

This Week's Citation Classic®

Kefalides N A. Structure and biosynthesis of basement membranes.

Int. Rev. Connect. Tissue Res. 6:63-104, 1973.

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This paper summarizes the knowledge, available up to 1972, on the structure and biosynthesis of basement membranes. The data presented are largely from the author's work and establish for the first time the presence of a new collagen (Type IV) found exclusively in basement membranes. The first observations on the biosynthesis, secretion, and extracellular aggregation of basement membrane collagen (Type IV) are described. [The SCI® indicates that this paper has been cited in more than 490 publications, making it the most-cited paper published in this journal.]

Finding New Collagen in the Basement (Membrane)

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The popularity of this article stems from the massive impetus in basement membrane research since 1975 when numerous laboratories in the US, Europe, and Japan became involved. Between 1965 and 1972, there was heightened activity in my laboratory in an attempt to characterize the structural and biosynthetic aspects of a new collagen type found exclusively in basement membranes (Type IV collagen). The first publication reporting the presence of this unusual collagen appeared in January 1966,¹ along with the observation that a large molecular weight glycoprotein could also be isolated from molecular basement membrane preparations. The latter was eventually identified as laminin, in a mouse tumor basement membrane, by R. Timpl, G.R. Martin, and colleagues, in 1979.² The presence of a small glycoprotein was suggested by our studies in 1972,³ and the work of A. Chung established its nature in 1981.⁴ It was given the name entactin.

The identification of these three macromolecules served to fulfill the charge given me by my mentor, Mark H. Lepper, at the University of Illinois. He suggested that I attempt to isolate and characterize the antigenic components of basement membranes, as I was embarking on my PhD thesis in biochemistry in the summer of

1962. Finding a collagen in basement membranes was a surprise to me and to many in the field of connective tissue research. It was easy to convince people of the presence of one or more glycoproteins in basement membranes, but to maintain that there was a collagen, and one that was different from the classical (Type I collagen) molecule found in skin, tendons, and bone, was a claim of heretic proportions.

In 1965, having received my PhD, I joined the laboratory of the late Albert Dorfman at the University of Chicago. In that atmosphere of electrifying research activity, I was encouraged by Martin B. Mathews and others to pursue my attempts to characterize this new collagen molecule that was turning out to be a bona fide glycoprotein.

Two developments that made the skeptics more receptive to the presence of Type IV collagen came with the discovery of Type II collagen in cartilage, by E. J. Miller and R. Trelstad, and the Type III collagen in fetal skin by Miller and colleagues. The demonstration of segment-long-spacing fibers of pepsin-treated Type IV collagen⁵ and the isolation of intact procollagen-like molecules of the same collagen from the lens capsule in my laboratory⁶ made a strong case. It was, however, the biosynthetic studies by M. Grant, C.C. Clark, and R.R. Minor in our laboratory that enabled us to examine its synthesis, post-translational modifications, secretion, and extracellular organization.⁷ At the time, I had suggested that additional basement membrane collagens might be found and, indeed, three new chains were described in the last three years.

The article summarized most of this work and it appeared at a time when other investigators in the field of connective tissue were becoming attracted to basement membrane research. The work of these new investigators led to the recognition that basement membranes play crucial roles in embryology by influencing cell differentiation and organ development, in tumor development and metastases, and in the pathogenesis of immunologically mediated renal disease.

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2. Timpl R, Rhode H, Robey P G, Rennard S I, Foidart J M & Martin G R. Laminin-A glycoprotein from basement membranes. *J. Biol. Chem.* 254:9933-7, 1979. (Cited 1,270 times.)
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