

This Week's Citation Classic®

Ruoslahti E, Engvall E & Hayman E G. Fibronectin: current concepts of its structure and functions. *Collagen Res.* 1:95-128, 1981.
[La Jolla Cancer Research Foundation, CA]

This article is a review on fibronectin, the prototypical adhesive protein of extracellular matrices and blood. The article focuses on the functions of the binding sites fibronectin has for collagens, fibrin, glycosaminoglycans, and cell surfaces as they were known around 1980. [The *SCI*® indicates that this paper has been cited in over 595 publications, making it the most-cited paper from this journal.]

Multiple Binding Sites of Fibronectin

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We wrote the article at the request of a friend and collaborator, Ted Miller, from the University of Alabama. Ted had started a new journal focusing on extracellular matrix research and wanted reviews from individuals in the field to get the journal off to a good start. Our article presumably did help the journal to get started, since it apparently is the most-cited paper published in that journal.

Eva Engvall, Ed Hayman, and I worked as a team at that time, first at the City of Hope and starting in 1979 at the La Jolla Cancer Research Foundation. I, together with Antti Vaheri, had contributed one of the several independent discoveries of fibronectin, but we needed to re-establish ourselves in the field after the move from Helsinki to the City of Hope. The invitation to write the review was an opening we wanted to make use of in bringing out our views on fibronectin. Others had written highly visible reviews on fibronectin,^{1,2} but they had become somewhat outdated because of the fast progress of the field. Also, much was made at that time of the fibronectin from plasma being different from the so-called "cel-

lular" fibronectin. We felt that the similarities were more striking than the differences. Indeed, despite the fact that these forms of fibronectin do represent different alternative splicing products of the fibronectin gene, to date no convincing proof of any functional difference between the various types of fibronectins has been obtained. The early results on functional differences have been found to be caused by contaminants in the cellular fibronectin preparations.

One main aspect we wanted to cover was the properties and location of the various binding sites in the fibronectin polypeptide. Engvall and I had published a paper (also a recent *Citation Classic*) showing that fibronectin bound to collagen and gelatin.³ Hayman and I had been able to show that the collagen-binding activity and the cell attachment activity of fibronectin could be localized in different fragments of the fibronectin polypeptide. This soon led to our isolation and sequencing of the cell attachment domain of fibronectin and the identification of the now well-known sequence Arg-Gly-Asp-X cell attachment site by Michael D. Pierschbacher, who joined the team in La Jolla.⁴ The availability of the cell attachment domain and the peptides that mimicked its function in turn made it possible for Robert Pytela to isolate a fibronectin receptor. At least 15 different adhesion receptors that belong to the same family as the original fibronectin receptor are now known and they are collectively called integrins.^{5,6}

There are two likely reasons for the frequent citation of our article. First, the fibronectin field became a very popular one about 10 years ago; as many as 500 publications on fibronectin have appeared each year. It was convenient for the authors of these papers to cite one or more reviews as an introduction. Second, I would like to think that our review may have been cited frequently because we had made some significant contributions to fibronectin research. This field has continued to progress extremely fast. Newer reviews now reflect this progress.^{5,6}

1. Vaheri A & Mosher D F. High molecular weight, cell surface-associated glyco-protein (fibronectin) lost in malignant transformation. *Biochim. Biophys. Acta* 516:1-25, 1978. (Cited 560 times.)
2. Yamada K M & Olden K. Fibronectins—adhesive glycoproteins of cell surface and blood. *Nature* 275:179-84, 1978. (Cited 1,215 times.)
3. Engvall E & Ruoslahti E. Binding of soluble form of fibroblast surface protein, fibronectin, to collagen. *Int. J. Cancer* 20:1-5, 1977. (Cited 1,315 times.) [See also: Engvall E. Citation Classic. *Current Contents/Life Sciences* 32(18):14, 1 May 1989.]
4. Pierschbacher M D & Ruoslahti E. Cell attachment activity of fibronectin can be duplicated by small synthetic fragments of the molecule. *Nature* 309:30-3, 1984. (Cited 330 times.)
5. Hynes R O. Integrins: a family of cell surface receptors. *Cell* 48:549-54, 1987.
6. Ruoslahti E & Pierschbacher M D. New perspectives in cell adhesion: RGD and integrins. *Science* 238:491-7, 1987.