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Angiogenesis and growth factor modulation induced by alternagin C, a snake venom disintegrin-like, cysteine-rich protein on a rat skin wound model

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ABSTRACT

In this work, we show that alternagin-C (ALT-C) and ALT-C PEP, a peptide derived from its sequence, were able to induce angiogenesis in wounded rat skin. A spherical cutaneous excision was made in the back of each animal and treated with three different concentrations of ALT-C or ALT-C PEP. After that, the skin was removed and analyzed to verify the presence of new vessels and the expression of growth factors. ALT-C and ALT-C PEP induced the formation of new vessels and modulated the expression of growth factors, mainly VEGF and FGF1. The expression of VEGF increased and it could be detected up to 7 days after injury. FGF1 also significantly increased, but at a lesser extent than VEGF. In conclusion, the present study shows for the first time the stimulation of angiogenesis in an injured tissue by a disintegrin-like protein and that ALT-C may exert this effect by modulating the expression of growth factors.

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Angiogenesis is a biological process by which new capillaries are formed from pre-existing vessels. It is essential in many physiological (embryo development, ovulation and wound repair) and pathological conditions (arthritis, diabetic retinopathy and tumors) [1–4]. Angiogenesis involves multiple steps, including migration and proliferation of endothelial cells, lumen formation, connection of new vascular segments with the preexisting circulation, and extensive remodeling of the extracellular matrix (ECM)[1] by proteases [5]. Angiogenesis is also influenced by integrins expressed on endothelial cells, vascular smooth muscle cells, fibroblasts, and platelets. These cells process signals from their microenvironment and respond by altering their cell–cell and cell–matrix adhesion, which allow migration and vascular remodeling over the period of days to weeks [6,7].

Angiogenesis depends on the stimulation of endothelial growth by cytokine production such as the vascular endothelial growth factor (VEGF); fibroblast growth factor-1 (FGF-1); transforming growth factor-α and -β (TGF-α and -β); platelet-derived growth factor (PDGF); insulin-like growth factor-1 (IGF-1), among others [8,9]. Several VEGF isoforms participate in the regulation of normal and pathological angiogenesis (VEGF-A, VEGF-B) and lymphangiogenesis (VEGF-C, VEGF-D). VEGF has also been implicated in practically every stage of angiogenesis, yet its role in the initiation of new blood vessel creation appears to be the most important. VEGF interacts with three subtypes of VEGF receptors present in the cellular membrane of endothelial cells known as VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3 (Flt-4) [10]. All these receptor types possess an internal tyrosin kinase domain and interaction of VEGF with particular subtypes of receptors activates a circuit of signaling pathways, e.g. PI3K/Akt, Ras/Raf- MEK/Erk, eNOS/NO, and IP3/Ca^{2+} [11–13]. These pathways participate in the generation of specific biological responses that may induce proliferation, migration, vascular permeability increase, or promotion of endothelial cell survival. The data in the literature suggest a similarity or overlap in the functional responses of cells to the engagement of VEGF/VEGF receptors and extracellular matrix/integrin systems during angiogenesis. Direct communication between VEGF and integrins is not completely understood yet but may reflect a convergence or cross talking of their downstream intracellular signaling pathways [14,15]. Integrins are a family of multifunctional cell adhesion receptors involved in a

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[1] *Abbreviations used:* ECM, extracellular matrix; VEGF, vascular endothelial growth factor; FGF-1, fibroblast growth factor-1; PDGF, platelet-derived growth factor; IGF-1, insulin-like growth factor-1; ALT-C, alternagin-C.

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variety of biological processes. Particularly the integrin α2β1, the major collagen receptor on both endothelial cells and platelets, has been implicated in endothelial cell proliferation, cell survival and tube formation of endothelial cells [16].

Snake venoms contain unique components that affect cell–matrix interactions, such as the disintegrin proteins. Disintegrins are non-enzymatic proteins released by the processing of precursor forms that have a metalloprotease domain. Snake venom metalloproteases (SVMP) are classified into classes I–III and several subclasses according to: (i) the presence or not of distinct domains, including the disintegrin domain; (ii) the proteolytic processing of these domains, which yields different forms of disintegrins and disintegrin-like proteins; and (iii) the post-translational dimerization of these domains (see Refs. [17,18] for recent reviews). The PI class of SVMP comprises proteins that have the catalytic domain only. Members of the PII class have a disintegrin domain, which is promptly released as a free disintegrin in the secreted venom. The disintegrin domain has been reported as a strong integrin ligand, which mediates several biological effects that suggest many potential applications [19]. Most disintegrins released from PII SVMP precursors have an RGD motif that is relevant for β3 (e.g. αIIbβ3, platelet fibrinogen receptor, and αVβ3, vitronectin receptor) and β1 integrin binding (e.g. α5β1, fibronectin receptor) [20–22].

SVMPs belonging to the III class have additional C-terminal domains named disintegrin-like and cysteine-rich domains, which

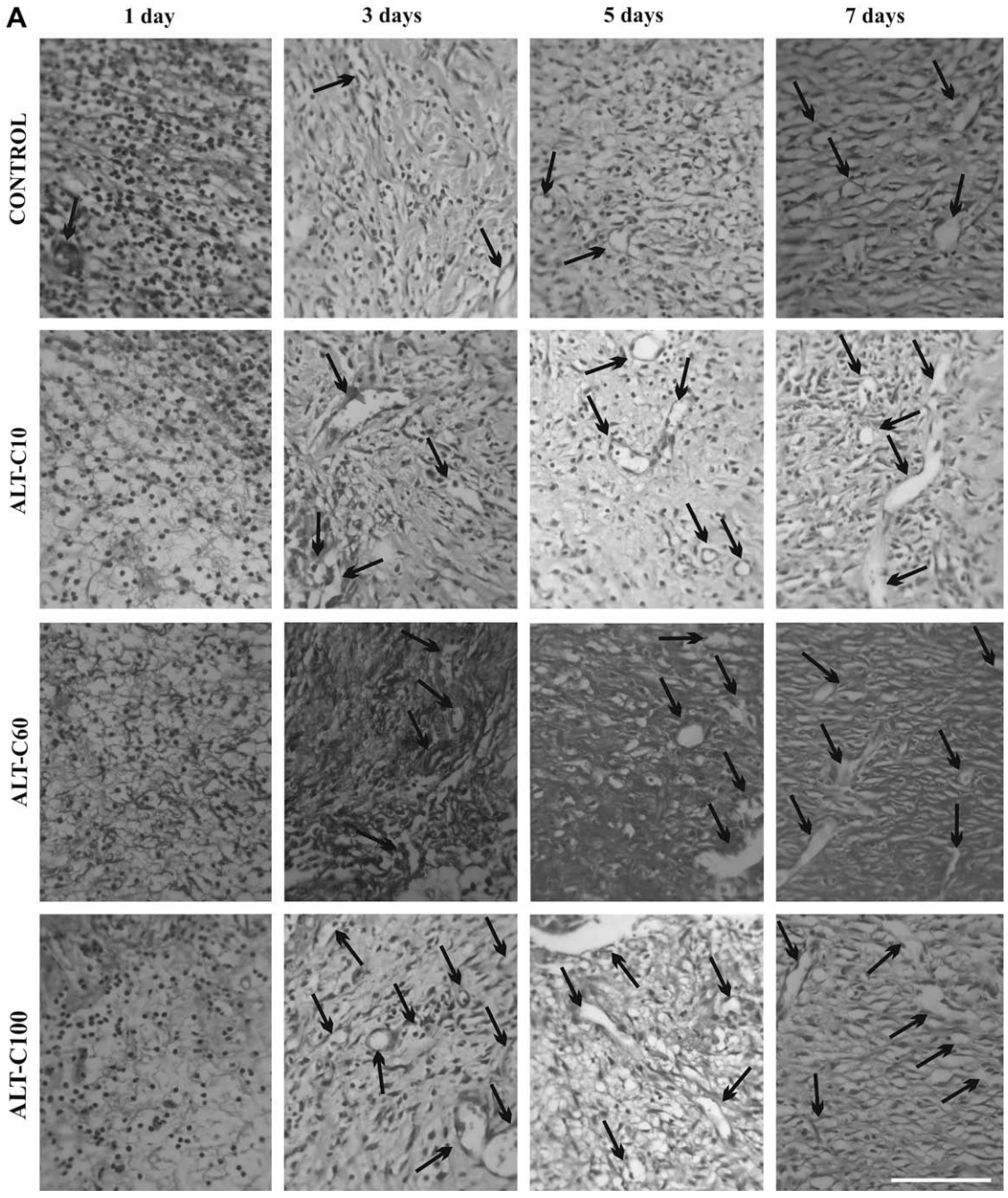

Fig. 1. Rat wounded skin of control and treated animals with different concentrations of ALT-C (A) or ALTC-PEP (B) groups, at 1, 3, 5 and 7 days after injury. Arrows indicate new blood vessel formed in the regenerating skin. Note that the increase in the blood vessel formation is correlated with time in the control group, and that both ALT-C and ALT-C PEP prominently induced angiogenesis. Scale bar = 100 μm.

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