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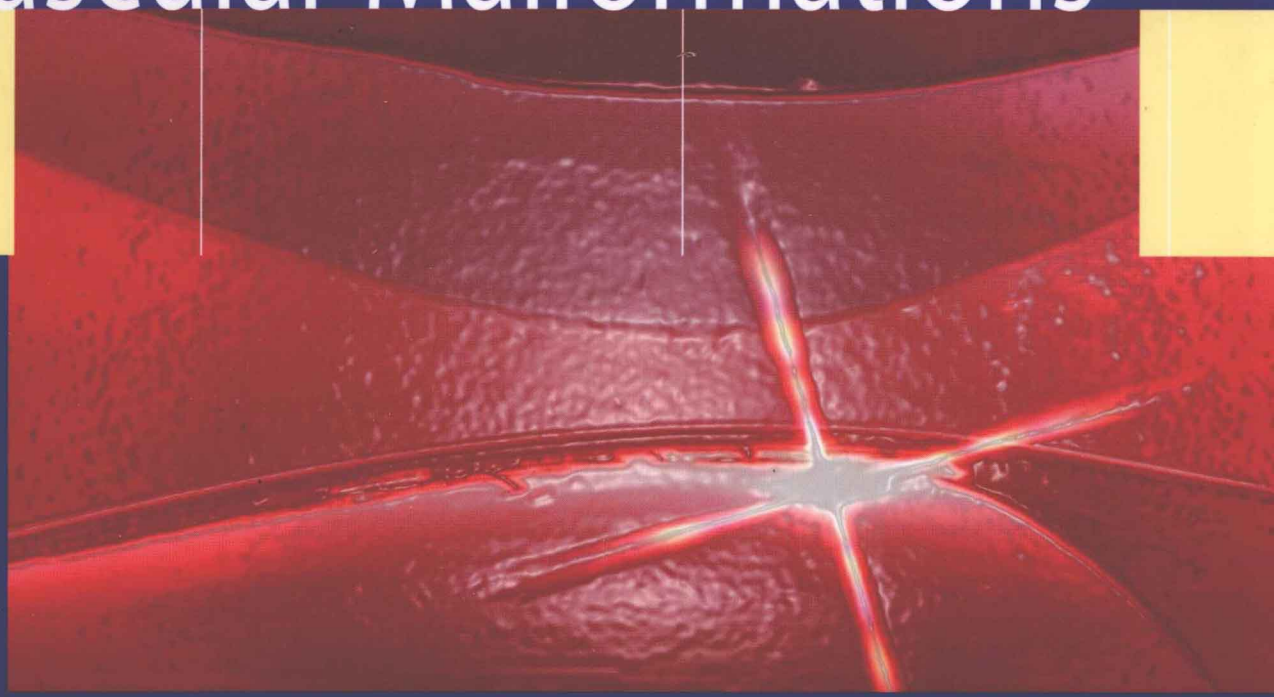
Editors

Hemangiomas and Vascular Malformations



An Atlas of Diagnosis and Treatment

Foreword by
J. Leonel Villavicencio

Springer

R. Mattassi • D.A. Loose • M. Vaghi (Eds.)

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Dedicated to our beloved teacher, Stefan Belov.
We grieve his untimely passing.
To him we dedicate the English edition of this atlas.
He showed us how to manage
the most difficult tasks in the field of angiology.
He taught us how to overcome loneliness
and how to defeat obscurantism with love, faith, and perseverance.
He led us to realize the critical difference between
simply getting good results and founding a new school of thought.
We hope that this atlas will contribute to the realization of his dream:
to systematize vascular malformations, to offer effective treatments,
and, finally, to expel angiodysplasias from the niche
of rare diseases for which no therapy is available.

Foreword

The field of congenital vascular malformations and the unfortunate patients that suffer from them will welcome this truly multidisciplinary international contribution to the study and treatment of a group of diseases that is gradually becoming better known, but not better liked, by the majority of our colleagues. Without question, the power of the internet with its access to world-wide medical literature, and the publication of complete issues of medical journals devoted to the subject of vascular malformations, have contributed to expanding knowledge and eliciting curiosity amongst physicians who some decades ago would not have wanted to deal with unusual, poorly understood and challenging diseases.

A group of authors from ten different countries, experts in their respective medical and surgical specialties, who have felt the pain of the many patients afflicted with vascular malformations, have made a combined effort to increase and update the growing knowledge of these diseases. The tremendous technological advances in non invasive as well as invasive diagnostic techniques, imaging, genetics, and therapeutic surgical and endovascular procedures, have given us new weapons with which to treat and improve the lives of many desperate patients afflicted by diseases that some years ago produced only sorrow, compassion and despair in their families and in the rare physicians who dared to tackle their problems.

Congenital vascular malformations exert a powerful and fascinating attraction in a small group of dedicated and compassionate physicians who see in these problems a challenge that is difficult to overcome. Often, the magnitude of the problem incites us to seek new avenues to solve it or, at least, to improve our patients' suffering.

A great deal of progress has been made in the understanding and management of congenital vascular anomalies. These new advances are shared with other physicians so that they can find, through the pages of this book, new ideas on how to treat their patients and hopefully, the solution to their patients' problems.

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Preface

When a curious tourist travels through an unknown country following a guidebook, at the end of his trip he may have a number of different feelings. If the land he visited was interesting and the guidebook brought him to the remarkable places and clearly explained the meaning of what he was seeing and how to move through the country, he may remain interested in his trip, love the new country and want to return in order to explore it more in detail. If the guidebook was unclear, did not give him the correct explanations or guide him to the best places, he will leave without an interest in the land, will lay down his guidebook and will not come back.

The goal of this atlas is to guide the reader through the difficult field of hemangiomas and vascular malformations, help him to understand them and give him answers to questions, mainly about practical approaches to these diseases. All the authors have made an effort to explain their topics in the simplest way with text and pictures.

If we succeed in our effort and this small atlas is appreciated by readers, we will be happy that we have accomplished the goal given to us by our teacher and friend, Professor Stefan Belov, who dedicated his life to the study of these diseases and strongly desired to publish an atlas to help colleagues understand hemangiomas and vascular malformations in order to propagate knowledge and possibilities for treatment. He passed away before he could see his idea become reality, but we hope that our efforts fulfil his wishes.

We thank all the authors who spent their time making this book a reality. Special thanks to all our friends at Springer-Verlag in Milan, and particularly Antonella Cerri and Alessandra Born.

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Part I
INTRODUCTION

Angiogenesis

1

Alice Agliano

Abstract

The vascular system is a complex network of vessels that carries oxygenated blood and nutrients throughout our bodies. It comes as no surprise that angiogenesis, the process of growing new blood vessels, occurs not only in health, but also in serious disease, where it may be either up- or down-regulated. While the growth of the vascular system is one of the earlier events of embryogenesis, angiogenesis also occurs in adulthood, during wound healing and restoration of blood flow to injured tissues. The healthy body controls angiogenesis through a perfect balance of modulators, regulated by a strong interaction between growth factors and inhibitors, the imbalance of which can lead to disease. Angiogenesis is a "common denominator" shared by diseases affecting more than one billion people worldwide; these diseases are caused by both excessive angiogenesis (cancer, diabetic eye disease, rheumatoid arthritis), and insufficient angiogenesis (coronary heart disease, stroke, delayed wound healing) [1].

Introduction

This chapter describes processes involved in angiogenesis from positive and negative regulators, through endothelial cell (EC) and pericyte recruitment, to the importance of the therapeutic anti-angiogenic applications that have recently been made available.

Vascular endothelial cells (EC) cover the entire inner surface of blood vessels in the body, and the growth of the vascular system is primarily a development process occurring during embryogenesis and postnatal life.

Early during embryogenesis, blood islands composed of progenitors of blood cells (hematopoietic cells), and endothelial progenitor cells (EPCs or angioblasts) differentiate from the mesoderm. The formation of the earliest blood vessels and their organization into a primordial vascular structure through induction, differentiation and assembly of EPCs is called vasculogenesis [2]; it may initially be a random process that subsequently becomes refined by selective branch regression and expansion.

During development and in the postnatal life the process responsible for the formation of new blood vessels is called angiogenesis. It involves the formation of vascular sprouts from pre-existing vessels, resulting in a highly branched vascular plexus; this is remodeled several times until a mature vascular system is formed. EPCs released from the bone marrow are present in peripheral blood and differentiate into ECs in the setting of both physiological and pathological neovascularization. This discovery, in the 1990s, revealed that vasculogenesis occurs also during adult life (Fig. 1.1) [3]. Angiogenesis is a fundamental process in reproduction, development and wound healing, and under these conditions is highly regulated. The ability of an organism to spontaneously develop collateral vessels represents an important response to vascular occlusive diseases which determine the severity of residual tissue ischemia. Neovascularization of ischemic cardiac or skeletal muscle may be sufficient to preserve tissue integrity and function, and in response to tissue ischemia, constitutes a natural host defense intended to maintain tissue perfusion required for physiologic organ function. In adult organisms, both hypoxia and inflammation are usually considered to be the major stimuli for ischemia-induced neovascularization [5]. Aberrant, retarded or overshooting vascularization may severely impair organ function and is often associated with diseases [6]: in arthritis, new capillaries invade the joint and destroy cartilage; while ocular neovascularization, which is often associated

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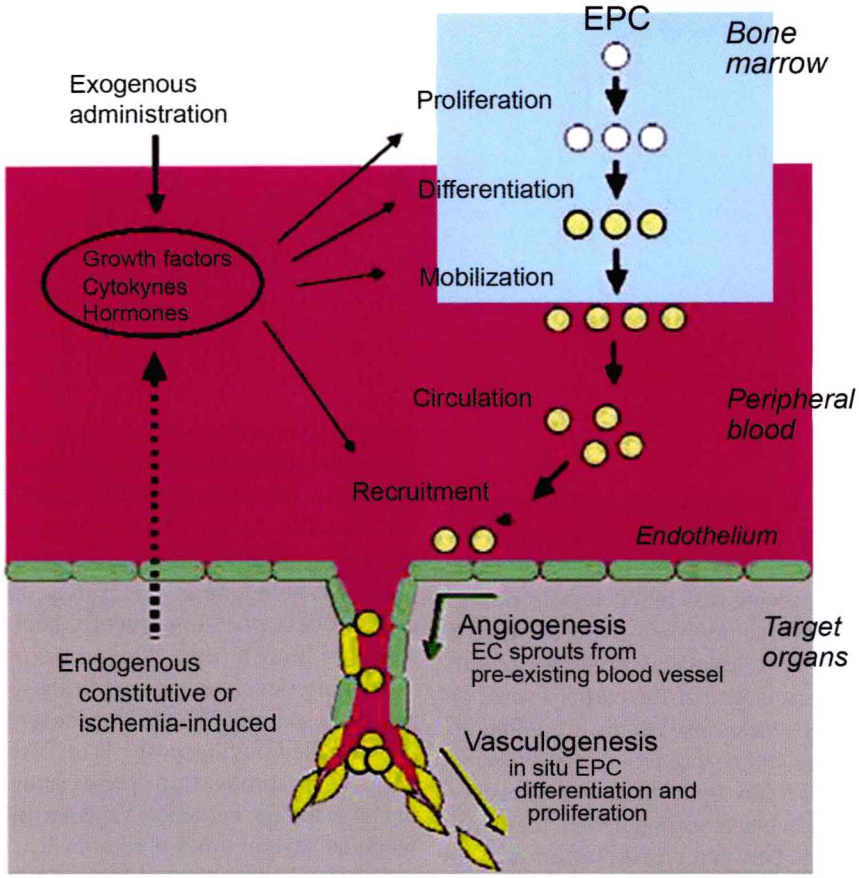

Fig. 1.1. Angiogenesis represents the classic paradigm for new vessel growth, as mature, differentiated endothelial cells (ECs) break free from their basement membrane (BM) and migrate and proliferate to form sprouts from parenteral vessels. Vasculogenesis involves participation of BM-derived endothelial progenitor cells (EPCs), which circulate to sites of neovascularization where they differentiate in situ into mature ECs. Growth factors, cytokines, or hormones released endogenously for therapeutic neovascularization act to promote EPC proliferation, differentiation, and mobilization from BM (via the peripheral circulation) to neovascular foci. Reproduced from [4], with permission

with diabetes, is the most common cause of blindness. Furthermore, uncontrolled angiogenesis may lead to psoriasis and juvenile hemangiomas, strongly vascularized lesions in which the number of newly formed vessels greatly exceeds the metabolic demand of the tissue concerned. Finally, tumor growth and metastasis are angiogenesis-dependent. A growing tumor needs an extensive network of capillaries to provide nutrients and oxygen. In addition, the new intratumoral blood vessels provide a way for tumor cells to enter the circulation and to metastasize to distant organs.

The Angiogenic Process

Angiogenesis is a complex process involving extensive interplay between cells, soluble factors and extracellular matrix components. The construction of a vascular network requires different steps, including the release of proteases from "activated" ECs, the degradation of the basement membrane surrounding the existing vessel, the migration of the ECs into the interstitial space, their proliferation, and lumen formation. The next steps involve the generation of a new basement membrane with the recruitment of pericytes, the fusion of the newly formed vessels and finally the initiation of blood flow.

In theory, organ-specific vascular patterns may result from guided sprouting. A newly formed sprout that extends into the surrounding tissue may follow tracks and gradients that provide attractive and repulsive signals. Alternatively, an initial random sprouting and vascular plexus assembly may be followed by organ-specific vessel remodeling and pruning. As of today, evidence indicates the existence of both of these mechanisms [7].

Tubular morphogenesis relies on functional specialization of individual cells, and guidance of a tubu-

lar sprout is mediated through directed migration of tip cells that utilize filopodia to sense guidance clues. ECs situated at the tip of the growing angiogenic sprout extend multiple long filopodia, and the following stalk cells proliferate and form a vascular lumen [8].

The tip cell guidance and migration depends on the shape of the gradient of vascular endothelial growth factor (VEGF) located on the filopodia. Apparently VEGF receptor-2 (VEGFR-2) activation leads to fundamentally different functional responses in the tip cell, where filopodia extension is promoted, compared to proliferation in the stalk cell, which in turn determines the initial vascular pattern [9]. An imbalance between the two processes may explain why abnormal vascular patterns develop in pathological angiogenesis.

Intussusceptive angiogenesis refers to the process by which new blood vessels grow and develop from pre-existing vasculature through insertion of tissue pillars into the capillary lumen and expansion of the latter to form new capillary networks. Four consecutive steps are described: a zone of contact is established between opposite capillary walls, then a reorganization of the inter-EC junction and central perforation occurs. An interstitial pillar core is formed and is invaded by pericytes and myofibroblasts [10].

Contrast sprouting angiogenesis is a prolonged process characterized by extensive proliferation of ECs, degradation of extracellular matrix and an increase in vascular permeability. Intussusception occurs in the virtual absence of EC proliferation, and is achieved at low vascular permeability levels.

In the studies conducted so far, it has been shown that the vascular system is initiated by vasculogenesis followed by an early sprouting phase, forming the primary capillary plexus. During the second intussusceptive phase, capillary sprouting is supervened by trans capillary pillar formation. The putative inducers of sprouting angiogenesis include angiopoietins and their Tie-receptors [11], platelet-derived growth factor (PDGF-B) [12] and ephrins and their Eph-B receptors [13] probably also influence vascular remodelling. VEGF appears to be an early promoter of angiogenesis while the angiopoietins and Tie-2 as well as the ephrins and their receptors appear to act a somewhat later stage [14] and are probably associated with the regulation of intussusception.

VEGF promotes formation of new capillary segment and vascular maturation through pericytes and smooth muscle recruitment. Such periendothelial cells are important for vascular integrity and maturation. Three major functional roles have been ascribed to pericytes: contractility, regulation of EC activity, and macrophage activity [15]. We now know that Tie-2/Angiopoietin-1 interactions maintain cell-cell contacts between ECs, stabilizing the vessel wall and promoting vessel maturation.

For angiogenesis to occur, profound changes in vessel architecture have to take place. Quiescent vessels are built up by a luminal lining in ECs, a basement membrane consisting of members of the collagen family, laminin and fibronectin, and an abluminal layer of perivascular cells, pericytes in capillaries and smooth muscle cells in larger veins and arteries. During angiogenesis, this structure needs to be temporarily destabilized. This is accomplished by secretion by ECs of matrix metalloproteinases (MMPs) which degrade the basal lamina, digest the extracellular matrix (ECM) and create additional space for the growing collateral vessel [16], and by secretion of angiopoietin-2 resulting in detachment of pericytes [17]. Another system plays a crucial role in the migration and invasion of ECs in fibrinous matrix – tissue-plasminogen activator (t-PA) and urokinase-plasminogen activator (u-PA) – where an interaction between integrins and u-PA receptor occurs. Perivascular fibrin serves as a substrate on which newly formed ECs can adhere and migrate to form new sprouts that develop into mature vessels. A considerable number of angiogenesis inhibitors have now been recognized that represent degradation products derived from extracellular matrix proteins or from proteases of the hemostatic system. The earliest recognized were angiostatin and endostatin; angiostatin exerts its anti-angiogenic activity by inducing endothelial apoptosis, while endostatin inhibits VEGF-induced migration and apoptosis [18].

During maturation, a new basement membrane is formed by the endothelium, and perivascular cells are recruited by secretion of angiopoietin-1. A number of functions have been proposed for pericytes: sensing of hemodynamic forces, the regulation of capillary blood flow and blood vessel morphogenesis. The recruitment of pericytes is mediated by PDGF-B signalling, expressed by ECs situated at the sprout tip, via PDGFRβ, expressed by the mural cells [19]. Also monocytes and macrophages contribute mechanistically and structurally to the formation of capillaries; the communication between them and ECs is bi-directional: the capillary advancement may be facilitated by monocyte presence, but their mobility can also be stimulated by ECs. Each process is mediated by VEGFR-1 which is highly expressed by monocytes. In order to form new capillaries ECs need to migrate. Since the tissue opposes mechanical resistance, the cells must create a "path" by degradation of the ECM. This process may be accomplished by monocytes and macrophages, which, because they are well equipped