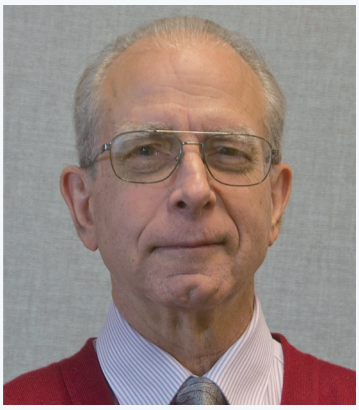

Hyaluronan – chondroitin sulfate – heparin, dueling glycosaminoglycans in hyperglycemic proliferating cells

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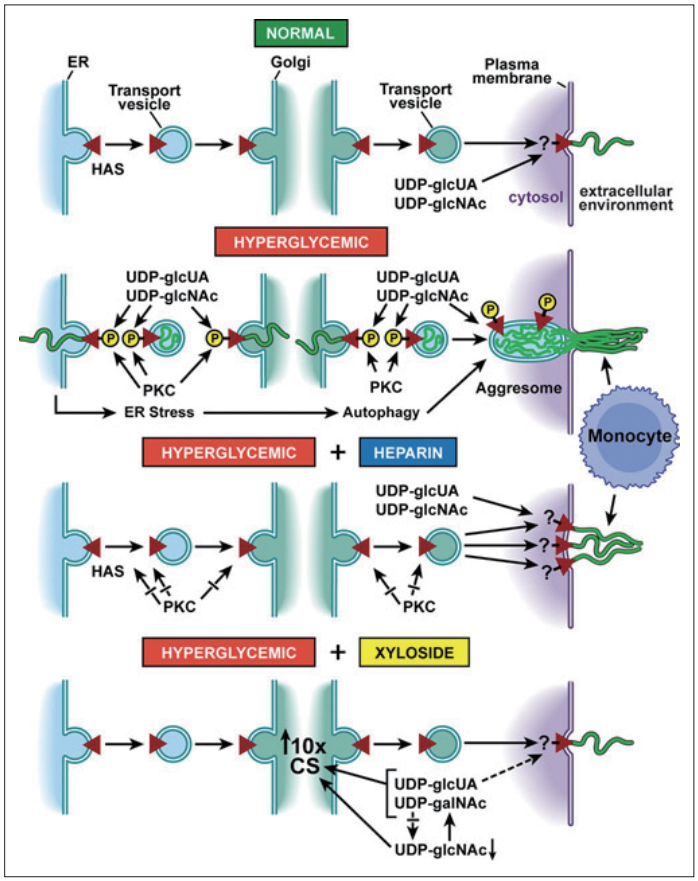
Professional Experience:

1969 - 1975	Asst. (1969-73) and Assoc. Prof. (1973-75) of Dentistry, Dept. of Oral Biol., Sch. of Dentistry, University of Michigan, Ann Arbor, MI
1969 - 1975	Asst. (1969-74) and Assoc. Prof. (1974-75) of Biol. Chem., Sch. of Med., Univ. of Mich., Ann Arbor
1972 - 1973	Fellow of the Swedish Medical Research Council, Lund University, Sweden
1975 - 1994	Senior Staff Fellow (1975-76), Research Chemist (1976-78), Chief, Proteoglycan Chemistry Section (1978-94), Laboratory of Biochemistry (current name: Bone Research Branch), National Institute of Dental Research, National Institutes of Health, Bethesda, MD
1977 - 1993	Instructor, Fndn. for Advanced Education in the Sciences, Grad. School at NIH, Bethesda, MD
1980 - 1981	Foreign Work Study Program, Department of Biochemistry, University of Monash, Australia
1989 - pres.	Adjunct Professor, Dept. of Biochemistry, Rush University, Chicago, IL
1994 - pres.	Adjunct Professor, Dept. of Biochemistry, Case Western Reserve University, Cleveland, OH
1994 - pres.	Staff, Sectn. of Connect. Tissue Biol., Dept. of Biomed. Eng., Cleve Clinic Fndn., Cleveland, OH
2001 - 2005	Co-Director, Orthopaedic Research Center, Cleveland Clinic Foundation, Cleveland, OH
2001 - pres.	Staff, Dept. of Orthopaedic Surgery, Div. of Surgery, Cleveland Clinic Fndn., Cleveland, OH
2004 - pres.	Staff, Cleveland Clinic Lerner College of Medicine, Dept. of Molecular Medicine, Cleveland, OH

Honors and Awards; Service on Committees

1976-1980	Pathobiological Chemistry Study Section
1979-1982	Executive Committee, Society for Complex Carbohydrates
1979	NIH Merit Award
1984	Vice Chairman, Proteoglycan Gordon Conference
1986	Chairman, Proteoglycan Gordon Conference
1986	Chairman, CIBA Foundation Symposium: The Function of Proteoglycans
1984	Juvenile Diabetes Foundation Medical Research Council
1984	PHS Superior Service Award
1987	President, Society for Complex Carbohydrates
1987	Convener, Society for Complex Carbohydrates Annual Meeting
1986	Doctor of Medicine, honoris causa, University of Lund, Sweden, 1986
1988 - 2001	Member Scientific Advisory Board, Ctr. for Osteoarthritis Research (SCOR), Rush Univ., Chicago, IL
1992	Karl Meyer Award for Glycoconjugate Research from the Society for Complex Carbohydrates
1999 - pres.	Member NIH Carbohydrate Resource Center Advisory Board, Univ. of Georgia, Athens, Ga.
1999 - pres.	Member, Science Advisory Committee, Rheumatoid Arthritis Program Proj., Rush Univ., Chicago, IL
2000	Chair, Sci. Committee, Hyaluronan 2000, Wales, 2000; Sci. Chair and co-editor of proceedings, Hyaluronan 2000, Sept. 2000, Wrexham, Wales, UK
2000	D.Med., honoris-causa, Univ. of Kuopio, Finland
2000 - 2002	Member, Advisory Board, Hope Heart Institute, Seattle, WA
2001	Scientific Chair, "The Many Faces of Osteoarthritis Conference", June 2001, Lake Tahoe, CA
2001 - pres.	Board Member, American Society for Matrix Biology
2003	Co-Organizer and Host, Hyaluronan 2003, October, 2003, Cleveland, OH
2005	Co-Director and Host, Cleveland Clinic Cartilage Innovation Summit, May 2005, Cleveland, OH
2005	Co-Founder, International Society for Hyaluronan Sciences (ISHAS)
2006	Co-Organizer, International Conference, Hyaluronan 2007, April, 2007, Charleston, SC
2007	Three early Journal of Biological Chemistry articles selected as JBC "Classics"
2009	Diplome of Honour, University of Patras, Greece
2010	Honoree, 8th International Society of Hyaluronan Sciences (ISHAS) Conference, June, 2010, Kyoto, Japan

Our previous studies have shown that mesangial cells stimulated to divide in hyperglycemic medium activate hyaluronan synthases that then synthesize hyaluronan into intracellular compartments, endoplasmic reticulum (ER), golgi, transport vesicles. This initiates an ER stress-autophagy response that upregulates cyclin D3, which induces formation of a monocyte-adhesive extracellular hyaluronan matrix after completing cell division [1), 2)]. The critical role of the cytosolic UDP-sugar substrates was shown by treating the dividing hyperglycemic mesangial cells with 4-methylumbelliferyl-xyloside, which increases chondroitin sulfate in the golgi by 8-10 fold. This decreases the cytosolic substrates sufficiently to prevent the intracellular HA response, the autophagy and the formation of the extracellular HA matrix. The intracellular HA response also occurs in kidney glomeruli of streptazotocin-treated diabetic rats. Over a 6 week period, the glomeruli have increasing numbers of autophagic mesangial cells surrounded by an extensive hyaluronan matrix with embedded macrophages, with resulting extensive nephropathy and proteinurea. Previous studies showed that daily IP injection of a small amount of low MW heparin in diabetic rats prevented the nephropathy and proteinurea over an 8 week period [3), 4)]. Our new studies show that mesangial cells stimulated to divide in hyperglycemic medium in the presence of 0.2 μM heparin do not activate hyaluronan synthesis in intracellular compartments nor induce the autophagy and cyclin D3 responses.



Nevertheless, at the end of cell division, the mesangial cells synthesize a much larger monocyte-adhesive matrix. In the heparin treated diabetic rat, the hyaluronan content in glomeruli increases greatly in weeks 1-2 and then declines to near normal by 6 weeks, at which time there are large numbers of macrophages present, but no evidence for autophagic mesangial cells. These results suggest that the dialogue between the mesangial cells and influxed macrophages in the diabetic glomeruli is pro-inflammatory with accumulation of a fibrotic hyaluronan matrix that compromises kidney function. In contrast, in the heparin treated diabetic rat the mesangial cells maintain their normal function after completing cell division, but still activate synthesis of the extensive hyaluronan matrix as an effective way to deal with the continued high glucose stress. In this case the influxed macrophages remove the matrix and do not initiate fibrotic responses, and by 6 weeks we propose that there is a steady state of hyaluronan synthesis by the mesangial cells and its removal by the macrophages. The figure shows the models that are supported by these studies.

References

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2) Wang A, de la Motte C, Lauer M, Hascall V. Hyaluronan matrices in pathobiological processes. FEBS J. (278):1412, 2011.
3) Gambaro G, Cavazzana AO, Luzi P, Piccoli A, Borsatti A, Crepaldi G, Marchi E, Venturini AP, Baggio, B. Glycosaminoglycans prevent morphological renal alterations and albuminuria in diabetic rats. Kidney Int. (42):285, 1992.
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