a disproportionate number of genes encoding transcription factors, survival factors, and pro-inflammatory regulators, the authors observed a significant enrichment of VEGFR1 (at the mRNA and protein levels) amongst the hemangiosarcoma-prone breeds compared to less susceptible breeds. It has been postulated that enhanced expression of VEGFR1 could be due to upregulation of Akt and ERK1/2 signaling, as these proteins have been reported to enhance its stabilization via blocking proteasomal degradation of VEGFR1 [40]. Moreover, a novel intracellular form of VEGFR1 has been recently discovered in breast cancer that promotes activation of the tyrosine kinase Src and enhances tumor cell invasion [41]. Similar mechanisms may exist in angiosarcoma. Point mutations in the KDR (VEGFR2) gene have been identified in a subset of primary and secondary angiosarcoma tumors from the breast and chest wall [19]. These mutant receptors appeared to function as constitutively active tyrosine kinases, and were susceptible to anti-angiogenic targeting by sunitinib and sorafenib. Interestingly, the authors reported low levels of VEGF-A in the angiosarcoma tumors, suggesting that angiosarcomas with low VEGF-A levels and constitutively activated VEGFR2 signaling may be better suited to targeting with tyrosine kinase inhibitors such as sunitinib or sorafenib, but not with antibody therapies such as bevacizumab [19].

In addition to VEGF signaling pathways, other angiogenic regulators are aberrantly expressed in angiosarcomas. Strong expression of ANGPT2, TIE1, and TEK mRNAs has been reported in cutaneous angiosarcomas [42], and Tie2 antagonists inhibit in vitro angiosarcoma cell survival and delay in vivo angiosarcoma tumor growth [43]. Reduced expression of thrombospondin-1 (THBS1) has been reported in MYC-amplified angiosarcomas (more on MYC amplifications in angiosarcomas below) [44], and its expression is either downregulated or lost across many cancers [45–48]. THBS1 is an extracellular glycoprotein that mediates cell-to-cell and cell-to-matrix interactions and inhibits angiogenesis via suppressing endothelial migration, proliferation, and survival [49,50]. Finally, hypoxia and subsequent HIF1-alpha protein stability has been suggested to contribute to angiosarcoma tumor progression. While sporadic cutaneous angiosarcomas have been shown to lack HIF1-alpha expression [51], other angiosarcoma subtypes (such as primary breast angiosarcoma and retroperitoneal angiosarcoma) are positive for its expression [25,52]. Indeed, using a chemically induced angiosarcoma tumor model, Laifenfield et al. [53] demonstrated that local tumor hypoxia in combination with macrophage activation and inflammation are initiating events for the formation of angiosarcomas. Hypoxia within the angiosarcoma tumor maintains genetic instability by suppressing BRCA1 and MLH1 activity, resulting in inhibition of DNA mismatch repair and homology specific dependent repair pathways [53–55]. As BRCA mutations have been associated with hereditary predisposition to angiosarcoma [56], the combination of
carcinogen-mediated DNA mutations, tissue hypoxia, and hereditary aberrations in DNA repair may play a significant role in determining the incidence of angiosarcomas.

**MYC Amplification in Angiosarcoma**

Benign atypical vascular lesions are common occurrences following radiation therapy and/or chronic lymphedema, and it is often difficult to differentiate between radiation induced benign vascular issues and secondary angiosarcomas due to overlapping clinical and microscopic features. Moreover, the prognosis of radiation-induced secondary angiosarcomas is significantly worse than found in sporadic angiosarcoma tumors, therefore identification of genetic biomarkers that could easily classify these groupings of vascular disorders could assist clinicians in employing the appropriate treatment option for each patient. It has been reported that the most frequent recurrent genetic alterations in secondary angiosarcomas include amplifications on chromosome 8q.24.21 (50%), 10p12.33 (33%), and 5q35.3 (11%) [57,58]. The 8q24.21 region contains oncogenes including MYC and amplification of this region is observed in several late-stage/aggressive cancers. Comparably, amplification of 10p12.33 is seen mainly in breast cancer while over-amplified 5q35.3 occurs in breast cancer, colon cancer, osteosarcoma, renal cell carcinoma, and squamous cell lung cancer. Analysis of 28 primary and 33 secondary angiosarcomas revealed that MYC amplification on chromosome 8q24.21 was found exclusively in 55% of angiosarcomas secondary to radiation or chronic lymphedema, but not in primary angiosarcomas [57]. In two other studies, the authors demonstrated that MYC amplification occurred in 100% of secondary angiosarcomas, but was absent in all cases of atypical vascular lesions [30,59]. A large scale study of 83 radiation induced sarcomas and 192 sporadic sarcomas indicated that MYC amplification was a distinguishing characteristic in radiation induced angiosarcomas, undifferentiated pleomorphic sarcomas, and leiomyosarcomas; however, the authors present significant evidence to suggest that angiosarcomas were unique amongst other sarcomas in that MYC amplifications were particularly frequent and at high levels in angiosarcomas, while other radiation induced sarcomas displayed low level MYC amplifications [60]. With sharp contrast to the previously mentioned studies Italiano et al. [61] reported data indicating that MYC is amplified in the majority of secondary angiosarcomas (67%) but is also amplified in a subset of primary angiosarcomas (50%). Taken together, these data indicate that MYC amplification is enhanced in radiation induced angiosarcomas, but may be an important mediator of primary angiosarcomas as well.

What are the effects of MYC amplification in angiosarcomas (Figure 3)? MYC is an oncogenic transcription factor perhaps correctly referred to as the “oncogene from hell [62]” which regulates the expression of approximately 15% of all genes to promote cell survival, proliferation, and plasticity [63]. MYC belongs to the basic helix-loop-helix (bHLHZ) superfamily of transcription factors and uniquely exerts its effects through both transcriptional activity and modulation of chromatin architecture via regulating histone acetyl-transferases [64,65]. MYC is expressed at high levels in most tumors, and several tumor types also contain translocations, amplifications, and mutations in key MYC regulators [66]. Aberrant MYC signaling in cancers is associated with poor clinical outcomes, increased rates of metastasis, tumor recurrence, and patient mortality. It is
believed that elevated MYC signaling amplifies the activity of all expressed genes in a
tumor cell, thus sending the cell’s gene expression program into overdrive and dramatically
overwhelming any inhibitory factors that might prevent cell proliferation [67]. Moreover,
MYC is upregulated during hypoxia via a HIF-dependent mechanism [68] and plays a major
role in regulating physiological and tumor angiogenesis and inflammation [69]. Almost
nothing has been reported regarding the contribution of MYC to the angiosarcoma
transcriptome, however a substantial upregulation of the miR-17-92 cluster (a miRNA
polycistron also known as oncomir-1) occurs in radiation induced secondary angiosarcomas
harboring MYC amplifications compared to secondary angiosarcomas without the
amplification [61]. Upregulation of this miRNA cluster occurs across diverse cancers and its
expression promotes tumor cell invasion and proliferation [70–76]. As mentioned above,
THBS1 expression is lost in MYC amplified angiosarcomas. Interestingly, members of the
miR17-92 cluster target THBS1 directly [61], demonstrating one mechanism by which
MYC amplification may induce an aberrant angiogenic phenotype in angiosarcomas. As
standard chemotherapy and even novel anti-angiogenic treatments have largely failed
patients stricken with angiosarcoma, strategies for exploiting MYC dependency in
angiosarcoma tumors are an attractive disease-specific goal. Unfortunately, despite intense
research efforts to inhibit MYC activity, this protein has thus far remained an elusive cancer
therapy target.

Conclusions and Future Directions

Limited data exists evaluating the molecular mechanisms controlling angiosarcomas,
however a wealth of recent publications have shown that key features of angiosarcomas
include aberrant angiogenic signaling, increased oxidative stress, and MYC amplification.
Future studies should focus on classifying heterogenous angiosarcomas based on unique
molecular profiles so that therapeutic treatments can be personalized specific to the genetic
and signaling aberrations unique to each individual tumor.

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References

1. Saaristo A, Karpanen T, Alitalo K. Mechanisms of angiogenesis and their use in the inhibition of
tumor growth and metastasis. Oncogene. 2000; 19:6122–6129. [PubMed: 11156525]
2. Benjamin LE, Keshet E. Conditional switching of vascular endothelial growth factor (VEGF)
expression in tumors: induction of endothelial cell shedding and regression of hemangioblastoma-
like vessels by VEGF withdrawal. Proc Natl Acad Sci U S A. 1997; 94:8761–8766. [PubMed:
9238051]
3. Zetter BR. Angiogenesis and tumor metastasis. Annu Rev Med. 1998; 49:407–424. [PubMed:
9509272]
4. Tateishi U, Hasegawa T, Kusumoto M, Yamazaki N, Inumga G, et al. Metastatic angiosarcoma of
the lung: spectrum of CT findings. AJR Am Roentgenol. 2003; 180:1671–1674. [PubMed:
12760941]
5. Jung SH, Jung TY, Joo SP, Kim HS. Rapid clinical course of cerebral metastatic angiosarcoma from the heart. J Korean Neurosurg Soc. 2012; 51:47–50. [PubMed: 22396844]

6. Meis-Kindblom JM, Kindblom LG. Angiosarcoma of soft tissue: a study of 80 cases. Am J Surg Pathol. 1998; 22:683–697. [PubMed: 9630175]

7. McIntosh BC, Narayan D. Head and neck angiosarcomas. J Craniofac Surg. 2005; 16:699–703. [PubMed: 16077321]

8. Yang WT, Hennessy BT, Dryden MJ, Valero V, Hunt KK, et al. Mammary angiosarcomas: imaging findings in 24 patients. Radiology. 2007; 242:725–734. [PubMed: 17325063]

9. Glazebrook KN, Maguit MJ, Reynolds CG. Angiosarcoma of the breast. AJR Am J Roentgenol. 2008; 190:533–538. [PubMed: 18212243]

10. West JG, Qureshi A, West JE, Chacon M, Sutherland ML, et al. Risk of angiosarcoma following breast conservation: a clinical alert. Breast J. 2005; 11:115–123. [PubMed: 15730457]

11. Fury MG, Antonescu CR, Van Zee KJ, Brennan MF, Maki RG. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J. 2005; 11:241–247. [PubMed: 16053668]

12. Budd GT. Management of angiosarcoma. Curr Oncol Rep. 2002; 4:515–519. [PubMed: 12354365]

13. Ray-Coquard I, Italiano A, Bonnios E, Le Cesne A, Robin YM, et al. Sorafenib for patients with advanced angiosarcoma: a phase II Trial from the French Sarcoma Group (Gsf/GETO). Oncologist. 2012; 17:260–266. [PubMed: 22285963]

14. Maki RG, D’Adamo DR, Keohan ML, Saulle M, Schuetze SM, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol. 2009; 27:3133–3140. [PubMed: 19451436]

15. Soini Y, Welsh JA, Ishak KG, Bennett WP. p53 mutations in primary hepatic angiosarcomas not associated with vinyl chloride exposure. Carcinogenesis. 1995; 16:2879–2881. [PubMed: 7586214]

16. Przygocki RM, Finkelstein SD, Keohavong P, Zhu D, Bakker A, et al. Sporadic and Thorotrast-induced angiosarcomas of the liver manifest frequent and multiple point mutations in K-ras-2. Lab Invest. 1997; 76:153–159. [PubMed: 9010458]

17. West JG, Weitzel JN, Tao ML, Carpenter M, West JE, et al. BRCA mutations and the risk of angiosarcoma after breast cancer treatment. Clin Breast Cancer. 2008; 8:533–537. [PubMed: 19073510]

18. Tate G, Suzuki T, Mitsuya T. Mutation of the PTEN gene in a human hepatic angiosarcoma. Cancer Genet Cytogenet. 2007; 178:160–162. [PubMed: 17954274]

19. Antonescu CR, Yoshida A, Guo T, Chang NE, Zhang L, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. Cancer Res. 2009; 69:7175–7179. [PubMed: 19723655]

20. Sarver AL, Phalak R, Thayaniy V, Subramanian S. S-MED: sarcoma microRNA expression database. Lab Invest. 2010; 90:753–761. [PubMed: 20212452]

21. Hadj-Hamou NS, Ugolin N, Ory C, Britzen-Laurent N, Sastre-Garau X, et al. A transcriptome signature distinguished sporadic from postradiation-induced sarcomas. Carcinogenesis. 2011; 32:929–934. [PubMed: 21470956]

22. Tokuyama W, Mikami T, Masuzawa M, Okayasu I. Autocrine and paracrine roles of VEGF/VEGFR-2 and VEGF-C/VEGFR-3 signaling in angiosarcomas of the scalp and face. Hum Pathol. 2010; 41:407–414. [PubMed: 19913279]

23. Brar R, West R, Witten D, Raman B, Jacobs C, et al. Breast Angiosarcoma: Case Series and Expression of Vascular Endothelial Growth Factor. Case Rep Oncol. 2009; 2:242–250. [PubMed: 20737044]

24. Stacher E, Gruber-Mösenbacher U, Halbwedl I, Del Tos AP, Cavazza A, et al. The VEGF-system in primary pulmonary angiosarcomas and haemangioendotheliomas: new potential therapeutic targets? Lung Cancer. 2009; 65:49–55. [PubMed: 19100646]

25. Al-Salam S, Balalaa N, Faour I, Akhter S, Alashari M. HIF-1α, VEGF and WT-1 are protagonists in bilateral primary angiosarcoma of breast: a case report and review of literature. Int J Clin Exp Pathol. 2012; 5:247–253. [PubMed: 22558480]
26. Itakura E, Yamamoto H, Oda Y, Tsuneyoshi M. Detection and characterization of vascular endothelial growth factors and their receptors in a series of angiosarcomas. J Surg Oncol. 2008; 97:74–81. [PubMed: 18041747]

27. Yonemori K, Tsuta K, Ando M, Hirakawa A, Hatanaka Y, et al. Contrasting prognostic implications of platelet-derived growth factor receptor-beta and vascular endothelial growth factor receptor-2 in patients with angiosarcoma. Ann Surg Oncol. 2011; 18:2841–2850. [PubMed: 21409488]

28. Yonemaru K, Sakai H, Murakami M, Yanai T, Masegi T. Expression of vascular endothelial growth factor, basic fibroblast growth factor, and their receptors (flt-1, flk-1, and flg-1) in canine vascular tumors. Vet Pathol. 2006; 43:971–980. [PubMed: 17099154]

29. Sabattini S, Bettini G. An immunohistochemical analysis of canine haemangioma and haemangiosarcoma. J Comp Pathol. 2009; 140:158–168. [PubMed: 19091326]

30. Guo T, Zhang L, Chang NE, Singer S, Maki RG, et al. Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. Genes Chromosomes Cancer. 2011; 50:25–33. [PubMed: 20949568]

31. Kosaka Y, Mimori K, Fukagawa T, Ishikawa K, Etoh T, et al. Identification of the high-risk group for metastasis of gastric cancer cases by vascular endothelial growth factor receptor-1 overexpression in peripheral blood. Br J Cancer. 2007; 96:1723–1728. [PubMed: 17486129]

32. Bianco R, Rosa R, Damiano V, Daniele G, Gelardi T, et al. Vascular endothelial growth factor receptor-1 contributes to resistance to anti-epidermal growth factor receptor drugs in human cancer cells. Clin Cancer Res. 2008; 14:5069–5080. [PubMed: 18694994]

33. Linardou H, Kalogeras KT, Kronenwett R, Kouvatseas G, Wirtz RM, et al. The prognostic and predictive value of mRNA expression of vascular endothelial growth factor family members in breast cancer: a study in primary tumors of high-risk early breast cancer patients participating in a randomized Hellenic Cooperative Oncology Group trial. Breast Cancer Res. 2012; 14:R145. [PubMed: 23146280]

34. Panteroudakis G, Nicolaou I, Kotoula V, Fountzilas E, Markou K, et al. Prognostic utility of angiogenesis and hypoxia effectors in patients with operable squamous cell cancer of the larynx. Oral Oncol. 2012; 48:709–716. [PubMed: 22366437]

35. Dobrzycka B, Terlikowski SJ, Kwiatkowski M, Garbowicz M, Kinals M, et al. Prognostic significance of VEGF and its receptors in endometrioid endometrial cancer. Ginekol Pol. 2010; 81:422–425. [PubMed: 20695190]

36. Nagaoka S, Yoshida T, Akiyoshi J, Akiba J, Hisamoto T, et al. The ratio of serum placenta growth factor to soluble vascular endothelial growth factor receptor-1 predicts the prognosis of hepatocellular carcinoma. Oncol Rep. 2010; 23:1647–1654. [PubMed: 20428821]

37. Chang YT, Chang MC, Wei SC, Tien YW, Hsu C, et al. Serum vascular endothelial growth factor/soluble vascular endothelial growth factor receptor-1 is a new independent prognostic marker in pancreatic cancer. Pancreas. 2008; 37:145–150. [PubMed: 18665074]

38. Ghanem MA, van Steenbrugge GJ, Sudaryo MK, Mathoera RB, Nijman JM, et al. Expression and prognostic relevance of vascular endothelial growth factor (VEGF) and its receptor (FLT-1) in nephroblastoma. J Clin Pathol. 2003; 56:107–113. [PubMed: 12560388]

39. Tamburini BA, Trapp S, Phang TL, Schappa JT, Hunter LE, et al. Gene expression profiles of sporadic canine hemangiosarcoma are uniquely associated with breed. PLoS One. 2009; 4:e5549. [PubMed: 19461996]

40. Zhang Z, Neiva KG, Lingen MW, Ellis LM, Nör JE. VEGF-dependent tumor angiogenesis requires inverse and reciprocal regulation of VEGFR1 and VEGFR2. Cell Death Differ. 2010; 17:499–512. [PubMed: 19834490]

41. Mezquita B, Mezquita J, Pau M, Mezquita C. A novel intracellular isoform of VEGFR1 activates Src and promotes cell invasion in MDA-MB-231 breast cancer cells. J Cell Biochem. 2010; 110:732–742. [PubMed: 20512933]

42. Brown LF, Dezube BJ, Tognazzi K, Dvorak HF, Yancopoulos GD. Expression of Tie1, Tie2, and angiopoietins 1, 2, and 4 in Kaposis’ sarcoma and cutaneous angiosarcoma. Am J Pathol. 2000; 156:2179–2183. [PubMed: 10854238]
43. Hasenstein JR, Kasmerchak K, Buehler D, Hafez GR, Cleary K, et al. Efficacy of Tie2 receptor antagonism in angiosarcoma. Neoplasia. 2012; 14:131–140. [PubMed: 22431921]

44. Zhou L, Picard D, Ra YS, Li M, Northcott PA, et al. Silencing of thrombospondin-1 is critical for myc-induced metastatic phenotypes in medulloblastoma. Cancer Res. 2010; 70:8199–8210. [PubMed: 20876797]

45. Salnikow K, Cosentino S, Klein C, Costa M. Loss of thrombospondin transcriptional activity in nickel-transformed cells. Mol Cell Biol. 1994; 14:851–858. [PubMed: 8264652]

46. Dameron KM, Volpert OV, Tainsky MA, Bouck N. Control of angiogenesis in fibroblasts by p53 regulation of thrombospondin-1. Science. 1994; 265:1582–1584. [PubMed: 7521539]

47. Fussenig NE, Boukamp P. Multiple stages and genetic alterations in immortalization, malignant transformation, and tumor progression of human skin keratinocytes. Mol Carcinog. 1998; 23:144–158. [PubMed: 9833775]

48. Lawler J, Miao WM, Duquette M, Bouck N, Bronson RT, et al. Thrombospondin-1 gene expression affects survival and tumor spectrum of p53-deficient mice. Am J Pathol. 2001; 159:1949–1956. [PubMed: 11696456]

49. Armstrong LC, Bornstein P. Thrombospondins 1 and 2 function as inhibitors of angiogenesis. Matrix Biol. 2003; 22:63–71. [PubMed: 12714043]

50. Volpert OV. Modulation of endothelial cell survival by an inhibitor of angiogenesis thrombospondin-1: a dynamic balance. Cancer Metastasis Rev. 2000; 19:87–92. [PubMed: 11191069]

51. Abedalthagafi M, Rushing EJ, Auerbach A, Desouki MM, Marwaha J, et al. Sporadic cutaneous angiosarcomas generally lack hypoxia-inducible factor 1alpha: a histologic and immunohistochemical study of 45 cases. Ann Diagn Pathol. 2010; 14:15–22. [PubMed: 20123452]

52. Rathmell WK, Acs G, Simon MC, Vaughn DJ. HIF transcription factor expression and induction of hypoxic response genes in a retroperitoneal angiosarcoma. Anticancer Res. 2004; 24:167–169. [PubMed: 15015593]

53. Laienfeld D, Gilchrist A, Drubin D, Jorge M, Eddy SF, et al. The role of hypoxia in 2-butoxyethanol-induced hemangiosarcoma. Toxicol Sci. 2010; 113:254–266. [PubMed: 19812364]

54. Corthals SM, Kamendulis LM, Klaunig JE. Mechanisms of 2-butoxyethanol-induced hemangiosarcomas. Toxicol Sci. 2006; 92:378–386. [PubMed: 16675516]

55. Klaunig JE, Kamendulis LM. Mode of action of butoxyethanol-induced mouse liver hemangiosarcomas and hepatocellular carcinomas. Toxicol Lett. 2005; 156:107–115. [PubMed: 15705491]

56. de Bree E, van Coevorden F, Peterse JL, Russell NS, Rutgers EJ. Bilateral angiosarcoma of the breast after conservative treatment of bilateral invasive carcinoma: genetic predisposition? Eur J Surg Oncol. 2002; 28:392–395. [PubMed: 12099648]

57. Manner J, Radlwimmer B, Hohenberger P, Mössinger K, Küffer S, et al. MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. Am J Pathol. 2010; 176:34–39. [PubMed: 20008140]

58. Baumhoer D, Gunawan B, Becker H, Füzesi L. Comparative genomic hybridization in four angiosarcomas of the female breast. Gynecol Oncol. 2005; 97:348–352. [PubMed: 15863129]

59. Fernandez AP, Sun Y, Tubbs RR, Goldblum JR, Billings SD. FISH for MYC amplification and anti-MYC immunohistochemistry: useful diagnostic tools in the assessment of secondary angiosarcoma and atypical vascular proliferations. J Cutan Pathol. 2012; 39:234–242. [PubMed: 22121953]

60. Käcker C, Marx A, Mössinger K, Svehla F, Schneider U, et al. High frequency of MYC gene amplification is a common feature of radiation-induced sarcomas. Further results from EORTC STBSG TL 01/01. Genes Chromosomes Cancer. 2013; 52:93–98. [PubMed: 23012233]

61. Italiano A, Thomas R, Breen M, Zhang L, Crago AM, et al. The miR-17-92 cluster and its target THBS1 are differentially expressed in angiosarcomas dependent on MYC amplification. Genes Chromosomes Cancer. 2012; 51:569–578. [PubMed: 22383169]

62. Whitfield JR, Soucek L. Tumor microenvironment: becoming sick of Myc. Cell Mol Life Sci. 2012; 69:931–934. [PubMed: 22033838]
63. Gearhart J, Pashos EE, Prasad MK. Pluripotency redux--advances in stem-cell research. N Engl J Med. 2007; 357:1469–1472. [PubMed: 17928593]

64. Frank SR, Schroeder M, Fernandez P, Taubert S, Amati B. Binding of c-Myc to chromatin mediates mitogen-induced acetylation of histone H4 and gene activation. Genes Dev. 2001; 15:2069–2082. [PubMed: 11511539]

65. Misteli T. Higher-order genome organization in human disease. Cold Spring Harb Perspect Biol. 2010; 2:a000794. [PubMed: 20591991]

66. Nesbit CE, Tersak JM, Prochownik EV. MYC oncogenes and human neoplastic disease. Oncogene. 1999; 18:3004–3016. [PubMed: 10378696]

67. Lovén J, Orlando DA, Sigova AA, Lin CY, Rahl PB, et al. Revisiting global gene expression analysis. Cell. 2012; 151:476–482. [PubMed: 23101621]

68. Li Z, Rich JN. Hypoxia and hypoxia inducible factors in cancer stem cell maintenance. Curr Top Microbiol Immunol. 2010; 345:21–30. [PubMed: 20582533]

69. Felsher DW. MYC Inactivation Elicits Oncogene Addiction through Both Tumor Cell-Intrinsic and Host-Dependent Mechanisms. Genes Cancer. 2010; 1:597–604. [PubMed: 21037952]

70. Chang TC, Yu D, Lee YS, Wentzel EA, Arking DE, et al. Widespread microRNA repression by Myc contributes to tumorigenesis. Nat Genet. 2008; 40:43–50. [PubMed: 18066065]

71. Li Y, Tan W, Neo TW, Aung MO, Wasser S, et al. Role of the miR-106b-25 microRNA cluster in hepatocellular carcinoma. Cancer Sci. 2009; 100:1234–1242. [PubMed: 19486339]

72. O’Donnell KA, Wentzel EA, Zeller KI, Dang CV, Mendell JT. c-Myc-regulated microRNAs modulate E2F1 expression. Nature. 2005; 435:839–843. [PubMed: 15944709]

73. Olive V, Bennett MJ, Walker JC, Ma C, Jiang I, et al. miR-19 is a key oncogenic component of mir-17-92. Genes Dev. 2009; 23:2839–2849. [PubMed: 20008935]

74. Mu P, Han YC, Betel D, Yao E, Squatrito M, et al. Genetic dissection of the miR-17–92 cluster of microRNAs in Myc-induced B-cell lymphomas. Genes Dev. 2009; 23:2806–2811. [PubMed: 20008931]

75. Yan Z, Shah PK, Amin SB, Samur MK, Huang N, et al. Integrative analysis of gene and miRNA expression profiles with transcription factor-miRNA feed-forward loops identifies regulators in human cancers. Nucleic Acids Res. 2012; 40:e135. [PubMed: 22645320]

76. Kandalam MM, Beta M, Maheswari UK, Swaminathan S, Krishnakumar S. Oncogenic microRNA 17-92 cluster is regulated by epithelial cell adhesion molecule and could be a potential therapeutic target in retinoblastoma. Mol Vis. 2012; 18:2279–2287. [PubMed: 22969266]
Figure 1.
Histological comparison of cutaneous angiosarcoma to normal skin. Hematoxylin and eosin staining of neonatal foreskin and cutaneous angiosarcoma. Normal skin is characterized by highly consistent external epithelium (epidermis) and underlying connective tissue (dermis). Angiosarcomas are highly malignant tumors composed of rapidly overproliferating and aggressively infiltrating aberrant vascular cells.
Figure 2.
An aberrant angiogenic signature as a hallmark of angiosarcomas. Angiosarcomas are characterized by major alterations in several key angiogenic processes including disrupted expression of VEGF ligands and their cognate receptors, disrupted expression of angiopoietin ligands and their cognate Tie receptors, reduced expression of thrombospondin 1 (THBS1), and alterations in global transcriptome patterns. Moreover, secondary angiosarcomas are characterized by an enhanced oxidative stress response.
MYC amplification as a hallmark of angiosarcomas. MYC amplifications are particularly frequent and at high levels in angiosarcomas, while other sarcomas display relatively lower levels of MYC amplifications. Increased MYC activity promotes cell survival, proliferation, and plasticity via its activity as a transcription factor and through modulation of chromatin remodeling.