Advances in Clinical Chemistry

Pages: 184
Publisher: Academic Press; 1 edition (January 4, 2019)
Format: pdf, epub
Language: English

[DOWNLOAD FULL EBOOK PDF]

Advances in Clinical Chemistry, 88

First Edition

Gregory S. Makowski

Hartford HealthCare Laboratories, Newington, CT

Hartford Hospital, Hartford, CT

Table of Contents

Gregory S. Makowski

The first volume of the 2019 Advances in Clinical Chemistry series is presented.

In Chapter 1, the role of vascular endothelial growth factor A as a biochemical factor linking cardiovascular and renal disease is explored. In this review, the impact of this pleiotropic mitogen on vascular endothelial cells and induction of angiogenic response is examined. In Chapter 2, the ability of extracellular vesicles to mediate intercellular communication is reviewed. These unique particles carry protein, nucleic acids, and lipids to distant and local target cells. Although matrix metalloproteinases are also carried, the role of these proteases on intercellular cargo remains to be elucidated. In Chapter 3, the peptidome of cancer cells is examined. The tumor microenvironment is susceptible to digestion via oncoproteases that facilitate tumor progression. The generation of these extracellular peptides may provide potential biomarkers regarding tumor aggressiveness and potential response to therapy. In Chapter 4, the expanding role of low molecular weight protein markers in chronic kidney disease are highlighted. Supplementing traditional indices with evolving markers such as neutrophil gelatinase-associated lipocalin, kidney

injury molecule-1, and N-acetyl beta-d-glucosaminidase is critical to more fully understanding disease stage and prognosis. In Chapter 5, metabolomics of exhaled breath condensate is explored. Acting as part of the natural matrix of the respiratory tract, the unique biomarkers provide new insight into the complex pathophysiology of chronic respiratory disease. In Chapter 6, evolving therapeutic technology has led to the need for innovative laboratory methods to monitor treatment. The novel bispecific immunoglobulin antibody, emicizumab, highlights one such case given its ability to bind factor IX on one arm and factor X on the other.

I thank volume eighty eight contributors as well as the peer reviewers. I thank my Elsevier colleagues, Shellie Bryant, and Denny Mansingh for expert editorial assistance and continued support.

I anticipate the first volume for 2019 will be of interest and useful. Comments and feedback are always appreciated.

I would like to dedicate volume eighty eight to Kayce on the occasion of her 40th birthday.

Chapter One Anti-angiogenic isoform of vascular endothelial growth factor-A in cardiovascular and renal disease

Ryosuke Kikuchi[a,*]; Megan Stevens[b]; Kazuhiro Harada[c]; Sebastian Olteanu[b]; Toyoaki Murohara[c]

[a] Department of Medical Technique, Nagoya University Hospital, Nagoya, Japan

[b] Institute of Biomedical and Clinical Sciences, University of Exeter Medical School, Exeter, United Kingdom

[c] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

* Corresponding author: email address: ryosuke-k@med.nagoya-u.ac.jp

Abstract

Accumulating evidence suggests that pathologic interactions between the heart and the kidney can contribute to the progressive dysfunction of both organs. Recently, there has been an increase in the prevalence of cardiovascular disease (CVD) and chronic kidney disease (CKD) due to increasing obesity rates. It has been reported that obesity causes various heart and renal disorders and appears to accelerate their progression.

Vascular endothelial growth factor-A (VEGF-A) is a major regulator of angiogenesis and vessel permeability, and is associated with CVD and CKD. It is now recognized that alternative VEGF-A gene splicing generates VEGF-A isoforms that differ in their biological actions. Proximal splicing that includes an exon 8a sequence results in pro-angiogenic VEGF-A165a, whereas distal splicing inclusive of exon 8b yields the anti-angiogenic isoform of VEGF-A (VEGF-A165b).

This review highlights several recent preclinical and clinical studies on the role of VEGF-A165b in CVD and CKD as a novel function of VEGF-A. This review also discusses potential therapeutic approaches of the use of VEGF-A in clinical settings as a potential circulating biomarker for CVD and CKD.

Keywords

VEGF-A; VEGF-A165b; Angiogenesis; Anti-angiogenesis; CVD; CKD

1 Introduction

In the 1980s, several groups identified vascular endothelial growth factor which is also known as vascular permeability factor (VEGF/VPF). Senger et al. [1] first identified VEGF as a molecule that induces vascular leakiness from the conditioned medium of tumor cell lines. Subsequently, several groups identified the VEGF molecule and cloned the cDNA. They found that this molecule was also a specific mitogen for vascular endothelial cells and could induce strong angiogenic responses [2–

5]. The VEGF gene family also includes VEGF-B, C, D, E, and placental growth factor [6–9]. Alternative exon splicing yields multiple isoforms of VEGF-A, ranging from 121 to 206 amino acids [9]. These isoforms differ in their ability to bind heparin, thereby playing distinct roles in angiogenesis [10]. VEGF-A has been shown to promote the growth and migration of vascular endothelial cells [7] and induce angiogenesis in a variety of animal models in vivo [3]. VEGF-A has also been shown to mobilize endothelial progenitor cells (EPCs), which are believed to contribute to postnatal vasculogenesis and the re-endothelialization of injured vessels [11,12].

Most of the spliced isoforms of VEGF-A were considered to exclusively elicit angiogenesis; however, in 2002, Bates et al. identified a novel family of VEGF-A isoforms arising from an alternative 3′ splice-site in the terminal exon 8 [13]. Proximal splice-site selection (PSS) in exon 8 results in the classical pro-angiogenic VEGF-Axxx isoforms, where xxx denotes the number of amino acids. On the other hand, distal splice-site selection (DSS) results in a family of anti-angiogenic VEGF-Axxxb isoforms (Fig. 1). VEGF-Axxxb isoforms can still dimerize and bind to VEGF receptor 2 (VEGFR-2) but cannot bind to the neuropilin receptor, and thereby do not induce intracellular signaling in endothelial cells, which is required for angiogenesis [14]. Because VEGF-Axxxb isoforms occupy the VEGF-A binding site of VEGFR-2, VEGF-Axxxb isoforms function as anti-angiogenic molecules [15].

Fig. 1 Alternative splicing of exon 8 of the VEGF-A gene. The VEGF-A pre-mRNA is comprised of eight exons; inclusion/exclusion of these exons gives rise to isoforms with differing amino acid lengths. An alternative 3′ splice site in the terminal exon (exon 8) results in a functionally different family of isoforms, termed VEGF-A xxxb. These isoforms have the same number of amino acids but a different C-terminus sequence. PSS, proximal splice site; DSS, distal splice site; UTR, untranslated region.

In this booklet, we summarize and discuss the progress of recent research on the anti-angiogenic VEGF-Axxxb in cardiovascular and renal disease. 2 Vascular endothelial growth factor-A (VEGF-A) 2.1 Angiogenesis

As mentioned, VEGF-A was first identified as a vascular permeability enhancing factor from the conditioned medium of tumor cell lines [1]. Subsequently VEGF-A was recognized as a potent angiogenic growth factor in addition to a permeability-inducing factor [2,3]. Among the VEGF-A isoforms, VEGF-A165 is the most predominant, with respect to both quantity and biological activity. VEGF-A165 is expressed in a variety of tumors and the extent of its expression is correlated with general tumor activities such as progression, invasion, and metastasis [16]. Gene ablation studies have revealed that VEGF-A plays pivotal roles in developmental vasculogenesis and postnatal angiogenesis. Surprisingly, a defect in a single VEGF-A allele results in a lethal embryonic condition due to a defect in vasculogenesis [17,18].

The VEGF family of proteins binds to several cell membrane receptor tyrosine kinases. The VEGF receptor (VEGFR) family consists of three subtypes, VEGFR-1, VEGFR-2, and VEGFR-3. All three receptor subtypes contain seven immunoglobulin-like domains in the extracellular region and a tyrosine kinase domain in the intracellular region [6–9]. VEGFR-1 and VEGFR-2 are expressed in endothelial cells and hematopoietic stem cells. VEGFR-1 is also expressed in monocytes and macrophages. On the contrary, VEGFR-3 expression is restricted to lymphatic endothelial cells. The VEGF proteins have different affinities for each of the three VEGFR subtypes. VEGF-A activates VEGFR-1 and VEGFR-2. In addition, heparin and neuropilin-1 can bind VEGF-A165 and are involved in VEGF-A-induced signal transduction of the VEGFRs [7,19].

VEGFR-1, also known as fms-like tyrosine kinase-1 (Flt-1), is slightly activated in response to VEGF-A; however, VEGFR-1 binds VEGF-A with a 10-fold higher affinity compared to VEGFR-2. VEGFR-1 mediates the proliferation of endothelial cells, migration of monocytes/macrophages,

and recruitment of bone marrow-derived endothelial and hematopoietic precursor cells [20–23].

VEGFR-2, also known as KDR in humans or Flk-1 in mice, has more potent tyrosine kinase activity than VEGFR-1 despite a lower affinity for VEGF-A binding. VEGFR-2 predominantly functions as a mediator of VEGF-induced intracellular signaling and thus, angiogenesis. Stimulation of VEGFR-2 promotes growth, migration, and tube formation in vascular endothelial cells and enhances vascular permeability. Failure to form blood vessels results in a lethal embryonic defect in VEGFR-2 deficient mice, indicating that VEGFR-2 plays a critical role in establishing circulatory systems during this stage of development [24].

Of the VEGFR-2 phosphorylation sites, 1175-PY has been shown to be essential for VEGF-A-induced proliferation of vascular endothelial cells, since intracellular injections of an anti-1175-PY-neutralizing antibody significantly suppressed VEGF-induced cell proliferation [25]. Furthermore, 1175-PY was found to be a binding and activation site for phospholipase C (PLC)-γ, which activates the PKC-Ca2 +-c-Raf-MEK-MAPK pathway and thereby stimulating endothelial proliferation [26]. 2.2 Anti-angiogenic isoforms of VEGF-A

VEGF-A is known to have several isoforms in humans, including VEGF-A121, VEGF-A165, VEGF-A189, VEGF-A206, and some other minor isoforms. The major VEGF-A isoforms interact with VEGFR-2 to promote angiogenesis. However, VEGF-A165 is the most predominant isoform because the shorter isoforms have a much lower binding affinity for VEGFR-2 [27]. Furthermore, longer isoforms have lower bioavailability due to their binding to heparin-containing proteoglycans in the extracellular matrix [28]. In contrast, VEGF-A165b is an alternative splicing isoform generated by differential splice site selection in the 3′-untranslated region of the VEGF-A gene. It was originally identified in the kidney in renal cell carcinoma [13]. Six amino acids in the C-terminus of VEGF-A165b are structurally different from those of VEGF-A165 despite them both having the same total number of amino acids. VEGF-A165b can interact with VEGFR-2 with the same affinity as VEGF-A165. However, the altered C-terminal sequence causes insufficient activation of VEGFR-2 due to its inability to bind to the co-receptor, neuropilin-1 [29], resulting in anti-angiogenic activity. 2.3 Therapeutic angiogenesis

It has been established that therapeutic control of angiogenic responses is a treatment option for different diseases. Since tumor cells release VEGF themselves and thereby stimulate nutritional vessel growth to feed the tumor, researchers have attempted to inhibit VEGF function to regress tumor growth, which is termed “tumor dormancy therapy” [30]. This concept actually resulted in the generation of a humanized monoclonal antibody drug against VEGF, bevacizumab [31]. On the other hand, Isner et al. utilized the robust angiogenesis function of VEGF-A for therapeutic neovascularization in patients with critical limb ischemia [32,33]. In a series of animal experiments, Isner et al. showed that injection of expression plasmid vectors encoding the VEGF-A gene into either the arterial walls or directly into the ischemic skeletal muscles induced angiogenesis in a rabbit hind limb ischemia model [34,35]. After careful examination of the safety issues using a swine model, they began a human trial of angiogenic VEGF-A gene therapy in patients with critical limb ischemia [32,33]. In the initial clinical trials, they found a significant increase in collateral vessels in critically ischemic skeletal muscle. Later, several clinical trials were conducted to investigate the induction of angiogenesis in patients with critical limb ischemia and ischemic heart disease using either plasmid vectors or adenovirus vectors expressing the VEGF-A gene, or recombinant VEGF-A protein [36–39]. Although these clinical trials showed some level of angiogenic responses, therapeutic drugs were not generated because of the limited efficacies and potential side effects such as edema and arterial inflammation. 3 VEGF-A and cardiovascular disease

VEGF-A produces various isoforms with distinct biological activities through alternative mRNA

splicing, with not only pro-angiogenic, but also anti-angiogenic effects. VEGF-A165b is the most well-studied and predominant anti-angiogenic isoform of VEGF-A. VEGF-A165b prevents the physiological consequences of the pro-angiogenic behavior of VEGF-A, such as increased vascular permeability, blood vessel growth, and vasodilatation. Recently, several reports have demonstrated the remarkable increase in VEGF-A165b in some diseases characterized by impaired angiogenesis, vascular damage, and hypoxia such as that observed in obesity, peripheral artery disease (PAD), and coronary artery disease (CAD). Moreover, insufficient angiogenesis could inhibit the healing process of the myocardium and endothelial cells after acute myocardial infarction (MI).

In this section, we will discuss the role of VEGF-A165b in cardiovascular disease, obesity, diabetes mellitus (DM), PAD, and CAD. 3.1 Obesity and diabetes mellitus

Obesity and its associated metabolism-related diseases have emerged as one of the most critical health care problems in the US and worldwide. Currently, nearly 70% of the US population is overweight or obese [40]. White and brown adipose tissues are highly vascularized, and since adipose tissue grows and regresses during changes in weight, precise regulation of angiogenesis within adipose tissues is required to maintain an adequate delivery of nutrients and oxygen. Therefore, a number of studies have suggested the importance of the microvasculature in controlling adipose tissue inflammation or metabolic function [41–43]. Studies of obese patients and mice have demonstrated that white adipose tissues (WAT) in these subjects display capillary rarefaction. VEGF-A levels in WAT have been reported to be decreased [44], increased [45,46], or unchanged [47] in obesity. These results are yet to be clarified. However, there is a general consensus that increases in WAT are associated with insufficient angiogenic responses to hypoxia.

A number of studies have demonstrated a close relationship between vascular and fat components as modulated by various growth factors, including adipokines or cytokines. Angiogenic growth factors and cytokines implicated in adipose tissue angiogenesis include the VEGF family, hepatocyte growth factor, platelet derived growth factor, and fibroblast growth factor. The role of VEGF-A, specifically, in adipose tissue angiogenesis has been the main factor studied.

Circulating levels of VEGF-A are increased in obese patients compared to lean controls, and VEGF-A levels decrease in obese patients after Roux-en-Y gastric bypass surgery [48]. Adipose tissue-specific VEGF-A knockout mice have reduced capillary density, increased inflammation or apoptosis in the adipose tissue, and develop severe insulin resistance and glucose intolerance when fed a high-fat diet [42]. In contrast, it has been reported that adipose-specific VEGF-A transgenic mice have an increased adipose capillary density and improved glucose tolerance under high-fat diet conditions [42]. However, a “VEGF-A paradox” exists, despite increased circulating levels of VEGF-A in obesity [49]. Endogenous angiogenesis inhibitors, such as endostatin and thrombospondin [50], may provide a counter-balance in regulating vessel growth and remodeling within adipose tissues. However, their interactions with VEGF-A in obese subjects are yet to be fully understood.

Recently, the first evidence of a relationship between anti-angiogenic isoforms of VEGF-A and human visceral adipose tissue was reported [51]. The expression levels of VEGF-A165b were significantly higher in visceral adipose tissues compared to subcutaneous adipose tissues in obese patients. On the other hand, the expression levels of VEGF-A165a, which is the pro-angiogenic isoform of VEGF-A, were significantly lower in visceral adipose tissues compared to subcutaneous adipose tissues in obese patients (Fig. 2). Consistent with findings in cancer biology, VEGF-A165b led to impaired angiogenesis and was found to be strongly correlated with reduced capillary growth in adipose tissues. Moreover, it has been shown that persistently obese patients that had previous bariatric surgery and were attempting weight loss had reduced circulating levels of

VEGF-A165b [51]. This result suggests that anti-angiogenic isoforms of VEGF-A have potential for use in clinical settings, which opens up the possibility of interventions targeted directly against VEGF-A165b to treat obesity and related disorders.

Advances in Clinical Chemistry, Volume 88, the latest installment in this internationally acclaimed series, contains chapters authored by world-renowned clinical laboratory scientists, physicians and research scientists. The serial discusses the latest and most up-to-date technologies related to the field of clinical chemistry, and is the benchmark for novel analytical approaches in the clinical laboratory. Provides the most up-to-date technologies in clinical chemistry and clinical laboratory scienceAuthored by world renowned clinical laboratory scientists, physicians and research scientistsPresents the international benchmark for novel analytical approaches in the clinical laboratory

---

Applied microbiology pdf - This platform is specific in books sharing across various users and nations, and ebook Advances In. Clinical Chemistry Volume 71 may be also saved from here. Advances in Clinical Chemistry, Vol. 37 - Best books online - The newcomer to the field of clinical chemistry is faced with the daunting of diagnosing diseases and other advances which relate to clinical chemistry. The aim of this book is to provide basic information regarding all branches of the subject â€ŽAdvances in Clinical Chemistry on Apple Books - Advances in Clinical Chemistry and Laboratory Medicine. Edited by Renz, Harald DOI (Book): https://doi.org/10.1515/9783110224641 · Copyright Clearance Advances in clinical chemistry - Book Review: â€œAdvances in Clinical Chemistry.â€• Show all Article Information, PDF download for Book Review: “Advances in Clinical Chemistry. Harvard physics book - Xing Fu Tang Singapore - Clinical Chemistry is an exciting field that combines analytics and instrumentation with. clinical chemistry, which encompasses a wide variety of tests and is a. Enzymology Pdf - Mode Pur - This fully revised and updated book puts the information right at the fingertips of any Clinical Chemistry is a interdisciplinary branch between chemistry and issues of chemical change in the archaeological materials, in order to advance the IFCC: The International Federation of Clinical Chemistry and - [1] With advances in technology and the rise of modern medicine, the evolving The purpose of this article is to analyze the current state of clinical chemistry.. and medicine, residents are beginning to see these fields as novel and important. Advances in Clinical Chemistry, Vol 88 - Benchmark for Novel - DUBLIN--(BUSINESS WIRE)--Dec 16, 2019--. The

â€œAdvances in Clinical Chemistry, Vol 88â€• book from Elsevier Science and Technology has been added to 9780120103416: Advances in Clinical Chemistry, Volume 41 - Clinical Chemistry Trainee Council clinical laboratory science, providing 2,000 pages per year of peer-reviewed papers that advance the science of the field. Buy Advances In Clinical Chemistry Vol 37 Book Online at - CJON is a vehicle to advance the mission of ONS, which is to promote excellence in Clinical Chemistry is the leading international journal of clinical laboratory. education articles, book reviews, employment opportunities, and updates on. Clinical Chemistry: Home - Buy a discounted Hardcover of Advances in Clinical Chemistry Volume 41 online from Australia's Earn 345 Qantas Points on this Book

---

Relevant Books

[DOWNLOAD] - Download book May 29 2019 online

[DOWNLOAD] - Book I Love You Like That: A Novel pdf

[DOWNLOAD] - Download book Lovesick free

[DOWNLOAD] - Download Free The Politics of Crisis Management: Public Leadership Under Pressure

[DOWNLOAD] - Download ebook How to be Made New free pdf