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Snake venom: source of potent disintegrin to block tumor cell migration and invasion

Integrins are transmembrane cell surface proteins that mediate cell attachment and link the cytoskeleton to the extracellular matrix. The interactions between cells and the extracellular matrix control cell survival, proliferation, differentiation and migration. Snake disintegrins are potent and specific antagonists of integrins. They have been demonstrated to bind with high affinity to integrins on several different cell lines, including tumor cells.

A prototype of disintegrin, Contortrostatin (CN), which was isolated from the venom of southern copperhead snake (*Agkistrodon contortrix*), had been shown to prevent cell binding to vitronectin and fibronectin. In a recently published article, **Schmitmeier *et al***[1] investigated the mechanism and compared the effects of CN on integrin-induced signaling and cellular cytoskeletal morphology in glioma cells. They found that CN not only mimicked the intracellular signaling cascade evoked by fibronectin, but that it was more potent than fibronectin. CN had a higher binding affinity to integrin receptors than fibronectin. Importantly, CN effectively disrupted the binding of integrin to fibronectin, leading to a decrease in integrin signaling and disrupting the cytoskeleton and cellular detachment. The result of this study provides a promising treatment of malignant gliomas. As CN is small, it is able to penetrate the blood–brain barrier, permitting the option of intravenous infusion in addition to the direct intratumoral infusion.

In this issue, **Olfa *et al***[2] investigated the effects of Lebestatin (LN), a disintegrin from Tunisian viper (*Macrovipera lebetina*). They found that LN could inhibit both adhesion and migration of integrin-expressing cells, as well as endothelial cells. In addition, the Arg residue, which is also present in CN, appeared to play an important role in integrin interaction and antiangiogenic properties.

Both studies showed that snake venoms can act as potent 'disintegrins', pointing to their potential use as antitumoral agents.

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References

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2 Olfa KZ, Jose L, Salma D, *et al*. Lebestatin, a disintegrin from Macrovipera venom, inhibits integrin-mediated cell adhesion, migration and angiogenesis. Lab Invest 2005;85:1507–1516.

The many avenues of angiogenesis in *Bartonella henselae* infection

Bartonella henselae is a causative agent of cat-scratch disease, bacillary angiomatosis (BA), peliosis hepatis, bacteremia and endocarditis. BA is characterized by fever and angioproliferative lesions. The association between angiogenesis and conditions that involve inflammation is strong. In particular, infiltration of polymorphonuclear leukocytes and macrophages is observed in BA. The exact mechanism of *B. henselae*-induced BA is unknown, although it has been shown that *B. henselae*-infected macrophages produce the proangiogenic mediator vascular endothelial growth factor (VEGF), in addition to VEGF produced by the *B. henselae*-infected endothelial cells.

In a recent article, **McCord *et al***[1] examined the expression and protein levels of the chemokine monocyte–macrophage chemoattractant protein-1 (MCP-1) in the human microvascular endothelial cell line (HMEC-1), in order to understand the response of endothelial cells to *B. henselae* infection. MCP-1 mRNA was induced at 6 and 24 h after treatment with *B. henselae,* whereas MCP-1 protein production was elevated at 6, 24 and 48 h. The upregulation of the MCP-1 gene expression and the protein production of HMEC-1 were dependent on NF-κB activity, but appeared to occur in a lipopolysaccharide- and endothelial cell toll-like receptor 4-independent manner. Furthermore, they showed that the low molecular weight fraction of the outer membrane proteins of *B. henselae* and the supernatant of *B. henselae*-treated HMEC-1 cells could significantly increase MCP-1 production in a dose-dependent manner, and that these bacterial factors are heat stable. Their findings suggest that macrophages that secrete VEGF and other angiogenic factors are recruited by MCP-1 to the endothelium during *B. henselae* infection and contribute to bacterial-induced angiogenesis.

In this issue, **Kitajima *et al***[2] investigated the effects of high levels of VEGF in the liver and created a transgenic rabbit model with increased hepatic expression of the human $VEGF_{165}$ transgene under the control of the human α1-antitrypsin promoter. The transgenic rabbits developed diffuse hemangiomas in the liver accompanied by thombocytopenia and anemia, resembling an entity known in human as Kasabach–Merritt syndrome. $VEGF_{165}$ expressed in the liver was exclusively bound to the extracellular matrix, hence inducing the hemangiomatosis.

Both studies confirmed the effect of VEGF overexpression in inducing angiogenic lesions. Progress in the molecular and biological understanding of the VEGF/VEGFR system may allow us to develop novel and promising therapeutic strategies and target proteins to overcome a variety of diseases.

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References

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2 Kitajima S, Liu E, Morimoto M, *et al*. Transgenic rabbits with increased VEGF expression develop hemangiomas in the liver: a new model for Kasabach–Merritt syndrome. Lab Invest 2005;85: 1517–1527.