ISSN 1349-9416 / CODEN GLYCAX

Glycoforum

Dec. 15, 1997

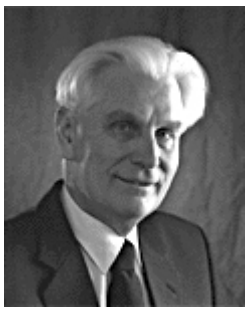
Hyaluronan: Structure and Physical Properties

（1997 Vol.1, A2）

Vincent C. Hascall / Torvard C. Laurent

Vincent C. Hascall
Department of Biomedical Engineering (Wb3), Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio 44195

Described in Biosketch of Editors



Torvard C. Laurent
Dr. Torvard Laurent received his Doctor of Medicine from the Karolinska Institute, Stockholm in 1958. After a 3 year fellowship from the Retina Foundation in Boston, Dr. Laurent established a research program at the University of Uppsala, where he attained a Professorship in 1966. He is currently Professor emeritus at this institution and Science Secretary for the Wenner-Gren Foundations, Stockholm. Dr. Laurent has conducted pioneering, internationally recognized research throughout his career on the chemistry of connective tissues, most notably on the physical and physiological properties, and medical applications of hyaluronan. His numerous honors include: Deputy Chairman, Swedish Medical Research Council, 1973-77; Chairman, Swedish Biochemical Society, 1973-76; President, Royal Swedish Academy of Sciences, 1991-94; and Chairman, Council of the Nobel Foundation, 1994-present. His busy schedule includes responsibility for organizing international conferences for the Wenner-Gren Foundations, where he recently organized and edited one on the 'Structure, Biology and Medical Applications of Hyaluronan'.

1. Introduction

1In 1934, Karl Meyer and his assistant, John Palmer, described a procedure for isolating a novel glycosaminoglycan from the vitreous of bovine eyes [1]. They showed that this substance contained an uronic acid and an aminosugar, but no sulfoesters. In their words: **'we propose, for convenience, the name "hyaluronic acid", from hyaloid (vitreous) + uronic acid.'** This marked the birth announcement for one of nature's most versatile and fascinating macromolecules. Today, this macromolecule is most frequently referred to as **'Hyaluronan'**, reflecting the fact that it exists *in vivo*

2. Chemical Structure

It would take an additional 20 years before Meyer's laboratory finally completed the work that determined the precise chemical structure of the basic disaccharide motif that forms hyaluronan [2]. During these years they showed that the uronic acid and aminosugar in the disaccharide are D-glucuronic acid and D-N-acetylglucosamine, and that they are linked together through alternating beta-1,4 and beta-1,3 glycosidic bonds, Fig. 1. Both sugars are spatially related to glucose which in the beta configuration allows all of its bulky groups (the hydroxyls, the carboxylate moiety and the anomeric carbon on the adjacent sugar) to be in sterically favorable equatorial positions while all of the small hydrogen atoms occupy the less sterically favorable axial positions. Thus, the structure of the disaccharide shown in Fig. 1 is energetically very stable.

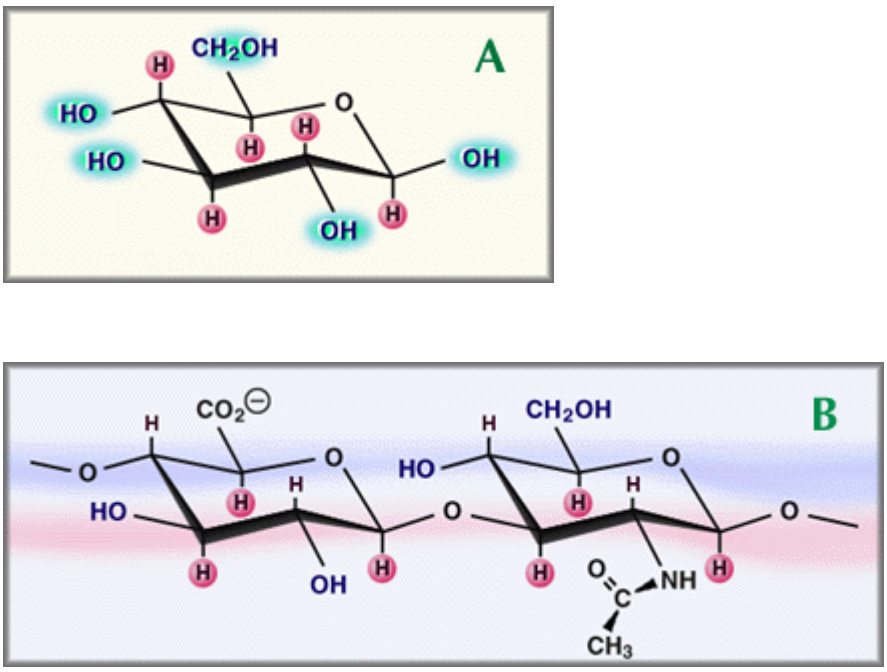


Fig. 1
Relationship between beta-D-glucose (A) and the repeat disaccharide of hyaluronan, D-glucuronic acid-beta-1, 3-N-acetylglucosamine-beta-1, 4 (B)
H ; axial hydrogens that contribute to the hydrophobic face

3. Polymer Structure

Hyaluronan synthase enzymes synthesize large, linear polymers of the repeating disaccharide structure of hyaluronan by alternate addition of glucuronic acid and N-acetylglucosamine to the growing chain using their activated nucleotide sugars (UDP - glucuronic acid and UDP-N-acetylglucosamine) as substrates.[1] The number of repeat disaccharides, **n**, in a completed hyaluronan molecule can reach 10,000 or more, a molecular mass of ~4 million daltons (each disaccharide is ~400 daltons). The average length of a disaccharide is ~1 nm. Thus, a hyaluronan molecule of 10,000 repeats could extend 10 μm if stretched from end to end, a length approximately equal to the diameter of a human erythrocyte. Fig. 2 shows an electron micrograph of a few intertwined hyaluronan molecules that have been deposited on a flat surface and rotary shadowed with heavy metal for contrast.

[1] These enzymes and the mechanism of hyaluronan synthesis will be the subject of later articles in this series.

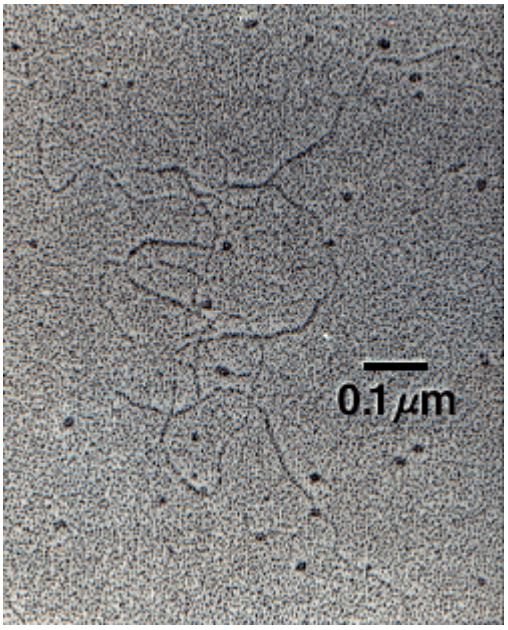


Fig. 2
The electron micrograph was kindly provided by Dr. Richard Mayne and Dr.

4. Solution Structure

In a physiological solution, the backbone of a hyaluronan molecule is stiffened by a combination of the chemical structure of the disaccharide, internal hydrogen bonds, and interactions with solvent. The axial hydrogen atoms (indicated in Fig. 1B) form a non-polar, relatively hydrophobic face while the equatorial side chains form a more polar, hydrophilic face, thereby creating a twisting ribbon structure.[2] Consequently, a hyaluronan molecule assumes an expanded random coil structure in physiological solutions which occupies a very large domain, Fig. 3. The actual mass of hyaluronan within this domain is very low, ~0.1% (wt/vol) or less when the macromolecule is present at a very dilute concentration in saline. This means that the domains of individual molecules would overlap each other at concentrations of 1 mg hyaluronan per ml or higher.

[2] See article 2 by John Scott.

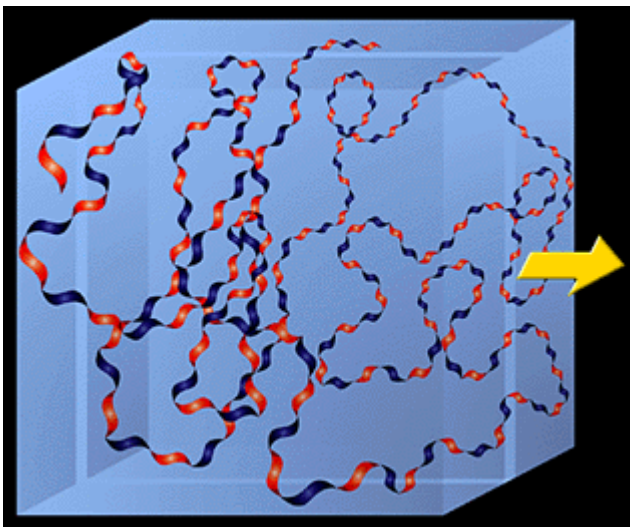


Fig. 3 Model of hyaluronan ribbon in a 3-dimensional domain.
The light blue box represents the domain of the molecule in solution. The alternating blue and red strand represents the ribbon structure with blue (hydrophilic) and red (hydrophobic) faces.
The slice is represented in Fig. 4.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.