

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

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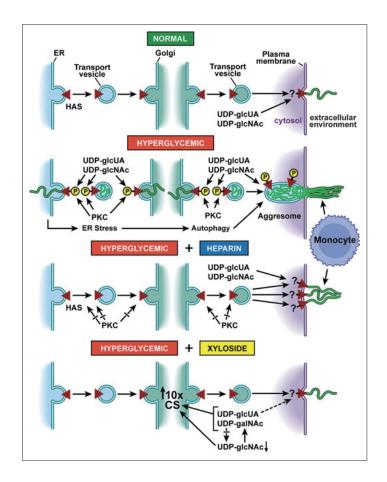
Professional Experience:

1976-1980

- 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
- Adjunct Professor, Dept. of Biochemistry, Rush University, Chicago, IL 1989 - pres.
- 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
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- Honors and Awards; Service on Committees

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 President, Society for Complex Carbohydrates 1987 1987 Convener, Society for Complex Carbohydrates Annual Meeting 1986 Doctor of Medicine, honoris causa, University of Lund, Sweden, 1986 Member Scientific Advisory Board, Ctr. for Osteoarthritis Research (SCOR), Rush Univ., Chicago, IL 1988 - 2001 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. Member, Science Advisory Committee, Rheumatoid Arthritis Program Proj., Rush Univ., Chicago, IL 1999 - pres. Chair, Sci. Committee, Hyaluronan 2000, Wales, 2000; Sci. Chair and co-editor of proceedings, Hyaluronan 2000, Sept. 2000, 2000 Wrexham, Wales, UK 2000 D.Med., honoris-causa, Univ. of Kuopio, Finland 2000 - 2002 Member, Advisory Board, Hope Heart Institute, Seattle, WA Scientific Chair, "The Many Faces of Osteoarthritis Conference", June 2001, Lake Tahoe, CA 2001 Board Member, American Society for Matrix Biology 2001 - pres. 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) Co-Organizer, International Conference, Hyaluronan 2007, April, 2007, Charleston, SC 2006 Three early Journal of Biological Chemistry articles selected as JBC "Classics" 2007 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 stressautophagy 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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