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A fibronectin-derived cell survival peptide belongs to a new class of epiviosamines

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Summary

In this issue, Lin et al. report the discovery of P12, a 14 amino acid peptide from the first fibronectin type III domain of fibronectin, which has the capability of enhancing cell survival in culture and improving wound healing in rat skin. P12 belongs to a new class of bioactive peptides that they have named epiviosamines. Epiviosamines may have clinical applications.

Fibronectin (FN) is an extracellular matrix (ECM) protein. It can bind a variety of integrins on the cell surface as well as many other molecules such as gelatin (denatured collagen), fibrin (fibrinogen), heparin/heparan sulfate, tissue transglutaminase, tenascin, fibulin and fibrillin. FN molecules also associate with each other to form matrix fibrils, which are crucial for development (Schwarzbauer and DeSimone, 2011). Thus, FN molecules have the ability to work as a scaffold for cells by interacting with other extracellular molecules, including themselves, for biological functions. An increasing number of studies has indicated recently that FN interacts with growth factors (see especially the review article by Hynes (2009)). Although insulin-like growth factors (IGF) seem to interact with FN indirectly through IGF binding proteins, many other growth factors appear to bind FN directly. Several studies have mapped the growth factor binding sites on FN. Vascular-endothelial cell growth factor (VEGF) interact with FN type III domains 12 to 14 (FNIII12-14) (Wijelath et al., 2006), which comprise the second heparin binding site (Hep-II), and VEGF-induced endothelial cell migration and proliferation were enhanced in the presence of FNIII12-14. Martino and Hubbell (2010) found that FNIII12-14 was the locus of interaction for growth factors from many families, including VEGF, platelet derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), and members of the neurotrophin families. Growth factor-induced cell proliferation was increased in the presence of FNIII12-14, although FNIII12-14 had no effect on growth factor-induced migration. In contrast to the studies of Martino and Hubbell, who broadly screened FNIII12-14 binding to growth factors, Lin et al. (2011) focused on the interaction between FN and PDGF-BB (the homodimeric BB isoform), which is a potent fibroblast survival factor. They found that PDGF-BB could bind FNIII1, FNIII13-14 and the variable (V) domain (also called connecting segment, CS) and that PDGF-BB-enhanced fibroblast

No conflict of interest

survival was increased in the presence of FN fragments containing these domains. Following up their previous study, Lin et al. (2013) in this issue report that PDGF-BB can bind a 14 amino acid peptide derived from FNIII1, called P12, which shows enhanced cell survival activity.

In the 1980's, before the integrins were discovered, many researchers found that FN had cell adhesion activity, and they attempted to map the cell binding site by dissecting the FN molecule with proteases and chemicals. Ruoslahti and his colleagues narrowed the binding site location down to a 108 amino acid region. Remarkably, the story didn't end there. With the use of synthetic peptides they discovered that the RGDS peptide was sufficient for cell binding. The fourth residue, serine, appeared to be variable, thus RGD was identified as the minimal binding sequence (see the essay by Ruoslahti (2003) for a historical perspective). (The RGD peptide is now recognized as being the shortest peptide that has biological activity.) It was then shown that engineered circular RGD peptides (cyclic RGD) have even stronger activities than linear peptides, probably because they mimic a naturally occurring loop structure. This discovery led to the development of many RGD-based drugs that target integrins. Later, Ruoslahti's group found an FN peptide that was able to induce FN aggregation. Since this peptide was derived from the C terminus of FNIII1, it was originally called III1-C, but it was renamed anastellin after discovery of its anti-angiogenic activity (Yi and Ruoslahti, 2001). Most recently, Gee et al. (2013) reported that the SLLISWD peptide from strand B of FNIII10 was also able to induce FN aggregation. They postulated that this peptide could exchange with β-strands in other FNIII domains, causing sequential domain swapping and the formation of FN aggregates. Lin et al. (2013) used similar tactics to find the shortest peptide required for fibroblast survival and PDGF-BB binding. By shortening a peptide derived from FNIII1 until activity was lost, they were able to identify P12, a 14 amino acid peptide (PSHISKYILRWRPK) that could not be truncated any further.

A striking feature of P12 is that it can recapitulate the activity of the parent domain (FNIII1) just as in the case of the RGD peptide. This is in contrast to the other FN derived peptides, anastellin and SLLISWD, whose activities are unique to themselves, so that their active sites are thought to be cryptic in the parent proteins. This makes me wonder where P12 is located in FNIII1. The tertiary structure of FNIII1 shows a typical FNIII β-sandwich structure (Gao et al., 2003), with three strands (A, B and E) on one side and four strands (C, C′, F and G) on the other (Fig. 1a). P12 is made up of the complete C strand, as well as several loop residues, mostly from the B-C loop (Fig. 1a in green). Because FNIII1 is a relatively stable FNIII domain in solution (Ohashi and Erickson, 2011), it is likely that the structure of P12 within FNIII1 reflects the structure of P12 alone. The surface-exposed residues, labeled in Fig. 1b and 1c, include several positively charged amino acids, suggesting an electrostatic interaction with PDGF-BB. However the N-terminal proline, which is required for activity, suggests that peptide conformation may play a role as well. This is purely speculative, however, until a structure can be obtained of P12 alone or as a P12/PDGF-BB complex.

Interactions between ECM proteins and growth factors were only thought to concentrate growth factors and to enhance their multimerization for signaling. However, recent studies indicate that binding of growth factors to ECM proteins may enhance interactions between multi-domain ECM proteins, such as FN, with cell surface receptors, mostly integrins

(Hynes, 2009). Thus, complexes of ECM proteins and growth factors appear to co-regulate signaling through both integrin and growth factor receptors. Surprisingly, the discovery of P12 reveals that a small peptide can mimic the role of FN with PDGF-BB, suggesting that some ECM-growth factor interactions may be less complex. P12 can not only bind to PDGF-BB, but also promote cell survival and improve rat skin burns in a dose dependent manner. This growth factor-induced cell survival activity led Lin et al. to propose that P12 belongs to a new class of bioactive peptides that they call epiviosamines, a name that combines the Greek word, *epivios*, which means “to survive in the face of adversity”, with *amine* for peptide. P12 and other yet to be discovered epiviosamines may have clinical potential, especially in the reduction of cell death after tissue damage.

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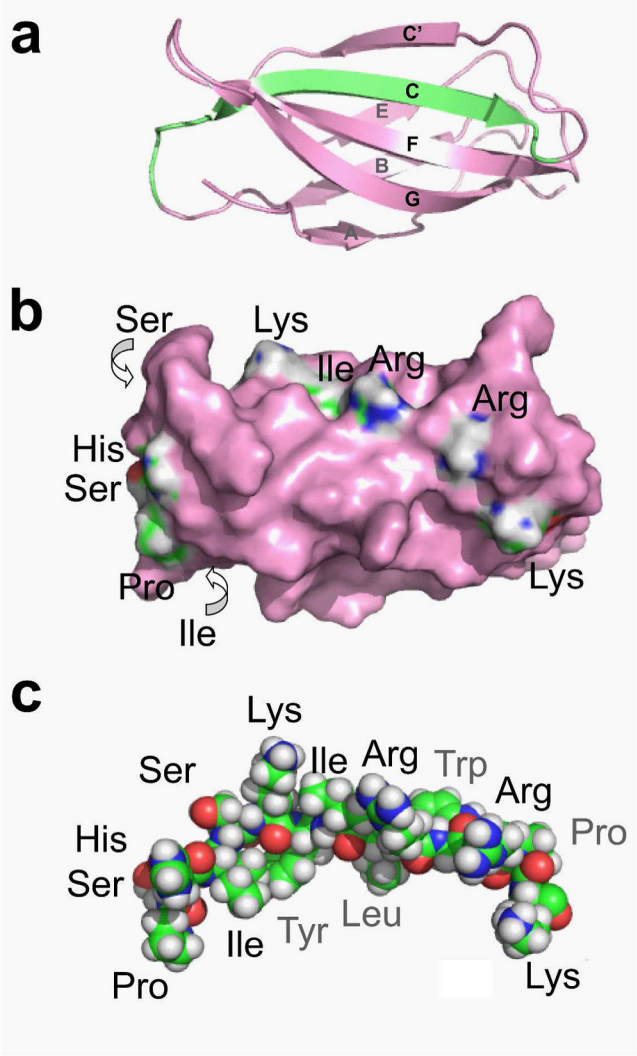

FIGURE 1.

Structural model of P12. (a) The parent domain, FNIII1, consists of a β-sandwich structure with A, B and E strands on one side, and C, C′, F and G strands on the other. The region corresponding to P12 is shown in green. (b) A surface-model shows that the majority of the P12 residues are exposed on the surface (labeled in black). Ile-4 and Ser-5 are hidden on the back (c) The structure of P12 extracted from III1 is shown with a space-filling model. Surface-exposed residues are labeled in black, other residues are in gray.