Review
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Angiogenesis: from plants to blood vessels

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Angiogenesis is a major pathological component of diseases such as cancer and coronary heart disease. Although major advances have been made and encouraging clinical results obtained, safer and more effective approaches are required. The identification of new drugs from plants has a long and successful history, and certain proangiogenic and antiangiogenic plant components have been used in traditional Chinese medicine (TCM) for thousands of years. Similar to Western combination therapy, TCM uses mixtures of plant extracts, termed *fufang*, to maximize efficacy and minimize adverse effects or toxicity. More evidence-based research and chemical optimization of these compounds could further enhance the effectiveness of these plant-based medicines in angiotherapy.

Medicines from plants

Since antiquity, plants have been used to treat many ailments. However, it was not until the 1800s that pure compounds were isolated from plants, paving the way for modern pharmaceuticals. In 1805, morphine was isolated from the opium poppy (*Papaver somniferum*) by the German pharmacist Friedrich Serturner. Following the isolation of salicylic acid from the bark of the willow tree (*Salix alba*), Felix Hoffmann synthesized aspirin in 1897. Ephedrine was isolated from the Chinese herb mahuang (*Ephedra*) in 1887 and became popular with American physicians in 1924 for its bronchodilatating and decongestant properties. Sodium cromoglyate, first used in 1968, is a khellin derivative that was isolated from Egyptian khella seeds (*Ammi visnaga*) by Roger Altounyan. The antimalarial drug artemisinin was developed in 1972 from the Chinese herb qinghao (sweet wormwood, *Artemisia annua* L.). These examples illustrate the rich history of plant-based medicines.

Angiogenesis is the growth of neovessels from existing vasculature. Usually, angiogenesis is tightly controlled by a balance of angiogenesis factors and inhibitors, and occurs only in embryonic development, wound healing and the female reproductive cycle. Angiogenic diseases result from new blood vessels growing either excessively (e.g. cancer, diabetic retinopathy and psoriasis) or insufficiently (e.g. chronic wounds and ischaemic heart disease). To date, the stimulation of angiogenesis using angiogenesis peptides has produced encouraging clinical results in treating coronary artery disease. Blocking angiogenesis with antibodies of angiogenesis factors or with enzyme inhibitors is effective for treating malignancy but there is room for improvement. Of particular relevance to this article is the fact that some of the plant-derived anticancer drugs (e.g. Taxol®, camptothecin and combretastatin) are antiangiogenic. In traditional Chinese medicine (TCM), many herbs are used in the treatment of angiogenic diseases such as chronic wounds and rheumatoid arthritis. Thus, it is rational to explore these medicinal plants as a source of novel angiomodulators. In this article, we review plant-based angiotherapy and discuss potential future TCM therapies.

Angiogenesis

Since Judah Folkman's seminal article about tumour angiogenesis [1], numerous articles have been written about the aspects of angiogenesis (e.g. Ref. [2]; see also *Angiogenesis*: http://www.kluweronline.com/issn/0969-6970/contents).

There are ten sequential steps of angiogenesis (Figure 1). Recent studies have shown the importance of leucocytes as providers of cytokines, chemokines and enzymes that are involved in angiogenesis. Angiogenesis stimulators and inhibitors target one or more of these steps.

(i) In response to hypoxia, injured or diseased tissues synthesize and release angiogenic factors;
(ii) angiogenic factors bind to their receptors on endothelial cells (ECs);
(iii) receptor binding leads to EC activation;
(iv) proteases are released to dissolve the basement membrane;
(v) ECs migrate and proliferate;
(vi) adhesion molecules (e.g. integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$) help to pull the sprouting blood vessel forward;

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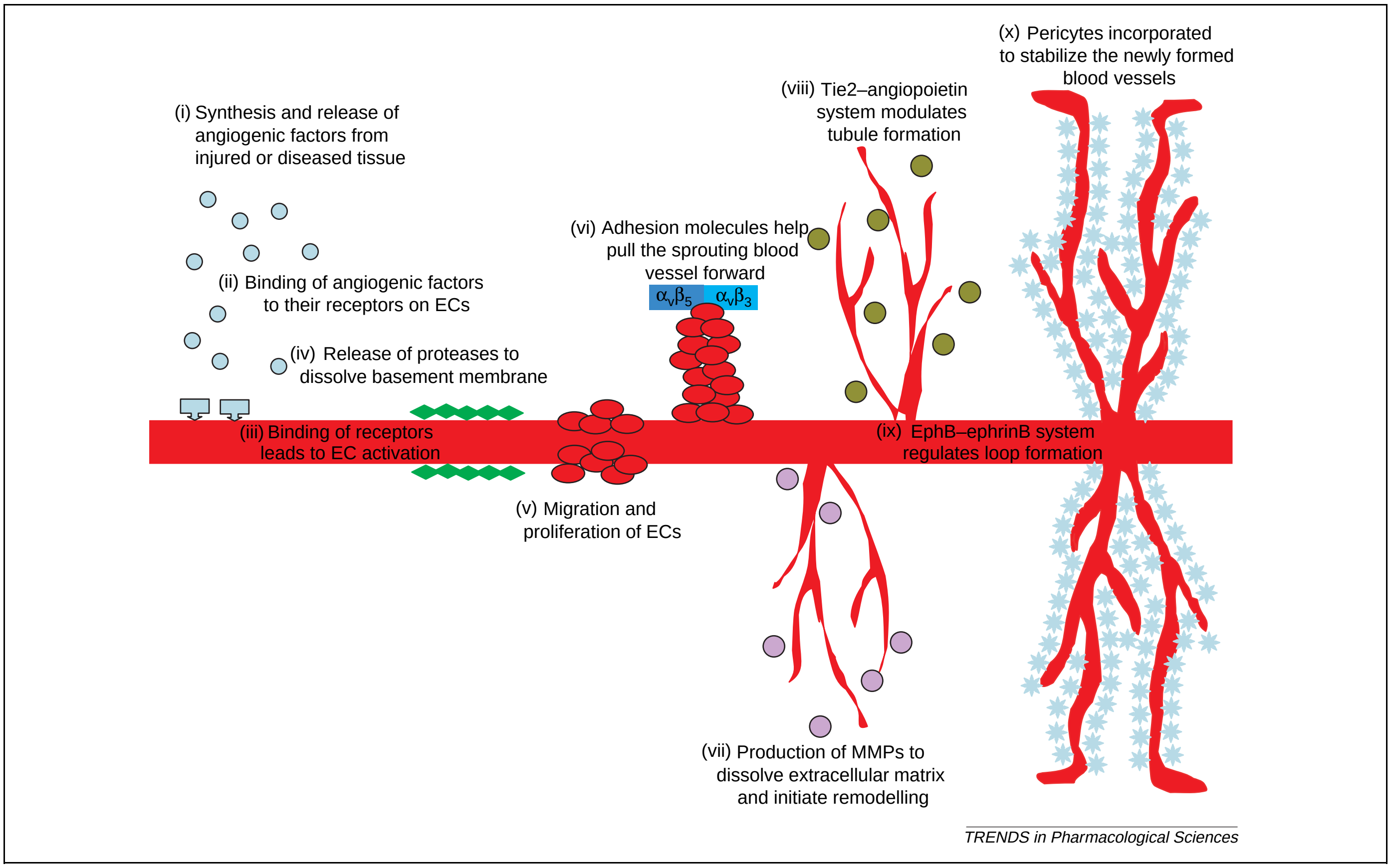

Figure 1. The ten sequential steps of angiogenesis. Only the key cellular and molecular events are depicted. Depending on the microenvironment (e.g. oxygen tension, leucocyte infiltration and release of antiangiogenic factors such as transforming growth factor-β and platelet factor 4), the newly developed vasculature either undergoes maturation into a functional network or regresses to maintain the original vascular density.

(vii) matrix metalloproteinases (MMPs) are produced to dissolve the extracellular matrix and to initiate remodelling;
(viii) angiopoietin–Tie-2 interaction modulates tubule formation;
(ix) the EphB–ephrinB system regulates loop formation;
(x) pericytes are incorporated to stabilize the newly formed blood vessel.

Angiogenesis is a common denominator of many diseases

In 1994, The Angiogenesis Foundation (http://www.angio.org) declared angiogenesis a ‘common denominator’ in the most important diseases of society. In many serious diseases states, the body loses control of angiogenesis.

Excessive angiogenesis

In diseases such as cancer (Figure 2), age-related macular degeneration, psoriasis and endometriosis, excessive angiogenesis occurs when diseased cells produce abnormally large amounts of angiogenesis factors [e.g. vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-2 and hepatocyte growth factor], overwhelming the effects of natural angiogenesis inhibitors (e.g. angiostatin, endostatin and thrombospondin). More than 70 other conditions (e.g. obesity and asthma) are associated with excessive angiogenesis. In these conditions, new blood vessels feed diseased tissues and destroy normal tissues; in cancer, tumour cells use the new vessels to escape into the circulation and lodge in other organs (tumour metastases). Antiangiogenic therapies, which are aimed at suppressing new blood vessel growth, are being developed to treat these chronic diseases.

Insufficient angiogenesis

In chronic wound, coronary artery disease, stroke and non-union fracture, inadequate (in size and/or number) blood vessels grow and circulation is not properly restored, leading to the risk of tissue death and, in the case of alopecia, hair loss. Insufficient angiogenesis is caused by the inadequate production of angiogenesis growth factors and/or excessive amounts of angiogenesis inhibitors. Therapeutic angiogenesis, which is aimed at stimulating neovascularization with growth factors, is being developed to reverse these conditions.

Angiotherapy

Angiotherapy is an operational term introduced to encompass several treatments that are aimed at ‘turning on’ or ‘turning off’ angiogenesis in disease [3]. Stabilization and maturation of the neovasculature is also crucial to the successful outcome of angiotherapy (Table 1). In diabetic retinopathy, the new blood vessels are immature and prone to haemorrhage. Instead of inhibiting the growth of these leaky vessels totally, it might be more beneficial to induce the proper incorporation of pericytes and the formation of

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