

Snake Venom Disintegrins in Angiogenesis

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Angiogenesis, the formation of new blood vessels, plays a critical role in various physiological and pathological conditions. Snake venom disintegrins (SVDs) have been identified as significant regulators of this process.

snake venom

angiogenesis

integrins

1. Introduction

1.1. Angiogenesis

Angiogenesis is a complex biological process involving the formation of new blood vessels from preexisting vessels [1]. It plays a crucial role in various physiological and pathological conditions, including embryogenesis, wound healing, and tumor growth [2]. The process of angiogenesis is tightly regulated by multiple signaling pathways and factors. Matrix metalloproteinases are primarily responsible for degrading the basement membrane surrounding existing blood vessels, allowing endothelial cells to migrate and proliferate toward the angiogenic stimulus [3]. One of the key proangiogenic factors is vascular endothelial growth factor (VEGF), which is essential for the formation of new blood vessels during embryonic development and is produced by various cell types, including tumors [4]. VEGF binds to specific receptors on endothelial cells, promoting their survival, migration, and differentiation [5][6]. Other factors involved in angiogenesis regulation include fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and angiopoietins [3]. These factors act synergistically to ensure the proper formation and remodeling of blood vessels. The regulation of angiogenesis is maintained through a dynamic balance between proangiogenic and antiangiogenic factors. This balance can be disrupted in various diseases, leading to either excessive or insufficient blood vessel formation [1]. Insufficient angiogenesis, on the other hand, can lead to tissue ischemia, impaired wound healing, and various cardiovascular diseases [2]. Peripheral artery disease (PAD) is an example where the narrowing or blockage of blood vessels reduces blood flow to the legs or arms, resulting in pain, skin ulcers, and an increased risk of amputation [2]. Therapeutic angiogenesis, which aims to promote blood vessel formation, has been investigated as a potential treatment approach for PAD, with the administration of VEGF or the use of gene therapy [1].

It is important to emphasize that integrins, a group of transmembrane proteins that play a crucial role in cell adhesion and communication between cells and the extracellular environment, are the focus of interest, as they play an important role in angiogenesis [7].

1.2. Integrins

Integrins play an essential role in the regulation of biological processes such as cell migration, adhesion, proliferation, differentiation and signaling [8]. Integrins are heterodimeric glycoproteins consisting of alpha and beta subunits, which together form a complex transmembrane receptor [9]. A total of 18 alpha subunits and eight beta subunits have been identified in mammalian cells, allowing the formation of 24 different heterodimers. The α subunit determines affinity to the extracellular matrix component (ECM), while the β subunit associates with cytoplasmic structural and regulatory proteins. These subunits have a long transmembrane domain and a short cytoplasmic domain associated with cytoskeletal proteins [10]. Although integrins are constitutively expressed on the cell surface, they need to be activated to interact with their ligands [11]. Such activation can occur in the presence of chemokines and cytokines and is characterized by a conformational change at the extracellular integrin domain that exposes their binding sites on the α and β subunits, allowing them to interact with their ligands on the ECM or with proteins on the membranes of neighboring cells. This interaction is primarily controlled by a conserved tripeptide pattern of arginine, glycine, and aspartate, commonly known as the Arg-Gly-Asp motif (RGD) [12][13][14]. They are crucial for cell adhesion, migration, and signal transduction by mediating interactions between cells and ECM proteins. The main role of these molecules is to provide a link between the cytoskeleton of the cell and certain ECM components, such as fibronectin, vitronectin, laminin, and collagen. In addition, they are responsible for triggering intracellular signal transduction pathways upon interaction with the ECM. Integrins can undergo conformational changes that influence their ligand binding properties and downstream signaling events [15]. They possess a unique arrangement of cysteine residues that enables them to adopt a compact and stable structure consisting of a well-defined loop disulfide array [16]. This structural motif is critical for their high-affinity binding to integrins as it allows them to bind to specific integrin subunits and block their ligand binding sites. In addition, integrins also interact with growth factor receptors to regulate cell migration, blood vessel development, and angiogenesis. Importantly, the understanding of the mechanism of action of integrins paralleled the discovery of proteins from snake venoms, called disintegrins, which act as potent inhibitors of platelet aggregation and integrin receptor-dependent cell adhesion [17][18].

1.3. Snake Venom Metalloproteinases and Snake Venom Disintegrins

Snake venom metalloproteinases (SVMPs) are a major component of most crotalid and viperid venoms [19]. SVMPs are known to be a class of key toxins involved in the pathophysiology associated with viperid venoms and are classified into classes and subclasses from P-I to P-III according to the organization of their domains, as shown in **Figure 1** [20]. In general, class PI includes metalloproteinases that have only a catalytic domain containing zinc; class PII, metalloproteinases that have a catalytic domain followed by a disintegrin domain containing the tripeptide RGD (arginine-glycine-aspartic acid); and class PIII, metalloproteinases that have a catalytic domain, a disintegrin-like domain, and a cysteine-rich domain [21].

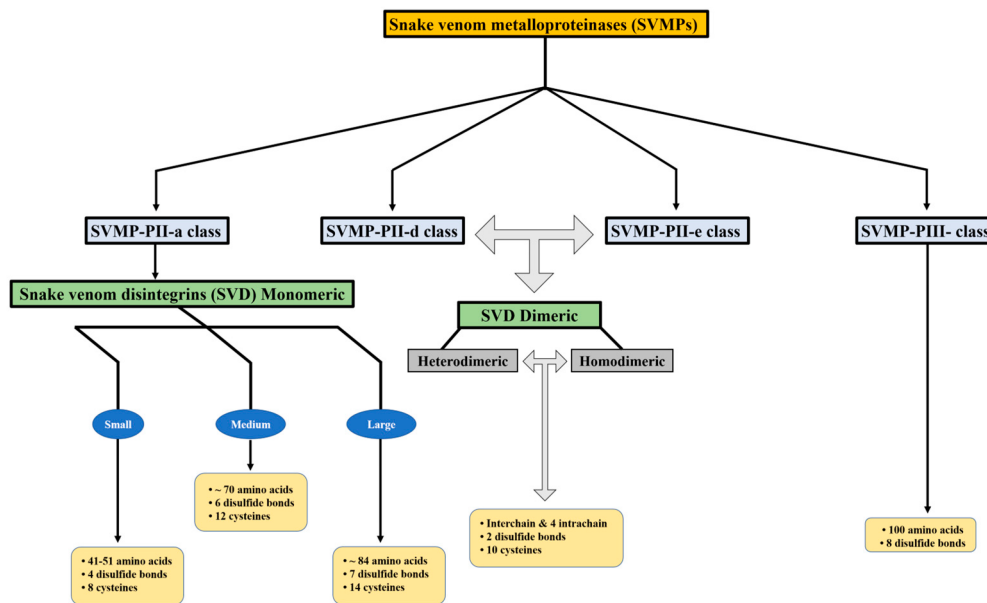


Figure 1. Disintegrins are categorized according to their structural composition. The number of disulfide bonds and length of the polypeptide chain determine this categorization.

Snake venom disintegrins (SVDs) are a class of proteins derived from SVMPs. The disintegrins present in snake venoms can be formed in the venom gland in two distinct ways: (1) By proteolysis of SVMPs of class P-II, where cleavage occurs between the catalytic domain and the disintegrin domain, leaving only the disintegrin domain. These disintegrins are known as RGD-dependent disintegrins, which are abundant in viperid venoms and contain the sequence XGD (X-Gly-Asp), MLD (Met-Leu-Asp), or K/RTS (Lys/Arg-Thr-Ser) on the exposed surface of the loop that specifically binds to integrins on the surface of different cell types [22][23]. The amino acid sequences immediately adjacent to the RGD site of disintegrins could form an extended RGD locus that, in conjunction with the conformational representation of the RGD sequence, could be involved in determining integrin selectivity and affinity [13]. The family of disintegrins containing the RGD motif is widely recognized as the most extensive and well-studied group. Most of these units function as monomers (small, medium, or large), but a subgroup has the ability to combine into dimers and form homo- or heterodimers [24]. (2) Proteolysis of class P-III SVMPs results in fragments that covalently link the disintegrin-like and cysteine-rich domains and are referred to as ECD-disintegrin-like/cysteine-rich domains (Figure 2). This disintegrin-like domain has a sequence of non-RGD tripeptides in its binding site [21][25].

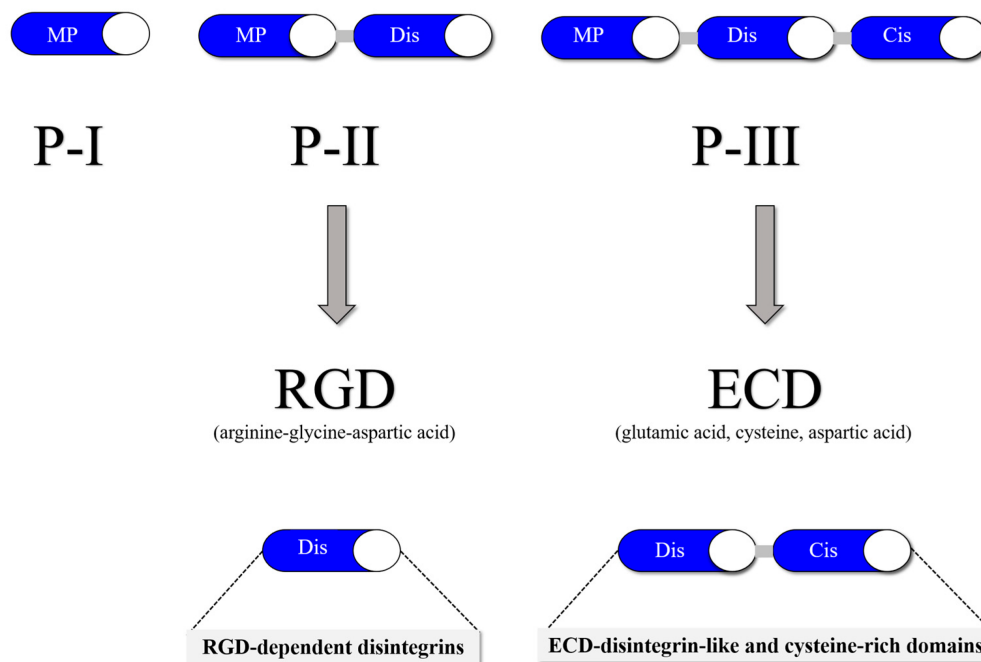


Figure 2. SVMP classification is divided into three classes: P-I (20–30 kDa), which in its mature form contains a metalloproteinase domain; P-II (30–60 kDa), which contains a disintegrin domain linked to the C-terminus of the metalloproteinase domain; and P-III (60–100 kDa), which consists of a metalloproteinase domain, a disintegrin-like domain and a cysteine-rich domain.

2. Utilization of SVD as Pro-Angiogenic Agents

While disintegrins are usually known for their antiangiogenic properties, recent research has also revealed their potential as proangiogenic agents. Alternagin-C (ALT-C) is an ECD-containing disintegrin-like/cysteine-rich disintegrin isolated from the venom of the snake *Rhinocerocephalus alternatus* that induces endothelial cell proliferation and angiogenesis both in vitro and in vivo by upregulating the expression of VEGF and its receptors [26]. ALT-C binds to the major collagen receptor $\alpha2\beta1$ integrin, inhibiting cell adhesion to collagen, triggering downstream signaling molecules, and inducing a significant increase in several genes related to cell cycle control (VEGF, inducible early growth response, interleukin 11, early growth response 2 and 3, and the insulin-induced gene) [27]. ALT-C also induced significant cytoskeleton dynamic changes with the polymerization of F-actin, focal adhesion kinase (FAK), and phosphoinositol 3-kinase (PI3K) activation, as well as erk-2 translocation [28]. ALT-C induced the formation of new vessels, and the expression of VEGF in the injured tissue indicated the usefulness and effectiveness of ALT-C as a proangiogenic disintegrin-like protein [29].

2.1. Tissue Regeneration and Wound Healing

Wound healing and regeneration are multifaceted biological phenomena that occur throughout the human lifespan. After an injury, various cellular processes are immediately initiated and coordinated to initiate a response [30]. Improper repair procedures can cause this process to be delayed, with immediate consequences for the individual, including physical discomfort, impaired rehabilitation progress, limb amputation, and in the most severe cases,

death from septicemia [31]. Like other natural healing processes, the repair mechanism also relies on the coordination of different cell activities vital for recovery. These activities encompass cell survival, growth, movement, and the creation of new cells. They are orchestrated through cellular interactions with both the extracellular matrix (ECM) that surrounds them and with other neighboring cells. These interactions are made possible by specialized receptors found on cell membranes, which belong to the integrin family [32]. A recent study led by Ferreira and colleagues [33] used an in vivo model with subcutaneous sponge implants to investigate the potential of jararhagin-C (Jar-C). Their goal was to understand how Jar-C might stimulate collagen deposition and the production of important soluble substances, including VEGF and transforming growth factor beta-1 (TGFβ-1). These substances play important roles in processes such as angiogenesis and fibrogenesis, which are closely associated with tissue repair. The results of the study suggest that Jar-C may have positive effects on tissue repair by promoting these natural responses in the body. Moreover, Alternagin-C is also the subject of research. Within 7 days, this cysteine-rich, disintegrin-like protein accelerates wound healing in rats by increasing type I collagen deposition and fibroblast density and reducing inflammation [34]. In another study, Rabelo et al. [35] revealed that ALT-C increased collagen synthesis in mouse fibrovascular tissue. From the above results, it can be concluded that SVD has the ability to promote angiogenesis by modulating endothelial cell behavior, facilitating cell migration, and upregulating proangiogenic factors.

2.2. Cardiovascular Diseases

Integrins have a considerable influence on the development of cardiac fibrosis. The diseased heart exhibits altered expression and integrin functions [36]. Targeting integrins and their associated proteins can be a potential therapeutic target for myocardial fibrosis. Certain disintegrins have been extensively researched and subsequently approved by the Food and Drug Administration (FDA), making them viable pharmaceutical agents in modern medicine. Tirofiban, marketed as Aggrastat®, is a synthetic pharmaceutical agent developed by Medicure International, Inc. of Winnipeg, MB, Canada. This drug is derived from the RGD domain found in Echistatin [37]. In addition, this compound undergoes a chemical change that increases its affinity for platelet glycoproteins, especially GPIIb/IIIa receptors [38]. Therefore, this drug is able to prevent platelet aggregation and other thrombotic activities by competing with fibrinogen for the RGD domain recognition site in the GPIIb/IIIa receptor [37][39][40]. In 1998, the Food and Drug Administration (FDA) approved tirofiban as a therapeutic intervention for acute coronary syndrome [41]. Additionally, in 1998, the FDA approved eptifibatide (Integrilin®, Millennium Pharmaceuticals, Inc., Cambridge, MA, USA), an alternative molecule to inhibit platelet aggregation. Schering-Plough subsequently acquired license rights to this drug in 2005 [42]. The development of this active substance took place in parallel with research into synthetic peptide analogs of barbourin, a disintegrin from *Sistrurus miliarius barbouri* [43].

Cardiovascular diseases, including acute myocardial infarction, coronary artery disease, endothelial dysfunction, and chronic ischemia, are considered one of the leading causes of death worldwide [44]. Therefore, there is great interest in pharmaceutical agents that offer a new and effective therapeutic approach to improve the functionality of the myocardium and/or facilitate its regeneration after injury. Platelets have been studied extensively because of their crucial role in primary hemostasis, the body's initial response to arterial injury. Only recently, however, have researchers begun to study their contribution to immunological processes, cardiovascular disease, cancer, and

various other pathological conditions [45][46][47]. The glycoprotein receptor GPIIb/IIIa has been extensively studied as a primary receptor on platelets for the functional effects of snake venom-derived disintegrins. Each individual platelet is equipped with approximately 80,000 GPIIb/IIIa receptors located both on the plasma membrane and in the α -granules [48]. After activation, the number of these receptors increases significantly, facilitating the formation of a permanent hemostatic plug [49]. Certain SVDs, including those of *Agkistrodon piscivorus piscivorus* and *Echis carinatus sochureki*, namely, Applagin and Echistatin, show remarkable affinity for the RGD motif on resting platelets. This specific binding results in the potent inhibition of platelet aggregation. Consequently, SVDs have emerged as promising candidates for drug development to antagonize platelet integrins, demonstrating their pharmacological potential as both platelet aggregation inhibitors and antithrombotic agents. From a clinical perspective, these drugs can effectively reduce the likelihood of acute ischemic episodes and serve as preventive measures against thrombotic sequelae. RGD disintegrins have been extensively studied and are considered the largest family within this category [17][50]. A number of disintegrins have been extracted from snake venoms, particularly viper venom, and characterized as agents with antithrombotic properties [51]. For example, trigramin inhibits platelet aggregation in platelet-rich plasma triggered by adenosine diphosphate (ADP), collagen, or epinephrine [52]. The same disintegrin has been shown to inhibit platelet aggregation both in vitro and in vivo by preventing the binding of fibrinogen to platelets induced by agonists of aggregation, such as ADP-activated platelets [53].

By promoting angiogenesis, SVDs have shown promise in preclinical models of cardiac ischemia. Previous studies have shown that administration of ALT-C in a single dose after a period of 7–9 days resulted in an increase in cardiac muscle contractile force in fish [29][54]. This intervention also led to an upregulation of the expression of important proteins involved in calcium processing and an increase in the level of VEGF in the myocardium. In addition, administration of ALT-C stimulated angiogenesis and thus protected cardiomyocytes from the deleterious effects of negative tropism caused by hypoxia/reoxygenation. Evaluation of the safety and efficacy of disintegrins in promoting angiogenesis and improving cardiac function in patients with cardiovascular disease requires the conduct of clinical trials.

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