Blood, Sweat, and Tears. Angiogenesis, Angiogenesis-Dependent Diseases, and Angiogenesis-Interfering Therapies

REVIEW

Abstract

Accumulating evidence indicates that defects in angiogenesis - the formation of either excessive or insufficient blood vessels from an existing vasculature - play important roles in the pathogenesis of a multitude of seemingly unrelated disorders such as cancer, a number of ocular conditions, certain skin diseases, as well as impaired wound healing. These findings have led to the development of various pro- and anti-angiogenic compounds and devices to treat these conditions. This article addresses a few historical highlights in the field of angiogenesis, describes the involvement of this phenomenon in the pathogenesis of a number of diseases, reflects on currently available anti- and pro-angiogenic therapeutic strategies, and presents a research program in Suriname aimed at the identification of plant-derived substances with potential angiogenesis-interfering properties.

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Introduction

Angiogenesis is the growth of new blood vessels from a preexisting vasculature [1]. Normally, this process is tightly controlled and does not occur in healthy individuals [1]. In fact, endothelial cells are in general quiescent and do not replicate in the healthy adult [2]. Exceptions are the process of wound healing, the female monthly reproductive cycle, the formation of the placenta during pregnancy, and the development of the embryo [2].

Under these conditions, angiogenesis is regulated by an intricate interplay between -stimulating growth factors and natural inhibitors. A

few well-known angiogenic growth factors are vascular endothelial growth factor (VEGF); acidic and basic fibroblast growth factor (a-FGF and b-FGF); granulocyte colony-stimulating factor (G-CSF); interleukin-8 (IL-8); platelet-derived growth factor-BB (PDGF-BB); transforming growth factor-alpha and beta (TGF- α and - β); and tumor necrosis factor-alpha (TNF- α) [3, 4]. Examples of angiogenesis inhibitors are angioarrestin; cartilage-derived inhibitor, also known as Neovastat[®] (AE-941); endostatin; human chorionic gonadotropin; interferon α , β , and γ ; interleukin-12; tissue inhibitors of metalloproteinases; plasminogen activator inhibitor; retinoids; and vasculostatin [3, 4].

Normally, angiogenesis is held in check by the constitutive overproduction of angiogenesis inhibitors with respect to angiogenic growth factors. When blood vessel formation is required -for instance, in the case of disease or injury- angiogenesis occurs in a highly organized succession of molecular events [5, 6]. Thus, macrophages and platelets in the damaged tissue are stimulated by the hypoxia in the lesion to release angiogenic factors which attract endothelial cells from undamaged blood vessels in intact tissues surrounding the lesion. The endothelial cells proliferate, migrate to the lesion through openings in basement membrane and extracellular membrane created by matrix metalloproteinases (MMPs), and proliferate there further to construct a vascular network that supplies the lesion. The capillary tips are pulled forward by integrins while their advancement to the lesion is facilitated by additional MMPs which dissolve the tissue in front of them. Finally, the endothelial cells combine to form new capillaries, arterioles, and venules which connect to form a new vascular network that is stabilized by pericytes.

This paper briefly addresses a few historical highlights in angiogenesis research; elaborates on a number of diseases caused by excessive or insufficient angiogenesis and currently available anti- and pro-angiogenic therapies; and concludes with

the potential contribution to this scientific area of plant-derived angiogenesis-interfering compounds from the Republic of Suriname.

Early developments

The exact molecular events involved in angiogenesis are only now becoming clear. However, the British surgeon John Hunter first used the term 'angiogenesis' in the year 1787 to portray the formation of blood vessels in the reindeer antler [4]. Almost one and a half century later (in 1935), the Boston pathologist Arthur Tremain Hertig gave an account of angiogenesis in the placenta of pregnant monkeys [4]. In 1939, Gordon Ide and his co-workers at the University of Rochester (NY, USA) were the first to present evidence on tumor-specific factors that stimulate the growth of blood vessels [4]. And in 1945, Glenn H. Algire and Harold W. Chalkley from the National Cancer Institute in Bethesda (MD, USA) postulated that the growth of a tumor is closely connected to the development of an intrinsic vascular network [7].

This concept gained momentum in 1971, when the American surgeon Judah Folkman, by many regarded as the godfather of angiogenesis, formulated the ground-breaking hypothesis that tumor growth is dependent on angiogenesis [1]. Folkman's theory was initially disregarded by most experts in the field, but became widely accepted because of supporting data from a number of landmark reports. For instance, human and animal tumors appeared to contain a soluble factor - tumor-angiogenesis factor (TAF) - that stimulated the proliferation of endothelial cells and the formation of new capillaries [1]. Furthermore, studies with tumor fragments implanted directly in the iris of rabbits always vascularized and grew exponentially, while implants at a distance from the iris did not become vascularized and remained arrested at a small size [8].

These insights led in 1975 to the identification of a diffusible factor in cartilage from newborn rabbits as the first angiogenesis inhibitor [9], and in 1984

to the purification of the first angiogenesis growth factor, b-FGF, from a rat chondrosarcoma [10]. Five years later, Napoleone Ferrara and his colleagues at Genentech, Inc. in San Francisco (CA, USA) discovered VEGF [11], now regarded as one of the most important angiogenic growth factors [12, 13]. VEGF turned out identical to vascular permeability factor (VPF) that was already described in 1983 [14], and was isolated in 1990 by Harold Dvorak's research group from Beth Israel Hospital in Boston (MA, USA) [15].

Taking these developments to their logical conclusion, Carl White, a pulmonary specialist at the National Jewish Medical Centre in Denver (CO, USA), was the first to provide clinical 'proof of concept' of anti-angiogenic therapy for cancer in 1988, by successfully treating an angiogenesis-dependent neoplasm - pulmonary hemangioma - with an anti-angiogenic agent, interferon α -2a [16]. Subsequently, TNP-470, a synthetic analogue of the terpenoid fumagillin isolated from the fungus *Aspergillus fumigatus* - originally used to control nosema disease in honey bees - was evaluated as the first angiogenesis inhibitor for treating cancer [17]. A few years later (in 1997), the first complete regression of tumors was reported in laboratory mice treated with repeated cycles of the anti-angiogenic substances angiostatin and endostatin [18].

Angiogenesis-dependent diseases

Ongoing research has revealed that excessive angiogenesis is not only pivotal to the progression and spread of cancer, but also to the development of a wide array of other pathologies. Well-investigated examples that will be addressed in detail in this paper next to cancer are ophthalmological ailments such as neovascular age-related macular degeneration [19], as well as malignant and non-malignant skin diseases [1-4] and other dermatological diseases such as genital and peri-anal warts [20] and actinic keratosis [21]. As in cancer, the diseased cells in these conditions also produce unnecessary

amounts of angiogenic growth factors, annihilating the effects of natural angiogenesis inhibitors, and resulting in the formation of undesired new blood vessels that sustain the diseased tissues and destroy normal tissues.

The key role of excessive angiogenesis in the above-mentioned diseases suggests that anti-angiogenic forms of treatment should represent successful therapeutic approaches by eradicating the undesired blood vessels. Such therapies should be lowly toxic to the healthy tissues and not evoke resistance because of the relatively long turn-over and the reasonable genomic stability of normal endothelial cells when compared to abnormal endothelial cells [22]. And in the case of cancer, anti-angiogenic therapies should prohibit tumor cells to escape into the circulation and to metastasize to other organs and tissues [22].

On the other hand, improving insights into the biology of angiogenesis made clear that the opposite - insufficient angiogenesis caused by the inadequate production of angiogenic growth factors - could lead to equally debilitating conditions. The deficient blood vessel growth in the diseased tissues results in an improper circulation, inadequate tissue repair and regeneration, and eventually tissue death. Examples of such conditions are chronic wounds such as diabetic lower extremity, vascular, and pressure ulcers [23] which will be dealt with in detail in this paper.

While anti-angiogenic therapies are aimed at interrupting excessive angiogenesis, pro-angiogenic therapies are intended to stimulate new blood vessel formation and promote neovascularization, thus improving perfusion, delivering survival factors to sites of tissue repair, mobilizing regenerative stem cell populations, and ultimately, restoring form and function of the damaged tissues [24].

Angiogenesis and cancer

As mentioned above, the expansion and spread of a tumor depends on the establishment of new blood

vessels [1-4]. The new vessels ensure the supply of oxygen and nutrients as well as the disposal of carbon dioxide and other waste products, and help disseminate tumor cells to distant sites throughout the body [1-4]. This turning point in the development of the tumor is called the 'angiogenic switch' and is accomplished by the overproduction of angiogenic growth factors with respect to angiogenesis inhibitors [1-4]. The evidence for this contention is compelling. Firstly, the angiogenic growth factors VEGF and b-FGF are commonly found in tumors where they act synergistically [25], while VEGF is overexpressed in both stromal and tumor cells of various solid malignancies including renal, lung, breast, and ovarian cancer [26]. Secondly, VEGF expression is positively regulated by oncogenes such as Ras [27] and negatively by tumor suppressors such as von Hippel-Lindau [28] which are often over- or under-expressed, respectively, in malignancy [29, 30]. Thirdly, inhibition of VEGF has been demonstrated to suppress tumor growth in animal models [31].

These insights led to the realization that the growth and spread of a tumor can be halted or slowed down with angiosuppressive or anti-angiogenic substances [1-4]. At this moment, there are three primary categories of approved anti-cancer therapies with recognized anti-angiogenic properties: monoclonal antibodies directed against specific pro-angiogenic growth factors and/or their receptors; small-molecule inhibitors of multiple pro-angiogenic tyrosine kinase growth factor receptors (TKIs); and inhibitors of mTOR, a serine/threonine protein kinase that regulates key cell functions including proliferation and motility. There are, furthermore, a few other approved anti-angiogenic agents that interfere with cancerous growth through so far incompletely understood mechanisms.

Anti-angiogenic therapies for cancer

The humanized monoclonal anti-VEGF antibody bevacizumab (Avastin®) was the first anti-angiogenic drug to demonstrate that inhibiting tumor blood

vessel growth prolonged survival of cancer patients [32, 33]. This was based on the key driving role of VEGF in tumor angiogenesis and its overexpression in most solid cancers [25, 26, 31]. Bevacizumab is so far the only anti-angiogenic monoclonal antibody approved for the treatment of cancer. It binds to VEGF, preventing its interaction with VEGF receptors, thereby inhibiting endothelial cell proliferation and angiogenesis [34]. Bevacizumab, usually in combination with chemo- or immunotherapy, is active against, among others, metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic non-small cell lung cancer; locally recurrent or metastatic breast cancer; and newly diagnosed advanced ovarian cancer [35, 36].

TKIs such as erlotinib (Tarceva®), sunitinib (Sutent®), axitinib (Inlyta®), pazopanib (Votrient®), and regorafenib (Stivarga®) interrupt signaling from, among others, the receptors for epidermal growth factor, VEGF, PDGF, and FGF, blocking certain intracellular signaling pathways in tumor cells, thus deregulating cellular processes associated with proliferation, differentiation, and angiogenesis [37]. These compounds are useful against various difficult-to-treat malignancies such as locally advanced or metastatic non-small cell lung cancer; locally advanced, unresectable, or metastatic pancreatic cancer; advanced renal cell carcinoma; soft tissue sarcomas; advanced, unresectable hepatocellular carcinoma; and metastatic colorectal cancer that has progressed after all standard therapies [38, 39].

At present, there are two mTOR inhibitors on the market as anti-cancer therapy, viz. temsirolimus (Torisel®) and everolimus (Afinitor®). Both compounds target part of the PI3 kinase/AKT pathway [40] that is overactive in many cancers, thus counteracting apoptosis and stimulating cell proliferation, tumor angiogenesis, and tumor growth [41]. These compounds are approved for the treatment of poor-prognosis malignancies such as previously untreated advanced renal cell carcinoma or advanced renal

cell carcinoma that had failed treatment with a TKI, and unresectable, locally advanced, or metastatic progressive neuroendocrine tumors of pancreatic origin [42, 43].

Other anti-cancer angiogenesis inhibitors in clinical use are interferon α -2a and -2b (Roferon-A[®] and Intron A[®], respectively), lenalidomide (Revlimid[®]) and thalidomide (Thalomid[®]), as well as recombinant human endostatin (rhEndostatin; Endostar[®]; Endu[®]). Interferon α is approved for treating hairy cell leukemia, malignant melanoma, follicular lymphoma, and AIDS-related Kaposi's sarcoma [44]. Lenalidomide and thalidomide are useful against multiple myeloma in combination with dexamethasone [45]. rhEndostatin inhibits endothelial cell proliferation and angiogenesis by blocking VEGF-induced tyrosine phosphorylation of a receptor for VEGF, and interferes with metastasis by down-regulating MMP activity [46]. It is so far only available in China, where it is used for the treatment of advanced non-small cell lung cancer [47].

Challenges and new developments

Despite the availability of this encouraging armamentarium of anti-angiogenic drugs against cancer, the successes that were hoped for have not been achieved. Unexpectedly, toxic effects were substantial while durable responses were infrequent and overall survival rates in general moderate [48, 49]. These disappointing results are attributable to the highly complex and multi-step nature of angiogenesis involving a variety of mediators and signaling pathways that are also engaged in many other physiological processes [48, 49]. As a consequence, targeting VEGF and/or VEGF-associated pathways - as is accomplished by most currently available anti-angiogenic compounds - is likely to affect multiple organs and tissues and to induce many different collateral effects (such as bleeding, disturbed wound healing, thrombosis, hypertension, proteinuria, edema, skin toxicity, leukopenia, and immunomodulation; [48, 49]).

The involvement of so many actors in new blood vessel formation makes it also difficult to effectively suppress undesired blood vessel formation by only targeting VEGF and/or VEGF-associated pathways. As an example, treatment of patients with glioblastoma or colorectal cancer using an inhibitor of VEGF receptor tyrosine kinase [50] or a bevacizumab-containing regimen [51], respectively, led to up-regulation of pro-angiogenic substances such as b-FGF [50, 51], obliterating the angiosuppressive effects of VEGF targeting, causing apparent resistance to the anti-VEGF therapies and tumor recurrence.

Moreover, cancer cells have the capacity to form *de novo* vessel-like structures and vascular networks which can connect with the surrounding vasculature, thus providing oxygen and nutrients to the tumor and promoting its further growth and spread [52]. This phenomenon is referred to as vasculogenic mimicry, and represents an alternative pathway for tumors to guarantee their blood supply [52]. Vasculogenic mimicry is characteristic for highly aggressive tumors and correlates with an advanced stage and a poor prognosis [52]. The precise mechanism of vasculogenic mimicry is not known, but it might be based on the trans-differentiation of cancer stem cells to endothelial-like and vascular smooth muscle-like cells [53]. Understandably, malignant cells with such plasticity can proliferate rapidly and metastasize widely, rendering the tumor they reside in highly aggressive.

The above-mentioned considerations emphasize the necessity to improve our understanding of the mechanisms underlying the toxicities of, and the resistance to angiogenesis inhibitors in order to develop more specific and more potent anti-angiogenesis treatments. The preliminary results obtained with agents directed specifically at FGF signaling [54] or at both VEGF and FGF pathways [55] are encouraging. The same holds true for attempts to block signaling for vasculogenic mimicry by perturbing processes associated with the extracellular membrane and/or the tumor microenviron-

ment [53], and those that may interfere with tumor cell plasticity by simultaneously attacking the tumor cell compartment with cytotoxic therapies and the endothelial cell compartment with anti-angiogenic agents [56].

Angiogenesis and ophthalmological conditions

Adequate vision requires the undisturbed flow of light through cornea, lens, vitreous body, and the superficial area of the retina where the sensory light receptors are located. Any non-transparent structure in the pathway of light entering the eye interferes with normal sight and affects adequate vision and can even cause blindness. This happens when blood vessels start to grow excessively in these normally minimally or non-vascularized structures, in general in response to hypoxia [19]. The hypoxia leads to undesired neovascularization as a result of up-regulation of VEGF and other growth factors, as well as the production of integrins and proteinases, and endothelial cell proliferation and migration [19].

One of the most common ophthalmological diseases associated with pathological blood vessel formation is neovascular (or 'wet') age-related macular degeneration. This condition is the leading cause of irreversible and severe vision loss in individuals of 50 years and older [57]. It involves the ingrowth of blood vessels from the choroid into the macula, leakage of fluid and blood from these abnormal vessels, swelling and damage of the macula, and loss of vision in the center of the visual field [57].

Another important cause of vision loss is diabetic retinopathy [58]. This condition is anticipated to become more prevalent in the near future as a consequence of the increasing prevalence of diabetes mellitus in many parts of the world [58]. The exact cause(s) of diabetic retinopathy is/are still unknown, but the long-term exposure to hyperglycemia is believed to cause severe damage to the vascular system in the retina, including capillary occlusion and retinal non-perfusion as well as serum leakage and

retinal edema [59]. The damage gradually progresses from mild stages to advanced proliferative stages, causing complications such as diabetic macular edema and proliferative diabetic retinopathy [59].

There is ample evidence to implicate angiogenic growth factors – particularly VEGF - in the vascular proliferation and the vasopermeability in the above-mentioned diseases. For instance, VEGF concentrations are substantially increased in ocular tissues from patients with diabetes [60]; the development of proliferative diabetic retinopathy in mouse models of ischemic retinopathy could be prevented by blocking VEGF activity [61]; and intravitreal injection of VEGF in primates caused neovascularization of the iris [62]. Furthermore, VEGF promoted leukostasis and vascular leakage and increased leukocyte counts in the retinas of diabetic animals [63] as well as in those of human diabetics [64], while blockage of VEGF decreased retinal leukocyte counts in experimental diabetes [65].

Anti-angiogenic therapies for ophthalmological conditions

Considering the importance of VEGF in ocular neovascularization, considerable research efforts have been dedicated to the development of anti-VEGF agents to improve vision in these conditions [66]. One such a substance is ranibizumab (Lucentis®) that is FDA-approved for treating macular edema following retinal vein occlusion, diabetic macular edema, and neovascular age-related macular degeneration [67-69]. Ranibizumab is a Fab fragment from the anti-VEGF monoclonal antibody bevacizumab that binds VEGF-A and its cleavage products, preventing their interaction with VEGF receptors 1 and 2 [70]. As ranibizumab lacks the Fc domain, it has a much shorter half-life – and thus potentially less side-effects - than other anti-VEGF agents [70]. However, bevacizumab - although not authorized for intraocular use - is probably as efficacious as ranibizumab in neovascular age-related macular degeneration but causes comparable side-effects and

is much more cost-effective [71, 72]. These considerations have led to the wide-spread off-label use of bevacizumab against this eye disease.

Other licensed anti-angiogenic drugs against ocular neovascularization are pegaptanib (Macugen®) and aflibercept (Eylea®). Pegaptanib is a pegylated aptamer that binds with high specificity to the 165 isoform of VEGF and was approved in 2004 as the first anti-angiogenic agent for treating neovascular age-related macular degeneration [73]. Aflibercept, a more recent anti-VEGF agent, is a soluble decoy receptor consisting of the VEGF-binding portions from VEGF receptors 1 and 2 attached to the Fc portion of the human IgG1 immunoglobulin [74]. It is also referred to as VEGF Trap-Eye because it binds with a very high affinity to VEGF [74]. Aflibercept is FDA-approved for the treatment of neovascular age-related macular degeneration and macular edema following central retinal vein occlusion [75].

Challenges and new developments

An important limitation to anti-angiogenic treatments for ocular diseases is the recurrence of new blood vessels following anti-VEGF treatment [76]. This necessitates repeated (intra-vitreous) injections to maintain a therapeutic effect [76]. However, prolonged targeting of VEGF may lead to serious side-effects because of interference with normal physiological processes that also depend on VEGF. For instance, chronic inhibition of VEGF eventually resulted in loss of vision in laboratory mice [77]. Also, bevacizumab has been reported to cause tractional retinal detachment as well as hypertension and other cardiovascular complications in patients with severe proliferative diabetic retinopathy [78, 79]. These observations signify the need to screen patients regularly for signs of these undesirable long-term effects.

On the other hand, a number of potentially ground-breaking developments may markedly advance the treatment of eye diseases caused by neovascularization. An example is the use of dou-

ble-stranded RNA-mediated interference (RNAi) to shut down the transcription of VEGF and other angiogenic growth factors. RNAi involves silencing of gene expression by degrading RNA to short RNAs that activate ribonucleases which can target homologous mRNA including that involved in undesired neovascularization [80]. Currently available data from preclinical and early clinical studies are encouraging [81, 82]. Another strategy against ocular neovascularization may involve the use of TKIs to impede the tyrosine kinase activity of VEGF receptors, comparably to their use as anti-angiogenic agents against cancer. Thus, cediranib (Recentin®) inhibited laser-induced choroidal neovascularization in mice [83], and regorafenib partly prevented alkali-induced corneal neovascularization in rats [84]. Clinical studies with these and other TKIs are ongoing.

Angiogenesis and dermatological conditions

Excessive angiogenesis has also been implicated in the pathogenesis of several malignant, pre-malignant, and non-malignant skin conditions [20]. Indeed, skin cancers also require a blood supply to grow larger than a few millimeters in diameter [20], while pre-cancerous skin lesions and warts have a higher density of capillaries when compared to surrounding normal skin [20]. Furthermore, excessive exposure to ultraviolet (UV) radiation - an important risk factor for many skin lesions [85] - triggers angiogenesis in the skin by increasing levels of stimulators such as VEGF and b-FGF while suppressing angiogenesis inhibitors [85]. Of note, the progression from pre-cancerous skin lesions to overt skin cancer is accompanied by the continued growth of new blood vessels [20].

Anti-angiogenic therapies for dermatological conditions

These considerations have spurred the development of various anti-angiogenic compounds for skin diseases. This has led, among others, to the iden-

tification of cyclooxygenase (COX) inhibitors such as non-steroidal anti-inflammatory drugs - which are commonly used to suppress pain and inflammation - as inhibitors of the production of VEGF and other angiogenesis-stimulating proteins in skin exposed to UV [86]. One such a compound is a 3 %-gel of the COX inhibitor diclofenac (Solaraze®) that has been approved for the topical treatment of actinic keratosis [87], an early form of squamous cell carcinoma [21].

Toll-like receptors (TLRs) are ubiquitous pattern-recognition receptors in, among others, skin cells, that alert the immune system to microbial products and reduce angiogenesis when stimulated. For this reason, the TLR-7agonist imiquimod (imidazoquinoline 5 %-cream; Aldara®) has been approved for the topical treatment of actinic keratosis as well as basal cell carcinoma [88] and genital warts [89]. Imiquimod not only boosts the immune system by stimulating the production of interferons and interleukins, but also inhibits angiogenesis by down-regulating b-FGF and MMP-9 and induces apoptosis of endothelial cells [90]. Another immune response-modulating agent with anti-angiogenic properties is alitretinoin (9-cis-retinoic acid). It is marketed as a 0.1 %-gel (Panretin®) for treating the skin lesions in AIDS-associated Kaposi's sarcoma, and counteracts angiogenesis by down-regulating VEGF [91].

Challenges and new developments

An important drawback of anti-angiogenic treatments against skin conditions is the occurrence of dermatological side-effects including hand-foot skin reactions (thick, well-defined hyperkeratotic lesions primarily on hands and feet, often accompanied by pain, numbness, tingling, and dry and/or cracked and peeling skin), as well as rash, skin discoloration, dry skin, alopecia, and hair and nail changes [92]. These side-effects are probably caused by capillary damage, inflammation, mechanical stress, and direct toxicity to keratinocytes and other cell types, and have been documented during treatment

of cancer with, among others, the antineoplastic agents capecitabine and 5-fluorouracil [93], but also during treatment with anti-angiogenic TKIs such as sorafenib and sunitinib [94]. Furthermore, the use of imiquimod cream may lead to local skin reactions including erythema, flaking, erosions, and crusting [95]. In addition, uncommon systemic effects have been reported, including headache, flu-like symptoms, fatigue, nausea, and myalgia [96].

For these reasons, alternative anti-angiogenic therapies for dermatological conditions are being pursued. Examples are epigallocatechin-3-gallate and dobesilate. Epigallocatechin-3-gallate is the active component of polyphenolic kunecatechins extracted from green tea leaves, and inhibits angiogenesis by preventing VEGF expression [97]. It is approved as sinecatechins ointment 15 % (Veregen®, previously Polyphenon E®) for treating external genital and peri-anal warts [98].

Dobesilate is a vasoprotective agent that is orally taken for treating vascular complications of diabetic retinopathy [99]. More recently, this agent was found to reduce vessel ingrowth in a-FGF-containing subcutaneous sponges in mice, suggesting that it could be effective for treating angiogenesis-dependent diseases involving FGFs [99]. Subsequent studies supported this supposition, showing that dobesilate could act as a topical inhibitor of a-FGF and b-FGF and that its molecular weight is sufficiently low to penetrate the upper layers of the skin [99]. Initial studies of dobesilate in patients with rosacea and basal cell carcinoma yielded promising results [99-101].

Angiogenesis and chronic wounds

Chronic wounds are considered wounds that do not heal spontaneously within three months [102]. Examples of such lesions are diabetic, vascular, and pressure ulcers, and they represent a major burden to patients, their families, health care professionals, and health care systems [23, 103]. Chronic wounds occur in all age groups, but the majority is seen in

older people [23, 103]. The number of individuals over 65 years throughout the world is expected to increase two- to three-fold in the forthcoming thirty years [23, 103], while the global incidence of conditions that impede wound healing such as diabetes mellitus, obesity, and vascular disorders are on the rise [23, 103]. For these reasons, chronic wounds are anticipated to become one of the most challenging public health concerns of the near future. Prevalence rates of pressure ulcers in Western countries, for instance, range from 4.7 to 32.1 % for hospital populations, 4.4 to 33.0 % for community-care populations, and 4.6 to 0.7 % for nursing-home populations [23]. And in the United States of America, the population prevalence rate for chronic non-healing wounds has been estimated at 2 % of the general population [100] at the staggering cost for care of over US \$ 50 billion per year [23, 103].

The process of wound healing involves a complex and dynamic, but highly regulated cascade of biochemical and cellular events that can be distinguished into four major phases: hemostasis; inflammation; proliferation; and maturation and remodelling [104]. Hemostasis involves the formation of a fibrin clot by the aggregation of thrombocytes [104]. During inflammation, bacteria and cell debris are removed by white blood cells [104]. In the proliferation phase, the wound begins to close as the wound area is rebuilt with new granulation tissue (largely consisting of collagen and extracellular matrix) that is revascularized by infiltration by a new network of blood vessels and subsequently covered by epithelial cells [104]. And during maturation and remodelling, newly formed collagen increases tensile strength to wounds while cellular and angiogenic activities cease [104].

The orderly and timely manifestation of these processes is imperative to restore the anatomic and functional integrity of the injured site [104]. In fact, chronic wounds occur because one or more events in the healing process fail(s) to proceed correctly [104]. This holds particularly true for events involved

in adequate revascularization because the quality of the granulation tissue - hence the condition of the wound - depends for an important part on the supply of oxygen and nutrients by ingrowing blood vessels [104].

Not surprisingly, angiogenic growth factors such as VEGF, PDGF, TGF- β , and FGF have also been found to play key roles in proper wound healing. For instance, chronic wounds contained substantially lower levels of these substances when compared to acute surgical wounds [105-107]; receptors for TGF- β were down-regulated in chronic venous ulcers [108]; fluid collected from chronic wounds inhibited the formation of capillaries by cultured human umbilical vein endothelial cells [109]; and chronic wounds contain relatively few blood vessels [110]. As a consequence, the circulation in the injured tissues is improperly restored, increasing the risk of tissue death and amputation of affected limbs [23, 103].

Pro-angiogenic compounds for treating chronic wounds

The above-mentioned considerations led to the development and approval in 1997 of the first angiogenesis-stimulating drug, recombinant human PDGF-BB (a cicatrizant formulated as a 0.01 %-prescription gel and marketed as becaplermin or Regranex™) for treating diabetic foot ulcers [111]. The Autologel™ System represents a slightly different approach to manage poorly healing wounds, delivering growth factors formulated as a bioactive gel prepared from platelet-rich plasma from the patient's own blood to the wound bed [112].

Other therapeutic angiogenesis-promoting approaches for non-healing chronic wounds are negative pressure wound therapy devices such as the vacuum-assisted closure system that induces angiogenesis through tissue micro-deformations and mechano-chemical coupling and signal transduction [113]; mist ultrasound, a low-frequency and low-intensity non-contact healing device that

accelerates wound healing by delivering 40-kHz ultrasound by a saline mist, thus increasing the blood flow through vasodilatation, increased angiogenesis, and the release of growth factors in the wound bed [114]; and hyperbaric oxygen, that promotes angiogenesis and wound healing by increasing VEGF expression and recruiting endothelial progenitor cells [115].

More recently, cell-based pro-angiogenic therapies for chronic wounds have been developed. Two such products are the bilayered skin substitute Graftskin (Apligraf®) and the human fibroblast-derived dermal skin substitute Dermagraft®. These products contain living or cryopreserved cells on a matrix capable of secreting and releasing human dermal collagen, matrix proteins, angiogenic growth factors, and cytokines into the wound bed to create a three-dimensional human dermal substitute containing metabolically active, living cells [116]. Similarly, the administration of CD34+ endothelial progenitor cells derived from bone marrow or peripheral blood have been found, among others, to enhance angiogenesis in ischemic tissues and to increase collateral vessel formation, improving the healing of leg ulcers [117].

Challenges and new developments

As mentioned above, wound healing is a well-coordinated, progressive series of events that involves a multitude of players operating during specific phases, at specific quantities and extents, and in specific sequences [23, 103]. Thus, impaired or stalled wound healing can result from failure of any of these processes to proceed correctly. As a consequence, attempts to solely restore the blood supply to the wound bed are probably not sufficient to heal chronic wounds, despite the pivotal role of angiogenesis in wound healing [105-110]. Rather, advances in wound care practice are more likely to come from improvements in our understanding of wound microenvironment and cell-extracellular matrix interactions that direct the morphology, differentiation,

migration, proliferation, and survival of cells during the proliferation and maturation/remodeling phases of wound healing [24, 118, 119].

Such insights have already led to the development of promising novel therapeutic approaches such as improved matrix and cell-based therapies. For instance, the use of the experimental heparan sulfate glycosaminoglycan mimetic OTR4120 - an artificial extracellular matrix component - stimulated angiogenesis and restored the biomechanical strength of pressure ulcers in streptozotocin-induced diabetic rats [120]. And topical application of allogeneic mesenchymal stromal cells from the bone marrow of non-diabetic rabbits improved angiogenesis and the healing of alloxan-induced ulcers in the ears of their diabetic counterparts [121].

Developments in Suriname

Man has probably used medicinal plants for his healthcare since his early days on Earth. One of the most appealing pieces of evidence for this statement is the discovery in 1960 of large amounts of pollen from medicinal plants at the Neanderthal burial site Shanidar IV in northern Iraq, dating human use of plant-based medicines at least to the Middle Paleolithic age some 60,000 years ago [122]. Today, approximately 80 % of humans living in developing countries still use medicinal plants for their day-to-day healthcare [123]. The remaining 20 % of the world population living in industrialized countries use in 25 % of cases medicines that have directly been derived from plants [123]. Examples are the analgesic morphine extracted from the opium poppy *Papaver somniferum* L. (Papaveraceae) [124]; the cardiac glycoside digoxin from the foxglove *Digitalis lantana* L. (Scrophulariaceae) [125]; the glycoside saponin diosgenin from yams from the genus *Dioscorea* (Dioscoreaceae) that serves as the raw material for 95 % of steroidal drugs such as oral contraceptives [126]; and the oral hypoglycemic agent metformin that was synthesized on the basis of the chemical structure of the anti-diabetic

compound galegine from the French lilac *Galega officinalis* L. (Fabaceae) [127].

These considerations emphasize the importance of medicinal plants to the development of therapeutics with novel chemical structures and unique mechanisms of action. This may also include plant-based substances for treating diseases caused by excessive or insufficient angiogenesis. Support for this expectation is provided by the identification of an increasing number of lead compounds from plant constituents with proven angiogenesis-interfering properties. The catechins in green tea that prevent VEGF expression [97] and are used for treating warts associated with sexually transmitted diseases [98] have already been mentioned. Additional examples are other nutraceuticals such as the polyphenol resveratrol in red wine and grape seeds, and the diarylheptanoid curcumin from *Curcuma longa* L. (Zingiberaceae) which inhibits endothelial cell proliferation as well as the production of VEGF, b-FGF, and other angiogenic cytokines [128-131]. Another notable example is the stilbenoid combretastatin A4 in, among others, the African bushwillow *Combretum caffrum* (Eckl. & Zeyh.) Kuntze (Combretaceae) [132], the lead compound for vascular disrupting combretastatins such as combretastatin A4 phosphate (CA-4-P, fosbretabulin or Zybrestat™) that shut down tumor blood flow, inducing necrosis in the center of the tumor [133].

The Republic of Suriname (South America) is located on the Guiana Shield, one of the regions with the highest biodiversity and the largest expanse of undisturbed tropical rain forest in the world [134]. This includes a minimum of 6,000 higher plant species [134], more than 600 of which are used for medicinal purposes [135]. Suriname's population of roughly 550,000 consists of a unique blend of ethnic groups, and cultures from all continents [136], all of whom have made their own specific contribution to Suriname's rich traditional medicine [135]. This has resulted in a myriad of (plant-derived) folk remedies against a wide variety of disorders, including,

among others, cardiovascular ailments, cancer, diabetes mellitus, airway diseases, pregnancy and childcare, skin problems, and even bone fractures [135].

So far, the scientific evidence to support the many claims of therapeutic efficacy of these traditional plant-based medications is scant. It is also not known whether, and to which extent the claims of therapeutic efficacy are related to interference with angiogenesis. For these reasons, the Academic Chair of Pharmacology at the Faculty of Medical Sciences of the Anton de Kom University of Suriname has received the special assignment to initiate a large-scale program to collect and evaluate Surinamese plants for their presumed angiogenesis-interfering properties. This effort is being undertaken in collaboration with the Suriname Conservation Foundation.

Research on plants with angiogenesis-interfering properties in Suriname

Candidate plants are primarily acquired on the basis of ethnopharmacological indications provided by Suriname's rich medicinal folklore, and chemosystemic clues from the literature. The collected plant parts are shipped to our laboratories where they are extracted according to the traditional methods. Thus, if a decoction is prepared from the dried leaves of a certain plant, than the leaves of that plant are collected, air-dried, and extracted in boiling water.

As angiogenesis involves, among others, the proliferation and migration of endothelial cells, as well as their rearrangement to form capillary-like structures [1, 2], the plant extracts are evaluated for their effects on the proliferation and motility of cultured human umbilical vein endothelial cells (HUVECs) using a sulforhodamine B cell proliferation assay [137], a migration assay using modified Boyden chambers [138], a scratch-wound healing assay [139], as well as a tube formation assay [140], respectively. In parallel, the plant extracts are assessed for their capacity to interfere with the regeneration of the amputated caudal tail fin of the

zebrafish *Danio rerio*, and their capability to affect total sub-intestinal vessel length of embryos of the Tg(fli1a:EGFP)y1/+ variant of these fish [141, 142]. So far, roughly 200 plant extracts have been prepared, approximately 90 of which have been evaluated in these assays. Our preliminary results have been presented on several international fora [143-145]. Plant extracts that prove active in these initial tests will be subjected to bioassay-guided purification in order to obtain the pharmacologically active ingredient(s). Also, molecular studies will be carried out in order to assess the samples for their mechanism of action.

Closing remarks

Since the first successful treatment of an angiogenesis-dependent disease in 1989 - the use of interferon α -2a against pulmonary hemangiomatosis [16] - excessive or insufficient angiogenesis has been implicated in the pathogenesis of more than seventy distinct diseases that affect hundreds of millions of individuals worldwide [146]. At the same time, a wide array of therapeutic anti-angiogenic or angiogenesis-stimulating therapies for correcting (the consequences of) faulty angiogenesis have been developed or are in development.

Some examples have been mentioned in this paper and include a number of encouraging modalities for treating certain cancer types, some dermatological conditions, a number of ophthalmological diseases, and chronic wounds. The implication of aberrant angiogenesis in the pathogenesis of a host of other pathophysiological processes opens the door for improved or entirely novel forms of treatment of other debilitating, difficult-to-treat conditions. A few examples are non-neoplastic skin conditions such as psoriasis, muco-cutaneous leishmaniasis, and lepromatous leprosy [147-149]; ischemic heart disease [150]; pulmonary arterial hypertension [151]; endometriosis [152] and other disorders of the reproductive system [153]; rheumatic disorders [154], Alzheimer's disease [155]; depression in the elderly [156], and even obesity [157] and photo-aging, *i.e.*,

the development of wrinkles by exposure to excessive UV-B radiation [158].

With these potential advances in mind, it is inevitable that the search for novel and safer angiogenesis-interfering agents is proceeding at a rapid pace. The challenge now is, to gain more insight into the complex interplay between the multiple pro- and anti-angiogenic factors and pathways that govern angiogenesis. In the meantime, attention should focus on the development of compounds directed at anti- and pro-angiogenic pathways and targets other than those explored so far (particularly those involving VEGF), and the evaluation of combinations of such substances with each other and with conventional drugs, not only with respect to dosages of administration, but also with respect to schedules of administration. Such approaches will hopefully result in the establishment of successful angiogenesis-interfering therapies that will acquire their rightful status in contemporary medicine - evidently at the cost of lots of blood, much sweat, and many tears.

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