

Wrote as hypothesis for "Diabetes" Madison

HARVARD MEDICAL SCHOOL
DEPARTMENT OF SURGERY

= Diagram + photos

PROFESSOR
ID
MY
LOGY



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? Ingleter
? show that neuro
B.M = FGF

March 16, 1988

Dr. Roger Madison, Ph.D.
Neuroscience
Children's Hospital
Enders 2

Dear Dr. Madison:

Thanks very much for the loan of your slides. I used three of them to give a Plenary talk at the Second World Conference on Diabetes Research in Monaco on March 7th.

In this talk, I put forward a new hypothesis that connects some of the work that you and Pat D'Amore have done with some of ours, and may help to explain diabetic neuropathy in a novel way. The idea is as follows:

(i) We have shown that basic FGF is stored in the basement membrane (Descemet's) of cornea as well as the basement membrane of vascular endothelium (both in vitro and in vivo) (Folkman et. al., Am. J. Pathol. 130:393-400, 1988); (Vlodavsky et. al., P.N.A.S. 84:2292-2296, 1987). We have further shown that FGF is bound to heparan sulfate in the basement membrane where it can be released by exogenous heparin or heparanase which competes for its binding site to heparan sulfate. However, it is not releasable by chondroitinase or by chondroitin sulfate ABC.

(ii) Also, heparin protects basic and acidic FGF from inactivation (prevents denaturation and degradation) (Gospodarowicz, J. Cell. Physiol. 128:475-484, 1986).

(iii) Robert Spiro, at the Joslin Clinic, has shown that hyperglycemia is associated with a marked increase in biosynthesis of new type IV collagen which is deposited into the basement membrane in the diabetic rat (Brownlee & Spiro, Diabetes 28:121-125, 1979). Collagen type IV was increased from 70% of basement membrane to over 80% and may be the most important cause of the thickened basement membrane found in almost all diabetic patients who have had the disease for more than 15 years.

(iv) Furthermore, Spiro showed that heparan sulfate proteoglycan in the basement membrane of diabetics is reduced by 30% of normal and appears to be crowded out by the excessive collagen production. Thus, human glomerular basement membrane contained 6.5 ug of heparan sulfate proteoglycan per mg of basement membrane in the normal patient as compared to only 2 ug/mg in the diabetic (Shimomura, H. & Spiro, Diabetes 36:374-381, 1987).

(v) Your paper with Pat D'Amore in which Gordeiro is first author entitled, "Acidic fibroblast growth factor enhances peripheral nerve regeneration in vivo", shows that the repair of sensory neurons is highly FGF-dependent in contrast to motor neurons which are not. This is of great interest because diabetic neuropathy is mainly sensory loss, i.e., sensory loss precedes and exceeds motor loss in most diabetics. There has been no satisfactory explanation for this.

In my Plenary Lecture, I proposed the following hypothesis.....that, "The reduction of heparan sulfate proteoglycan in the basement membrane of the diabetic, may reduce the reservoir for basic FGF".

This idea is testable. For example, one could compare the amount of releasable FGF or stored FGF in the cornea of diabetic rats versus the corneas of normal rats. Also, diabetic rats could be used in a study similar to yours, of sciatic nerve transection.

There is one minor inconsistency. Your study apparently used acidic FGF. Did basic FGF fail to produce the same nerve regrowth as acidic FGF? Also, we do not know whether the basement membrane of the endoneurium contains stored acidic FGF or basic FGF, or both.

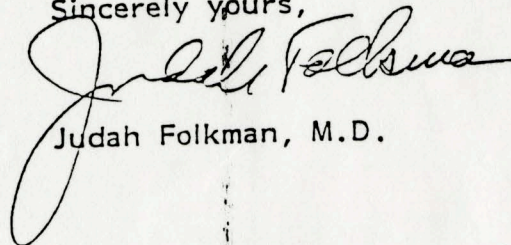
Nevertheless, I would appreciate your comments about this hypothesis, and I will also discuss this with Pat.

The Juvenile Diabetes Association wants a copy of my speech for reprinting. However, this hypothesis was only a small part of the talk, and it may be more prudent to publish the hypothesis separately.

I would appreciate your thoughts.

Best regards,

Sincerely yours,



Judah Folkman, M.D.

JF/pb

cc: Patricia D'Amore, Ph.D.

P.S. I will bring the slides to your office JF