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## Angiogenesis in cutaneous disease: Part II

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This review will discuss the role of angiogenesis in specific cutaneous diseases. Scientific evidence now points to the role of angiogenesis in tumor development and many other cutaneous disorders. Angiogenesis is a complex process that involves angiogenic growth factors and inhibitors, many of which could be a potential target for pharmacologic intervention. Antiangiogenic agents have recently been applied to dermatologic diseases with promising efficacy. (J Am Acad Dermatol 2009;61:945-58.)

**Learning objectives:** After completing this learning activity, participants should be able to recognize cutaneous diseases where angiogenesis is likely to be an important factor, recognize scenarios where angiogenic therapy may be useful in conjunction with traditional therapies, and be able to use angiogenic-mediating agents in the treatment of dermatologic disease.

**Key words:** angiogenesis; antiangiogenic agents; dermatology.

Angiogenesis is the growth of new blood vessels from preexisting ones. It is a normal process in growth, development, the female reproductive cycle, and wound healing. However, it is also a key element in disease pathogenesis.<sup>1</sup> In part I of this review, we described the process of angiogenesis and angiogenesis regulation. We also discussed therapeutic agents developed to inhibit or promote angiogenesis. In part II, we will review the role of angiogenesis as it relates to cutaneous diseases, including squamous cell carcinoma (SCC), fibrohistiocytic tumors, malignant melanoma, cutaneous lymphoma, Kaposi sarcoma (KS), angiosarcoma, hemangiomas, hemangioendotheliomas, vascular malformations, pyogenic granulomas, angiofibromas, psoriasis, rosacea, atopic dermatitis (AD), keloids, and diabetic ulcers. It is our intent that review and discussion of angiogenesis in cutaneous disease will foster further innovative research on this important topic, resulting in better understanding of

disease pathogenesis and novel and effective dermatologic therapeutics.

### ANGIOGENESIS IN CUTANEOUS DISEASE

#### Squamous cell carcinoma

##### Key points

- **SCC has been associated with altered levels of angiogenic factors**
- **Most SCCs are best treated with traditional surgical methods, but there are a small number of cases with aggressive recurrent or metastatic disease for which additional treatment could be considered**
- **Case reports and an ongoing clinical trial are evaluating the use of antiangiogenic therapy for aggressive SCC**

The epithelial cancer SCC has been noted to contain increased angiogenic growth factors, and there are some reports of treatment using antiangiogenic agents. Larcher et al<sup>2</sup> used a mouse SCC model in which keratinocytes were transduced with a retrovirus carrying v-H-ras and their results showed highly increased vascular endothelial growth factor (VEGF) mRNA levels. Inhibiting this oncogene signal transduction pathway reduced VEGF production and resulted in smaller tumors in these mice.<sup>3</sup> Thrombospondin-1 (TSP-1) has been reported to be down-regulated in cutaneous SCC, and the overexpression of TSP-1 in two stable transfected SCC cell lines inhibited tumor growth in vivo.<sup>4</sup> These results conflict with those of Castle et al,<sup>5</sup> who found that subcutaneous inoculation of athymic mice with human SCC cell lines

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transfected with TSP cDNA antisense expression vector reduced TSP production and inhibited tumor growth.

Although most primary cutaneous SCCs have a high clinical cure rate, the small subset of cancers that recur or metastasize has a poor prognosis. Epidermal growth factor receptor (EGFR) has been shown to be overexpressed in metastatic cutaneous SCC, and cetuximab has been used for the treatment of aggressive or metastatic disease.<sup>6,7</sup> At this time, there are only case reports in the literature, but a phase II trial is underway. A single case report noted repeated responses to cetuximab in a patient with an inoperable, rapidly growing cutaneous SCC with strong human EGFR expression.<sup>8</sup> Cetuximab was administered intravenously (IV) at a loading dose of 400 mg/m<sup>2</sup>, followed by weekly infusions of 250 mg/m<sup>2</sup>. After the seventh weekly dose, a complete clinical response was achieved. Discontinuation of infusions resulted in recurrence. Additional infusions achieved tumor response, but the patient became refractory to treatment and died. Bauman et al<sup>9</sup> reported excellent responses in two cases of elderly patients with extensive cutaneous SCC recurrence treated with palliative cetuximab (150 or 250 mg/m<sup>2</sup>). Complete clinical clearance was achieved and responses were maintained at last reported follow-up, 5 months after the initiation of treatment. A patient with oropharyngeal carcinoma that had a cutaneous SCC metastasis with overexpression of EGFR still had a fatal outcome 3 months after the initial diagnosis of cancer, in spite of chemotherapy and treatment with cetuximab.<sup>10</sup>

Ramadan et al<sup>11</sup> reported the complete clinical clearance of cutaneous SCC in a patient with multiple myeloma. The patient developed a moderately differentiated SCC on the left temple. He was started on bortezomib (1.3 mg/m<sup>2</sup> IV on days 1, 4, 8, and 11) to improve his hematologic status before proceeding to SCC surgery. Bortezomib not only stabilized the myeloma but, unexpectedly, the SCC regressed and eventually disappeared, with complete healing of the skin occurring several months after the discontinuation of bortezomib. There was no evidence of

recurrence of his SCC, even after he succumbed to multiple myeloma 1 year later.

### Fibrohistiocytic tumors

#### Key point

- **Malignant fibrohistiocytomas have increased expression of angiogenic factors as compared to dermatofibroma and dermatofibrosarcoma protuberans**

Koga et al<sup>12</sup> used immunohistochemistry to look at levels of hypoxia-inducible factor (HIF)-1 $\alpha$  expression in various fibrohistiocytic tumors. They found significantly higher levels in malignant fibrous histiocytoma compared to dermatofibroma and dermatofibrosarcoma protuberans. Furthermore, cases of malignant fibrohistiocytomas expressing high levels of HIF-1 $\alpha$  showed greater angiogenesis (as measured by microvessel density) than those with low levels of HIF-1 $\alpha$ . Increased HIF-1 $\alpha$  expression and angiogenesis may be

associated with the malignant potential of fibrohistiocytic tumors.

### Malignant melanoma

#### Key points

- **Malignant melanoma (MM) has been associated with increased levels of many angiogenic factors**
- **Antiangiogenic agents have shown potential efficacy for the treatment of MM**
- **Antiangiogenic agents appear to be most effective for MM when used in combination with chemotherapy**

MM is a cancer of melanocytes, and dermatologists are familiar with the deadly potential of this disease. Angiogenic growth factors are up-regulated in melanoma cells and there are studies of successful treatment of melanoma using antiangiogenic therapies, especially when used in combination with cytotoxic therapies.

Angiogenesis mediators are increased in human melanoma cell lines. Several studies have demonstrated an increase in VEGF, basic fibroblast growth factor (bFGF), platelet-derived growth factor

### CAPSULE SUMMARY

- Squamous cell carcinoma, fibrohistiocytic tumors, malignant melanoma, cutaneous lymphoma, Kaposi sarcoma, angiosarcoma, hemangiomas, hemangioendotheliomas, vascular malformations, pyogenic granulomas, angiofibromas, psoriasis, rosacea, atopic dermatitis, keloids, and diabetic ulcers are some of the angiogenesis-dependent diseases seen by dermatologists.
- Antiangiogenic therapies may be a treatment option for a wide range of cutaneous diseases.
- Antiangiogenic therapies can be used as single therapy or in combination with conventional therapies.

(PDGF)-AB, interleukin (IL)-8, and transforming growth factor-beta (TGF $\beta$ ).<sup>13-15</sup> The transfection of nonmetastatic and IL-8-negative melanoma cells with the IL-8 gene produced highly malignant and invasive tumors in mice.<sup>16</sup> Overproduction of VEGF and its receptors VEGFR1 and VEGFR2 was shown in melanoma xenografts, and treatment with phosphatidylinositol 3-kinase (PI3 K)-specific inhibitors reduced the survival of these tumor cells.<sup>17,18</sup> Akt was shown to be overexpressed in mice models during the transformation of melanoma cells from the radial to vertical growth phases.<sup>19</sup> Activated Akt expression was shown to be increased in Spitz nevi and melanomas as compared with benign intradermal nevi.<sup>20</sup> Akt production may protect melanoma cells from apoptosis and make them less responsive to chemotherapy and radiation. Using a microarray analysis, one study showed that patients with strong phosphorylated Akt expression in their melanoma tissue, along with weak expression of p53 up-regulated modulator of apoptosis, had a lower 5-year survival rate.<sup>21</sup> Using Akt/protein kinase B signaling inhibitor-2, a small-molecule Akt inhibitor, reduced melanoma cell survival in a dose- and time-dependent manner.<sup>21</sup> Mammalian target of rapamycin (mTOR) activation is also strongly associated with MM compared to benign melanocytic lesions.<sup>22</sup>

Endostatin levels were elevated in stage III and stage IV melanoma patients compared to healthy control individuals, and endostatin levels might have a utility for disease monitoring.<sup>23</sup> Animal studies revealed the efficacy of recombinant endostatin to suppress melanoma tumor growth and melanoma metastasis formation.<sup>24-28</sup> The clinical usefulness of endostatin remains uncertain, because a phase II clinical trial evaluating endostatin alone and in combination with interferon- $\alpha$ 2b (IFN $\alpha$ 2b) showed no antitumor response.<sup>29</sup>

Recent studies have shown some efficacy using antiangiogenic agents for metastatic melanoma, especially when used in combination with chemotherapy. Bevacizumab has been used in several trials. Twelve patients were administered paclitaxel 70 mg/m<sup>2</sup> weekly and bevacizumab 10 mg/kg IV biweekly for five consecutive weeks every 6 weeks.<sup>30</sup> Cycles were repeated until disease progression or treatment intolerance. Two patients achieved a partial response for 5.6 and 3.9 months, respectively. Eight patients, whose tumors were growing at the time of treatment, experienced disease stabilization for a median of 4 months (range, 2.8-8.8 months), and two patients had progressive disease despite treatment. In a randomized phase II trial, bevacizumab (15 mg/kg IV every 2 weeks) was administered with and without daily low-dose IFN $\alpha$ 2b (1 MU/m<sup>2</sup>

subcutaneously daily), an inhibitor of bFGF.<sup>31</sup> Bevacizumab prolonged disease stabilization in about 25% of the patients (8/36); however low-dose IFN $\alpha$ 2b did not augment the activity of bevacizumab. Bevacizumab (5 mg/kg) in combination with chemotherapeutic agents cisplatin/carboplatin or fotemustine achieved disease regression in two out of three patients after three courses of therapy.<sup>32</sup> Longer follow-up was not provided.

Sorafenib has shown some effect for advanced melanoma. In a phase II clinical trial in advanced melanoma patients, sorafenib was well tolerated but had little or no antitumor activity when used as a single agent.<sup>33</sup> Combination therapy has been more promising. A phase I trial combined sorafenib with carboplatin and paclitaxel in advanced melanoma patients and was able to induce one complete response and nine partial responses.<sup>34</sup> In a phase II trial, oral sorafenib (400 mg twice a day) and IV dacarbazine (1000 mg/m<sup>2</sup> on day 1 of a 21-day cycle) showed a 50% improvement in progression-free survival as compared to placebo plus dacarbazine.<sup>35</sup> However, overall survival was not improved. Additional investigations are ongoing.

mTOR inhibitors have shown promise for melanoma treatment. Bevacizumab in combination with sirolimus caused the loss of half of the VEGFR2-positive melanoma cells in a culture study.<sup>36</sup> Sirolimus was shown to inhibit the proliferation of MM cell lines, especially when combined with celecoxib, a cyclooxygenase 2 inhibitor.<sup>37</sup> Combined treatment of six melanoma cell lines with sorafenib and sirolimus led to an approximately twofold increase of cell death compared with sorafenib alone.<sup>38</sup> A study using human melanoma xenotransplants in mice did not show a significant antitumor effect from temsirolimus alone; however, temsirolimus in combination with dacarbazine reduced tumor weight compared to dacarbazine monotherapy.<sup>39</sup> Another combination regimen using temsirolimus and cisplatin showed superior melanoma growth inhibition compared to monotherapies.<sup>39</sup>

Other newer antiangiogenic therapies, including batimastat, marimastat, bortezomib, and ABT-510, have also been evaluated for use in melanoma. Batimastat was shown to inhibit metastatic spread and to delay tumor growth in murine melanomas.<sup>40</sup> A phase II study of marimastat in MM showed a partial response in two of 28 patients, stable disease in five patients, and disease progression in 21 patients.<sup>41</sup> Preclinical studies revealed bortezomib to be effective at inhibiting the *in vitro* growth of several human melanoma cell lines.<sup>42</sup> A phase II study of bortezomib alone in the treatment of metastatic melanoma proved to be ineffective.<sup>43</sup>

Bortezomib may achieve better results if used in combination with chemotherapeutic drugs. A phase II trial evaluating the clinical efficacy of ABT-510 in metastatic melanoma was terminated early because it did not demonstrate definite clinical efficacy.<sup>44</sup> Again, combination therapy may be more effective.

### Cutaneous lymphoma

#### Key points

- **The mTOR pathway may play a major role in the pathogenesis of cutaneous lymphoma**
- **Sirolimus inhibited anaplastic large cell lymphoma growth in a cell culture study**
- **Bortezomib is being studied for the treatment of cutaneous lymphoma**

Phosphorylated mTOR has been found in the nucleus of cutaneous anaplastic large cell lymphoma (ALCL) tumor cells, especially in cells undergoing mitosis. The expression of mTOR pathway proteins, including phosphorylated ribosomal protein S6 kinase, was detected in the cytoplasm of these cells.<sup>45</sup> The mTOR pathway may influence cutaneous ALCL and sirolimus and other mTOR inhibitors may be useful therapeutic options. In an *in vitro* study of cell cultures, only sirolimus inhibited growth of cutaneous ALCL, as compared to cyclosporine A, FK-506 (tacrolimus), and prednisone.<sup>46</sup> In a case study, primary ALCL refractory to 15 years of treatment with radiation and multiple chemotherapy regimens was successfully treated with oral sirolimus 2 mg/day in combination with radiation.<sup>45</sup>

Bortezomib has been studied in a phase II trial for treatment of cutaneous T-cell lymphoma and peripheral T-cell lymphoma with isolated skin involvement. In a study of 12 patients, two achieved complete remission and six achieved partial remission with results lasting 7 to 14 months or more.<sup>47</sup>

### Kaposi sarcoma

#### Key points

- **The KS herpesvirus is believed to induce angiogenesis via the PI3K/Akt pathway**
- **Sirolimus, imiquimod, and thalidomide are being evaluated as therapies for KS**

KS is an angiogenic tumor thought to be caused by infection or reactivation of human herpes virus 8, also known as KS herpesvirus (KSHV). KSHV infection activates many endothelial cell signaling pathways, including PI3K/Akt. Montaner et al<sup>48</sup> used primary human umbilical vein endothelial cells and showed that KSHV G protein-coupled receptor expression potently induces the kinase activity of Akt. GPCR was found to increase VEGF secretion by stimulating HIF-1 $\alpha$  to activate p38 and mitogen-activated protein

kinase (MAPK).<sup>49</sup> KSHV-GPCR also prevented the apoptosis of human umbilical vein endothelial cells that normally occurs with serum deprivation. This protection from apoptosis was not seen with use of wortmannin (an inhibitor of Akt) or in Akt-deficient mutants.<sup>48</sup> In an animal model, transduction of the vGPCR gene played a critical role in inducing angioproliferative tumors very similar to human KS.<sup>50</sup>

Immunohistochemical staining did not find significant VEGF in KS lesions.<sup>51</sup> However, Cornali et al<sup>52</sup> found high amounts of VEGF mRNA and protein present in KS spindle cells. VEGF was also found when lesions were biopsied after photodynamic therapy (PDT).<sup>53</sup> Bevacizumab was shown to enhance the responsiveness of KS to PDT.<sup>53</sup>

Several studies have shown the efficacy of sirolimus for the treatment of iatrogenic KS in renal transplant patients. Importantly, this treatment did not sacrifice the immunosuppression necessary to prevent organ rejection.<sup>54-56</sup> In another case report involving KS in a patient on immunosuppressive therapy for pemphigus vulgaris, sirolimus (2 mg/day) eliminated KS lesions while still retaining adequate immunosuppression to control the pemphigus.<sup>57</sup> Sirolimus was used in one immunocompetent patient with classic Mediterranean KS and achieved complete clinical, histologic, and immunohistochemical regression of 16 of 17 of the patient's lesions.<sup>58</sup>

Imiquimod and thalidomide have also been used for treatment of KS.<sup>59,60</sup> In a prospective, open-label, phase II clinical trial using imiquimod 5% cream to treat KS, eight of 17 patients showed clinical improvement of the lesions.<sup>60</sup> Rubegni et al<sup>61</sup> reported the treatment of three non-AIDS related-KS patients with thalidomide 100 mg/day. All experienced partial remission at 4 months, and two patients achieved complete remission at 12 months.

### Angiosarcoma

#### Key points

- **The up-regulation of VEGF has been noted in angiosarcomas**
- **Long-term remission has been demonstrated in a case report in which angiosarcoma was treated with radiation and bevacizumab**

Angiosarcoma is a vascular tumor that has been shown to have up-regulation of VEGF. Bevacizumab, an antibody against VEGF, has been used for the treatment of angiosarcoma.<sup>62</sup> Two patients had angiosarcoma of the nose and were treated with combination bevacizumab and radiotherapy before surgical resection. One patient was treated with a bolus infusion of bevacizumab 5 mg/kg every 2 weeks for a total of four doses, whereas the second



patient was treated with a bolus infusion of bevacizumab 10 mg/kg every 2 weeks for a total of three doses. Pathologic evaluation showed no residual angiosarcoma, and both patients remained recurrence free at the time of final reported evaluation (8.5 months for one, 26 months for the other).

## Hemangiomas

### Key points

- **Angiogenic factor expression changes as hemangiomas progress from proliferative to involuting phases**
- **Topical imiquimod has been used to treat infantile hemangiomas, but results are variable with a recent study indicating limited efficacy**

Hemangiomas are the most common benign tumor of newborns, affecting approximately 10% of all infants.<sup>63</sup> Infantile hemangiomas are characterized by early proliferation of endothelial cells in the first year of life, followed by spontaneous involution. Angiogenic markers have different expression patterns during the various infantile hemangioma stages. In the proliferative phase, high expression of proliferating cell nuclear antigen, type IV collagenase, and VEGF were noted by Takahashi et al.<sup>64</sup> In the involuting phase, they noted elevated expression of tissue inhibitors of metalloproteinases (TIMP). Expression of bFGF, urokinase, CD31, von Willebrand factor, and SMC-actin were present in both proliferating and involuting phases.<sup>64</sup> Interestingly, many endogenous angiogenesis suppressors, including TIMP-1 and IFN $\beta$ , were unregulated in the involuting and involuted phases as compared to the proliferative phase.<sup>64,65</sup> Yu et al<sup>66</sup> studied hemangioma-derived endothelial cell cultures and found an increase in mRNA expression of angiopoietin-1 (Ang1) and Tie2 and a down-regulation of Ang2. Giatromanolaki et al<sup>67</sup> used immunohistochemistry in 25 cutaneous capillary hemangiomas (phase not specified) and noted increased expression of VEGF and HIF-2 $\alpha$ , but not HIF-1 $\alpha$ . Ritter et al<sup>68</sup> showed increased insulin-like growth factor (IGF)-2 and integrins in hemangiomas using microarray analysis.

Both endogenous and exogenous angiogenesis inhibitors have been used successfully to reduce experimentally induced hemangioma tumor growth. Daily injections of batimastat into murine hemangiomas resulted in delayed tumor growth but not tumor eradication.<sup>69</sup> Other inhibitors including TIMP-2, VEGF toxin conjugate, and synthetic compound TNP-470 (fumagilin derivative) have also reduced tumor growth in early experimental hemangioma models.<sup>70-72</sup>

There are multiple reports of treatment of infantile hemangiomas with a short course of topical imiquimod 5% cream. Martinez et al<sup>73</sup> reported the successful use of topical imiquimod applied three times a week to treat two patients with infantile hemangiomas. Welsh et al<sup>74</sup> applied topical imiquimod 5% cream five times a week to infantile hemangiomas and achieved complete resolution or excellent improvement in seven out of 10 patients. Hazen et al<sup>75</sup> reported a case report of a chest wall hemangioma that resolved after 10 weeks of topical imiquimod therapy. One retrospective study showed complete regression and resolution in infantile hemangiomas after treatment with imiquimod 5% cream; superficial lesions (as compared to mixed or deep lesions) were the best responders.<sup>76</sup> The most common side effect was crusting and irritation, and no systemic toxicity was noted.<sup>76</sup> Despite these promising results, a recent study indicates that imiquimod therapy may not be as beneficial for the treatment of hemangiomas as previously thought. A phase II study in sixteen infants in which imiquimod was applied three to seven times a week for 16 weeks to hemangiomas showed improvement in only superficial coloration, while lesion size remained unaffected.<sup>77</sup>

Arbiser<sup>78</sup> recently reported use of eosin 2% solution applied three times a day unoccluded for hemangiomas with superficial ulcers and once a day under hydrocolloid wound dressing for hemangiomas with deep ulcers. Duration of application ranged from 3 to 14 weeks. Of the 21 ulcers, 16 healed completely without recurrence and 5 required additional types of therapy. Arbiser reports that eosin inhibits production of Ang2 in endothelial cells and ulceration in hemangiomas may be a result of imbalance between Ang2 and VEGF.<sup>78</sup>

Another recent study used propranolol for the treatment of aggressive hemangiomas of infancy.<sup>79</sup> Inhibition of endothelial cell VEGF production was proposed as a mechanism, but further evaluation will be required.

## Hemangioendotheliomas

### Key point

- **Antiangiogenic treatment has been experimentally used for treatment of hemangioendotheliomas**

Hemangioendotheliomas are rare vascular tumors characterized by an epithelioid endothelial cell proliferation. They were named because their aggressiveness falls between benign hemangiomas and aggressive angiosarcomas.<sup>80</sup> Antiangiogenic agents have been investigated for therapy. Angiostatin and recombinant endostatin were shown to inhibit

murine hemangioendotheliomas.<sup>26,81</sup> In experimentally induced hemangioendotheliomas, the application of imiquimod 5% cream significantly decreased tumor growth.<sup>82</sup> These tumor cells showed decreased proliferation, increased tumor apoptosis, increased expression of TIMP-1, and decreased activity of matrix metalloproteinase (MMP)-9.

Although antiangiogenic therapy for hemangioendotheliomas is not currently considered the standard of care, there are a number of case reports that show promising results. Belmont et al<sup>83</sup> reported a nonresponsive pulmonary epithelioid hemangioendothelioma that was treated with a combination of carboplatin–paclitaxel and bevacizumab (15 mg/kg and 450 mg, respectively) for five cycles followed by bevacizumab alone for a total of 13 cycles. The patient showed stabilization and significant clinical improvement was maintained at 13 months after initiation of treatment. Another patient with a non-resectable hepatic epithelioid hemangioendothelioma with extensive pulmonary metastases was successfully treated with thalidomide 200 mg/day.<sup>84</sup> Serial computed tomography scans showed no disease progression over a 3-year period; after 3 years, the patient was switched to thalidomide 100 mg/day and remained asymptomatic.

## Vascular malformations

### Key points

- **Multiple angiogenic factors that are overexpressed in vascular tumors are not present in vascular malformations**
- **Antiangiogenic agents may have a role in treatment of these lesions when combined with other treatment modalities, such as laser therapy**

Vascular malformations are not proliferating tumors but, rather, result from inborn errors of vascular morphogenesis. Multiple cellular markers that are seen in vascular tumors such as VEGF, bFGF, type IV collagenase, and urokinase are not present in vascular malformations.<sup>64</sup> The overexpression of Akt1 in murine endothelial cells resulted in the development of vascular malformations characterized by dysfunctional endothelial cell remodeling.<sup>85</sup>

Marler et al<sup>86</sup> showed increased levels of urine MMPs in patients with both vascular tumors and vascular malformations compared to control subjects. An increased expression of urinary MMPs correlated with the extent and activity of the vascular anomalies and may offer a method for monitoring treatment efficacy in patients with vascular malformations. An imbalance of Tie2 signaling will lead to vascular dysmorphogenesis. A family with inherited

venous malformations was found to carry an activating Tie2 mutation.<sup>87</sup> Akt has also been linked to vascular malformations in specimens of mice endothelial cells and biopsies from patients with Sturge–Weber syndrome.<sup>88</sup>

Although vascular malformations are not proliferating, antiangiogenic therapy may still play a role in therapeutic management. Our group and others have looked at the use of combination selective photothermolysis and antiangiogenic therapy for the treatment of port wine stain (PWS), a capillary vascular malformation. Currently, the standard of treatment for PWS is the pulsed dye laser (PDL). Complete lesion blanching is disappointing, occurring in less than 20% of patients treated with PDL.<sup>89</sup> In a wound healing response, inflammatory cells migrate into the area secreting cytokines that are potent up-regulators of HIF- $\alpha$  and VEGF.<sup>90</sup> The PDL-induced wound healing response may lead to new vessel formation.<sup>89,91</sup> Phung et al<sup>89</sup> showed that normal skin treated with a combination of PDL and daily topical application of sirolimus for 14 days showed a decrease in reformation and reperfusion of vessels as compared to skin treated with PDL alone. Kelly et al<sup>92</sup> randomly assigned subjects with PWS to treatment protocols using either PDL plus imiquimod or PDL plus placebo. Treatment was well tolerated, and the average reduction in erythema measured by noninvasive reflectance measurements was greater in the PDL plus imiquimod group when compared to the PDL plus placebo group. These results indicated that application of an agent with antiangiogenic effects like imiquimod may improve the selective thermolysis–based treatment of cutaneous vascular lesions, including PWS. Chang et al<sup>93</sup> reported similar results.

## Pyogenic granulomas

### Key points

- **Pyogenic granulomas express many angiogenic factors**
- **Topical imiquimod has been reported as a successful treatment for pyogenic granulomas**

Pyogenic granulomas are common benign vascular lesions of the skin and mucosa. Some early studies in angiogenesis revealed that factors extracted from pyogenic granulomas could induce neovascular proliferation in the skin membrane of hamsters and could increase vascularity of normal skin samples grafted onto chick embryo chorioallantoic membranes.<sup>94,95</sup> More recent studies have identified these angiogenic factors, which are likely to play an important role in the pathogenesis of pyogenic granuloma. Immunohistochemistry studies revealed that VEGF,

bFGF, Tie2, Ang1, Ang2, ephrin-B2, and Eph-B4 are up-regulated in pyogenic granulomas on human gingiva as compared to healthy gingiva.<sup>96,97</sup> Moreover, the angiogenic inhibitor angiostatin was expressed significantly less in pyogenic granulomas.<sup>97</sup> TIMPs were found to be up-regulated in stromal cells and in cells surrounding proliferating vessels of pyogenic granulomas.<sup>98</sup> Shimizu et al<sup>99</sup> noted the increased expression of inducible NO synthase, mainly in the endothelial cells of pyogenic granulomas.

There are many treatment options for pyogenic granulomas, but several studies used the antiangiogenic effects of imiquimod.<sup>100-104</sup> Using imiquimod cream 5% daily, the resolution of facial pyogenic granulomas was seen in five of five children within 2 to 4 weeks.<sup>102</sup> Side effects were minimal and only small mildly erythematous or hypopigmented macules remained after treatment. Imiquimod was also successful in treating pyogenic granulomas that were recurrent and resistant to other therapies.<sup>101,103,104</sup>

### Angiofibromas

#### Key points

- **Tuberous sclerosis complex mutations cause dysfunction of the tuberin/hamartin proteins, blocking inhibition of the mTOR pathway and resulting in abnormal growths and blood vessel proliferations**
- **Sirolimus has shown promise for the treatment of tuberous sclerosis-related tumors**

Tuberous sclerosis is an autosomal dominant disorder that results from gene defects in the tuberous sclerosis complex (TSC) genes 1 and 2, on chromosomes 9 and 16, respectively. Normally, TSC1 and 2 produce hamartin and tuberin complex proteins that are known to inhibit the mTOR pathway.<sup>105-107</sup> TSC mutations cause dysfunction of the tuberin/hamartin proteins, blocking inhibition of the mTOR pathway and resulting in abnormal growths and blood vessel proliferations in several organs, including the skin. Characteristic cutaneous manifestations of tuberous sclerosis include facial angiofibromas.<sup>108</sup> Facial angiofibromas are seen in 70% to 80% of patients. They may be disfiguring, and do not resolve without treatment.

Angiofibromas are characterized by the proliferation of vascular and interstitial cells that express angiogenic factors, including VEGF.<sup>109,110</sup> Kenerson et al<sup>111</sup> found elevated levels of phosphorylated mTOR and its effectors in primary renal tumors of TSC and found sirolimus to be an effective treatment in Eker rats that carry a germ line mutation of the TSC2 gene. A study using 0.4% and 0.8% topical sirolimus showed improved survival and reduced

tumor growth in nude mice bearing subcutaneous TSC-related tumors.<sup>112</sup> One case study reported dramatic improvement of angiofibromas in a patient with TSC using sirolimus for immunosuppression after renal transplant.<sup>113</sup>

### Psoriasis

#### Key points

- **Angiogenesis is thought to play a role in the dilated vasculature of the papillary dermis in psoriasis**
- **Sirolimus in combination with cyclosporine has been used to treat psoriasis**
- **Other antiangiogenic agents are currently being studied as treatments for psoriasis**

Psoriasis, characterized by erythematous, well demarcated, scaly plaques, is a chronic inflammatory disease of the skin. The underlying pathogenesis of psoriasis is a complex interplay of abnormal epidermal differentiation and proliferation and activation of the immune system. Angiogenesis appears to play a role in psoriasis pathogenesis, as shown by dilated and tortuous vessels in the papillary dermis. VEGF is known to be elevated in psoriatic skin.<sup>114,115</sup> Transgenic delivery of VEGF to mouse skin resulted in a psoriasis-like inflammatory skin condition.<sup>116</sup> Man et al<sup>117</sup> found that calcium enhances VEGF and VEGFR expression in psoriatic epidermis. When VEGF expression was blocked by bevacizumab, calcium continued to enhance protein levels of VEGFRs independent of VEGF. In 2005, Krueger et al<sup>118</sup> hypothesized that the dysfunction of T<sub>H</sub>1-mediated cellular immunity leads to the excessive production of proinflammatory cytokines, including tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), IL-2, interferon gamma (IFN $\gamma$ ), and TGF $\beta$ . TGF $\beta$  then stimulates keratinocytes to produce VEGF. Nickoloff et al<sup>119</sup> showed that keratinocytes from psoriatic skin had a sevenfold reduction in TSP-1 production and addition of a highly purified TSP-1 suppressed the angiogenic activity in these keratinocytes.

Ang1, Ang2, and Tie2 have also been found to be up-regulated in psoriatic lesional skin.<sup>120</sup> Ang1 is highly expressed by stromal cells in the papillary dermis of psoriatic skin and is proposed to help maintain and stabilize newly formed vessels.<sup>120,121</sup> Ang2 is also expressed highly in the papillary dermis; however, its signal is limited to the endothelial cells.<sup>120</sup> In one study, five psoriatic patients treated with psoralen plus ultraviolet A light phototherapy and two patients treated with tazarotene for 8 weeks resulting in clinical improvement were shown to



have decreased Ang1, Ang2, and Tie2 mRNA levels in involved skin.<sup>120</sup>

Sirolimus has been used both systemically and topically to treat psoriasis. Although systemic sirolimus alone proved to be ineffective in treating severe psoriasis, it was used successfully in combination with subtherapeutic levels of cyclosporine in order to limit nephrotoxicity.<sup>122</sup> Topically applied sirolimus has also shown some effect on plaque psoriasis, but response to topical steroids was better.<sup>123</sup>

Neovastat has shown promising results in phase II studies for the treatment of psoriasis.<sup>124</sup> There has also been one case report of a patient whose chronic cutaneous psoriasis improved after systemic therapy with the VEGFR-TK inhibitor, SU-011248, during monotherapy for treatment of renal cell carcinoma.<sup>125</sup> In another case report, two weeks of daily topical application of dobesilate, a fibroblast growth factor inhibitor, significantly improved skin lesions in chronic plaque psoriasis.<sup>126</sup>

## Rosacea

### Key points

- **VEGF overexpression has been noted in rosacea**
- **Cathelicidins, antimicrobial peptides with known angiogenic and inflammatory properties, have been linked to rosacea**
- **Topical dobesilate has been reported to clinically improve rosacea**

Rosacea is a common skin disease that has varied clinical presentations, including erythema and telangiectasia, papulopustules, phymatous changes, and ocular symptoms. Rosina et al<sup>127</sup> performed videocapillaroscopy on erythematotelangiectatic rosacea lesions and showed increased neoangiogenesis and blood vessel enlargement. Immunohistochemistry revealed increased VEGF expression in lesional versus nonlesional skin of rosacea patients.<sup>128</sup> Smith et al<sup>129</sup> showed expression of both VEGFR1 and 2 in rosacea vascular endothelium and infiltrating mononuclear cells.

Recently, cathelicidins with known angiogenic and inflammatory properties have been implicated in the pathogenesis of rosacea.<sup>130</sup> Cathelicidins are antimicrobial peptides that are believed to directly kill microorganisms, participate in the innate immune system, and form a chemical shield of protection on the skin.<sup>130-132</sup> LL-37 is the C-terminal part of the only human cathelicidin identified to date, called human cationic antimicrobial protein.<sup>133,134</sup> LL-37 is expressed by polymorphonuclear leukocytes, lymphocytes, macrophages, and epithelial cells. LL-37 interacts with endothelial cells and stimulates

angiogenesis both in vitro and in vivo.<sup>135</sup> LL-37 modulates the expression of VEGF via HIF-1 $\alpha$  in human keratinocytes. When compared to healthy skin, rosacea was found to have increased levels of LL-37 and other cathelicidin peptides that were posttranslationally modified to have increased protease activity.<sup>136</sup>

Cuevas et al<sup>137</sup> used topical dobesilate, an inhibitor of FGF, for the treatment of erythematotelangiectatic rosacea and reported improvement of erythema and telangiectasia after 2 weeks.

## Atopic dermatitis

### Key point

- **Pathophysiology theories for AD include immune and barrier dysfunction, but angiogenesis may also play an important role**

AD is a common, chronic inflammatory skin disease characterized by pruritus, eczematous lesions and lichenification. Pathophysiology theories for AD have focused on immune dysfunction or defective barrier function, but angiogenesis may also play an important role. An epidermal IL-4–transgenic mouse model was developed that closely resembles human AD clinically, histopathologically, serologically, bacteriologically, and immunologically.<sup>138-141</sup> The dermal blood vessels in this mouse model show changes consistent with angiogenesis, including elongation, sprouting, and intussusception.<sup>142</sup> Chen et al<sup>143</sup> recently noted a progressive increase in blood vessel number, diameter, and percent dermal area occupied by CD31<sup>+</sup> and VEGFR2 vessels as the disease evolves from start to a chronic state. They also reported an increase of transcripts of VEGF-A, Ang1, Ang2, guanylate-binding protein-1, and the endothelial cell adhesion molecule, vascular/endothelial-cadherin. IL-6 and IFN $\gamma$  were thought to stimulate the VEGF-A mRNA production in the skin.<sup>143</sup>

In human AD lesions, VEGF121, an isoform of VEGF-A that mainly regulates vascular permeability, was noted to be overexpressed in the stratum corneum.<sup>144</sup> Groneberg et al<sup>145</sup> hypothesized that participation of mast cells could underlie the neovascular processes in AD. They showed that there was migration of mast cells from the papillary dermis to the basal lamina in the epidermis, and these mast cells were localized close to endothelial cells. Mast cell density within skin tissues has been demonstrated to correlate with blood vessel density, and mast cells are thought to lead to the expression of proangiogenic factors.<sup>146</sup> Endothelial cells were positive for CD105, a marker of vascular proliferation, and gene expression

profiling for angiogenic factors was positive for TNF- $\alpha$ , VEGF-B, IL-8, Ang1, Ang2, and some MMPs.<sup>144</sup>

## Keloids

### Key points

- **Increased expression of angiogenic factors has been noted in keloids**
- **Sirolimus has been evaluated in a cell culture study as a possible therapeutic option for keloids**

Wu et al<sup>147</sup> showed elevated expression of HIF-1 $\alpha$  and VEGF in keloid tissue compared to normal skin. Ong et al<sup>148</sup> also found elevated expression of VEGF in keloid scars and higher levels of mTOR. They cocultured keratinocytes and fibroblasts extracted from keloid scars and exposed the cell cultures to sirolimus (2 and 0.01  $\mu$ g/mL). VEGF expression, cell cycle proteins, and extracellular matrix proteins were observed to be down-regulated in a dose-dependent manner.

## Diabetic ulcers

### Key points

- **Proangiogenic factors may be deficient in chronic diabetic ulcers**
- **Topical PDGF has been shown to improve healing of diabetic wounds**

A recent study showed an increase in Akt phosphorylation in wound margin keratinocytes in normal skin repair, with near absence of Akt phosphorylation and VEGF in chronic wounds of diabetic mice.<sup>149</sup> Insulin is thought to contribute to VEGF release in wound healing through the Akt-mediated pathway.

Another study revealed a decrease in HIF-1 $\alpha$  protein in the wound of leptin receptor—deficient diabetic mice as compared to nondiabetic mice. Reduction of HIF-1 $\alpha$  resulted in decreased DNA-binding activity and decreased expression of HIF-1 target genes, including VEGF. Restoration of HIF-1 $\alpha$  in these diabetic wounds restored expression of VEGF, enhanced angiogenesis, and accelerated wound healing. This supports the role of HIF-1 $\alpha$  in wound healing. Reduced HIF-1 $\alpha$  may contribute to impaired wound healing and may offer a therapeutic target.<sup>90</sup>

The topical application of recombinant human PDGF on cutaneous wounds in diabetic rats showed accelerated reepithelialization, increased thickness of granulation tissue, and higher density of capillary buds.<sup>150</sup> Recombinant human PDGF-BB has been studied extensively for the treatment of lower extremity ulcers. A recent randomized, prospective, blinded clinical trial of 922 patients found that the application of once-daily PDGF in combination with

good wound care significantly improved healing in diabetic neurotrophic foot ulcers.<sup>151</sup>

## CONCLUSION

Angiogenesis research is proceeding rapidly, and scientists and clinicians are gaining a better understanding of the role of this process in normal and disease states. Angiogenesis plays an important role in a wide range of cutaneous diseases. Increased understanding of this important topic will result in better understanding of disease pathogenesis and may foster development and implementation of novel and effective dermatologic therapeutics.

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