Production and Application of Hyaluronic Acid

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Hyaluronic acid (HA) is a glycosaminoglycan widely distributed in the human body, especially in body fluids and the extracellular matrix of tissues. It plays a crucial role not only in maintaining tissue hydration but also in cellular processes such as proliferation, differentiation, and the inflammatory response. HA has demonstrated its efficacy as a powerful bioactive molecule not only for skin antiaging but also in atherosclerosis, cancer, and other pathological conditions.

hyaluronic acid biomaterial bioactive molecule metabolic pathways bioproduction fermentation processes

1. Introduction

HA is a linear glycosaminoglycan polymer present in the extracellular matrix of vertebrate tissues, including connective, epithelial, and neural tissues [1]. It is involved in several biological processes such as embryonic development, wound healing, cancer progression, angiogenesis, inflammation, and bone regeneration [2][3][4]. HA has been found to regulate essential cellular processes such as cell adhesion, proliferation, and differentiation [5][6].

In addition to belonging to vertebrate connective tissues, HA could be found in several bacterial strains (e.g., groups A and C streptococci and *Pasteurella multocida*) as a component of their capsules and mucus with the role of conferring adherence, protection, and molecular mimicry necessary to evade the host's immune system during their infection process [7].

Over the past 20 years, HA has garnered an exponential interest due to the continuous scientific discoveries regarding its intrinsic properties and subsequent applications. Ongoing research continues to investigate the mechanisms underlying its biological activity.

HA applications cover several fields ranging from cosmetic formulations to viscosurgery, ophthalmology, orthopedic surgery, rheumatology, tissue regeneration, and targeted cancer therapy [8]. This broad range of applications is possible due to the specific bioactivity exhibited by HA based on its molecular weight (MW). Furthermore, in addition to the use of pure HA, an emerging trend is the combination of HA with other bioactive ingredients or materials for several applications such as facial volume restoration [9][10][11], osteoarthritis treatment [12][13][14] (NCT00653432, NCT05683327), cosmetic medicine [15][16][17][18][19], nasolabial fold reduction [20][21], cancer treatment [22][23][24][25] (NCT05024773), atherosclerosis diagnosis and treatment [26], psoriasis treatment [27][28],

urinary tract infection treatment [29][30], tissue engineering [31][32][33][34], antioxidant and anti-inflammatory effects [35][36][37], and wound healing [38][39].

The aging population, the consequent increase in demand for antiaging products, and the rise in age-related diseases along with the introduction of technologically advanced products, the growing preference for non-invasive techniques, the adoption of aesthetic procedures, and the need for faster and natural-like results are all factors that have affected and will continue to impact the growth in research and the market size of HA in the coming years.

2. HA Microbial Metabolic Pathways

Several studies on HA biosynthesis focused on natural producer microorganisms such as group A and C streptococci and *Pasteurella multocida*, which produce HA as a component of their capsules and mucus [40][41].

Generally, HA is synthesized via two different metabolic pathways, resulting in the production of two precursors: UDP-GA and UDP-NAG [42] (**Figure 1**).

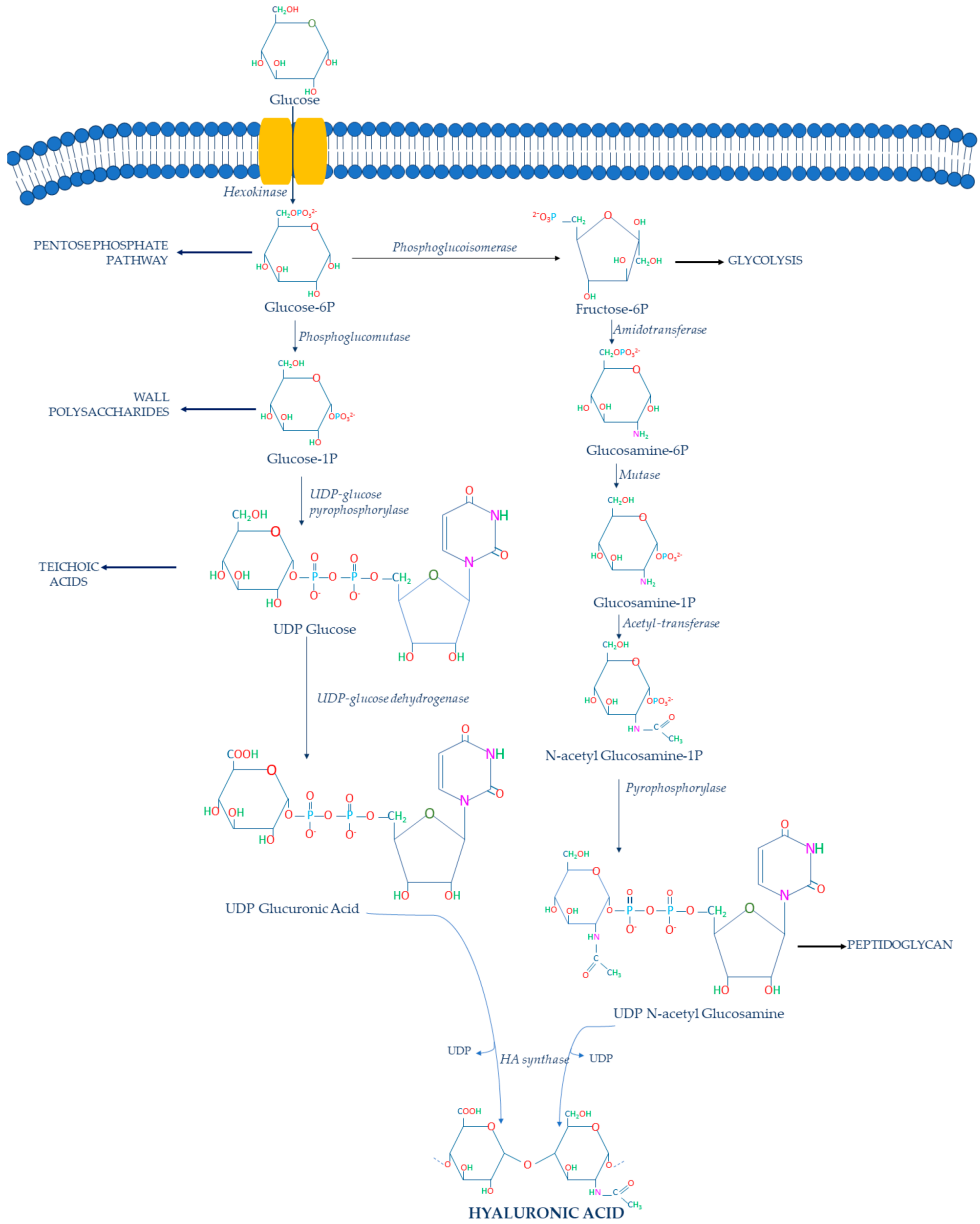


Figure 1. HA biosynthetic pathway in *S. zooepidemicus*.

Glucose is imported into the bacterial cell and phosphorylated by hexokinase, converting it into glucose-6-phosphate (glucose-6P) in the cytoplasm. Then, it is converted by the phosphoglucomutase in glucose-1-phosphate (glucose-1P), after which the UDP-glucose pyrophosphorylase catalyzes the formation of UDP-glucose. This UDP-glucose is subsequently oxidized by the UDP-glucose 6-dehydrogenase to obtain the first HA precursor: UDP-GA. However, other metabolic pathways compete with this conversion since the glucose-1P can be used for glycogen production [40] and the UDP-glucose can be converted to trehalose-6P [40]. These two metabolic pathways represent a metabolic limit for HA production [43].

The second HA precursor is produced through a second pathway in which glucose-6P is converted to fructose-6-phosphate (fructose-6P) by the phosphoglucoisomerase. UDP-glucose 6-dehydrogenase and phosphoglucoisomerase are the most important competing enzymes because the first one directs glucose-6P into

the Pentose Phosphate Pathway, while the latter converts glucose-6P into fructose-6P via the Embden–Meyerhof–Parnas pathway [43]. Cells typically utilize the majority of glucose-6P for these two competing metabolic pathways rather than UDP-GA synthesis [44]. Furthermore, cells can use the phosphoglucoisomerase to convert fructose-6P into glucose-6P, which can be utilized in the Pentose Phosphate Pathway [40]. Then, glucosamine-6-phosphate (glucosamine-6P) is formed from fructose-6P by the action of amidotransferase. Glucosamine-6P is the substrate of the mutase that leads to the formation of the glucosamine-1-phosphate (glucosamine-1P).

Amidotransferase, on the other hand, competes with the UDP-NAG cascade by converting glucosamine-6P to fructose-6P [43]. Indeed, fructose-6P can be converted into fructose-1,6-bisphosphate through the ATP-dependent phosphofructokinase, which is utilized in the Embden–Meyerhof–Parnas pathway for energy generation and cell growth [43]. In addition, it must be considered that if cells have a limited amount of carbon sources to feed these two main metabolic pathways, a significant portion of cellular glucosamine-6-phosphate could be converted to fructose-6P and glucose-6P to meet the metabolic needs of cells [43]. Consequently, cells will have a limited reserve of glucosamine-6P to synthesize glucoamine-1P.

Glucosamine-1P is further acetylated and phosphorylated by pyrophosphorylase to form the second precursor: UDP-NAG. In this case, reduced flux to UDP-NAG due to competing pathways also is a significant limitation to HA synthesis [40]. Consequently, at the end of these metabolic pathways, UDP-GA and UDP-NAG are polymerized by the hyaluronic acid synthase (HAS), which catalyzes the formation of the HA chain [45]. The biosynthetic pathway of HA in bacteria shows that the HAS is a key enzyme that catalyzes the polymerization of HA chains. In particular, the streptococcal HAS is classified as a class I HAS because it is an integral membrane protein that catalyzes the addition of UDP-GA acid and UDP-NAG to the growing HA chain [46] (**Figure 2**A).

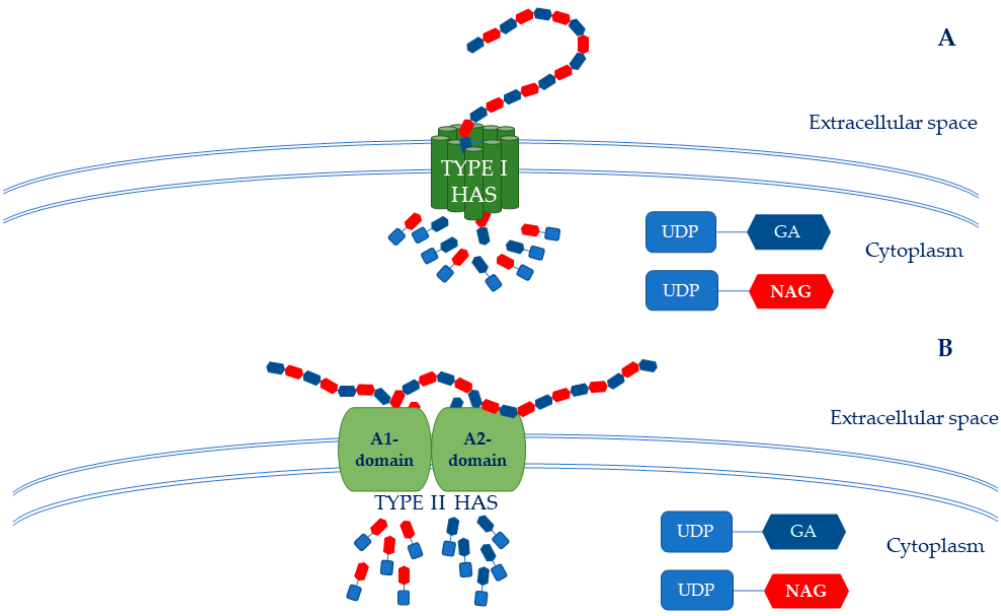


Figure 2. HAS structure. (**A**) The Type I HAS is an integral membrane protein that catalyzes the adding of UDP-GA and UDP-NAG to the HA growing chain. (**B**) The Type II HAS is a membrane-associated protein composed of A1

and A2 domains that work together as a single peptide. The A1 domain is a β-1,4-N-acetylglucosaminil-transferase, while the A2 domain is a β-1,3-glucuronyl-transferase.

Conversely, the HAS of *P. multocida* belongs to class II because it is a membrane-associated glycosyl transferase. This enzyme also has two independent active sites: (i) an “A1” domain that performs the UDP-NAG transferase activity, and (ii) and an “A2” domain that carries out the UDP-GA transferase activity (**Figure 2**B). Therefore, HAS catalyzes the sequential elongation of a growing HA chain at the non-reducing end with its β-1,3-glucuronyl-transferase and β-1,4-*N*-acetylglucosaminil-transferase domains, which work synergistically as a single polypeptide [46].

Hence, it is clear that HA production is an energy- and carbon-intensive process for the bacterial cell. Its metabolic pathway consumes large quantities of its donor substates, thereby linking HA synthesis to glucose metabolism. As already mentioned, glucose-6P is an important substrate of the Pentose Phosphate Pathway, while fructose-6P is an important intermediate of the glycolytic pathway. Moreover, some intermediates of HA biosynthesis are also required for cell wall biosynthesis [47]. In particular, glucose-1P is an important wall polysaccharide, UDP-glucose is used by streptococci for teichoic acid biosynthesis [48], and finally NAG is a component of the structural unit of peptidoglycan [49].

It is easy to see that HA synthesis is strongly influenced by the cellular availability of the two precursors [50] and thus to cells’ metabolic needs. Moreover, it has been observed that if each precursor is not supplied at sufficient rates, the amount of the synthesized HA and its MW are reduced [51]. The carbon source must be shared equally between the two pathways to correctly produce HA. Due to this, several studies were conducted in order to maximize hyaluronic acid production.

3. HA Fermentation Process in Engineered Host Microorganisms

As previously mentioned, industrial and scientific research is looking for optimized HA production methods with controlled parameters, high yields, low production costs, a high MW, and a high purity of the final product. HA bacterial production through metabolic engineering represents a promising strategy. Over the last years, several microorganisms have been engineered in order to produce HA. Different fermentation methods and culture media have been tested. Not only natural microbial producers of HA have been engineered in order to optimize the characteristics of the final product, but non-natural producers such as GRAS microorganisms (i.e., *E. coli*, *B. subtilis*, and *B. megaterium*) have been as well.

First of all, several researchers attempted to maximize HA production by tuning the microorganism culture conditions rather than engineering them. Parameters such as the initial pH of the broth, temperature, time of incubation, and agitation speed were evaluated as important parameters that influenced the yield of HA. Among several bacteria, *S. equi* spp. *zooepidemicus* was the most investigated. Güngör et al. found that the growing conditions that allowed them to improve the HA final yield (12 g/L) were pH 7.8, an incubation temperature of 33

°C, an incubation time of 24 h, and an agitation speed of about 187 rpm [52]. In another recent study, UV-induced mutagenesis on *S. zooepidemicus* allowed the researchers to further increase the HA yield, which reached about 4.2 g/L after 36 h of fermentation [53]. In this case, the optimal fermentation was obtained by incubating it at 37 °C and pH 7.4 in a fermentation broth that contained glucose as the carbon source, phosphate as the essential nutrient, peptone 250 as the nitrogen source, and dibasic potassium phosphate as the phosphate source [53]. Then, to enhance the efficiency of the hyaluronic acid production, a semi-continuous fermentation process that consisted of two-stage 3–L bioreactors was developed, and recombinant hyaluronidase *SzHYal* (300 U/L) was added into the second stage bioreactor to reduce the broth viscosity. In this way, an HA yield of 30 g/L was successfully attained [53]. Another strategy showed that as an alternative to glucose, molasses could be used as a carbon source in the fermentation medium of *S. zooepidemicus* [54]. Indeed, the presence of this alternative and cheaper sugar allowed an increase in the yield of the HA up to 0.2 g/L compared to standard conditions (43 mg/L) [54]. In addition to the pH, the incubation temperature, agitation speed, soil composition, and size of inoculum are key parameters of the fermentation process that affect the yield of the final product. Some researchers found that a streptococcal inoculum size of 10% had the greatest effect on the fermentation process and also that an agitation speed of 300 rpm could increase the HA yield [55]. This may have occurred because at this rate of speed, a greater subdivision of air bubbles could occur with a consequent larger surface area for the gas–liquid mass transfer, which therefore led to a reduction in the thickness of the gas and liquid films responsible for the resistance to the mass transport [55]. In this way, it is easy to understand that several parameters must be optimized in order to enhance the microbial production of HA starting from natural producer microorganisms.

With the aim of reducing extracted product endotoxins, recombinant non-natural microbial producers were designed, developed, and investigated in depth [40]. A variety of organisms including *B. subtilis*, *B. megaterium*, and *E. coli* have all been genetically engineered in order to produce HA [56][57][58]. Genetically modified *E. coli* strains have several potential advantages when compared to *Streptococcus* strains and therefore offer a promising alternative [40]. Additionally, compared to *Streptococcus* strains, several *E. coli* strains are non-pathogenic [43], and they can be grown at a high cell density using cheap and simple media. As a result, the fermentative process of *E. coli* could be improved through metabolic engineering [59]. For these reasons, many studies have been carried out with recombinant *E. coli*. In particular, a recent study compared the HA production in different *E. coli* strains (pLysY/lq, Rosetta2, Rosetta2 (DE3) pLysS, and Rosetta-gami B (DE3) pLysS) and *B. megaterium* (MS941) cells [57]. Firstly, the researchers used different fermentation conditions for *E. coli* cells. Initially, they engineered the bacterial cells by transforming them with different plasmids. The first introduction of the *hasA* gene of *S. equi* spp. *zooepidemicus* in *E. coli* Rosetta2 cells allowed them to obtain a yield of 8.8 mg/L [57]. Then, the introduction of a second set of genes, which were *hasA*, *hasB* and *hasC* genes in *E. coli* pLysY/lq cells, allowed them to reach a yield of 208.3 mg/L (by adding $MgCl_2$, K_2HPO_4, and sorbitol to the fermentation broth) [57]. Nasser et al. also attempted to obtain HA from Rosetta2 (DE3) pLysS, with a successful yields of 346.7 mg/L in Super Optimal broth with Catabolite repression (SOC) medium and 500 mg/L in terrific broth (TB) medium [57]. Lastly, they analyzed the ability of Rosetta-gami B (DE3) pLysS to produce HA by transforming it with *hasA* (hyaluronic acid synthase gene), *hasB* (UDP-glucose dehydrogenase gene), *hasC* (UDP-glucose pyrophosphorylase gene), *hasD* (acetyltransferase gene), *hasE* (phosphoglucoisomerase gene) genes; in this way, they obtained 585 mg/L of HA [57].

In this case, it is also possible to note that the composition of the fermentation medium and the bacterial strain affect the HA yield. In a study by Nasser et al., it emerged that *B. megaterium* was able to produce a higher amount of HA rather than *E. coli*. Indeed, by expressing only the *hasA* gene along with the addition of xylose, $MgCl_2$, K_2HPO_4 and sorbitol to Luria-Bertani (LB) fermentation broth, they were able to obtain 50 mg/L of HA. By expressing *hasA*, *hasB*, and *hasC* with the addition of sucrose to LB fermentation broth, the yield of HA was about 2116.7 mg/L. In TB broth instead, the yield was decreased (2016 mg/L). At this point, they modified the fermentation medium, and they observed that in A5 + sodium 2-hydroxy-3-(morpholin-4-yl)propane-1-sulfonate (MOPSO) medium (containing yeast extract and a mineral medium based on MOPSO buffer), the amount of HA was about 1990 mg/L. As a final step, they introduced *hasA*, *hasB*, *hasC*, *hasD*, and *hasE* genes in *B. megaterium* cells. In LB medium with sucrose, the HA yield was about 2350 mg/L; in A5+MOPSO medium, the HA amount was about 2436 mg/L [57].

Another study used *E. coli* Rosetta (DE3) as the host to obtain the production of HA by optimizing the fermentation medium and inserting the *hasA* and *hasE* genes [57]. In this case, the fermentation broth contained glucose as the carbon source, $MgSO_4$ as the Mg^{2+} donor, and KH_2PO_4 and K_2HPO_4 as the phosphate sources [57]. This study further demonstrated the effect of fermentation temperature on HA yield, since the maximum HA biosynthesis was observed when fermentation was run at less than 37 °C. Finally, it was observed that the gene expression inductor concentration also could affect the HA yield. The highest HA concentration was obtained when the cell growth was at the lowest; that is, when the concentration of the gene expression inductor was the highest. Indeed, in these conditions, the cellular growth decreased and the HA concentration increased [57].

As previously mentioned, bacilli also can be used for HA production since they are safe, can be easily genetically tractable, and are able to grow in simple culture media [60]. In particular, in a recent study *B. subtilis* 3NA was engineered by overexpressing the *hasA* gene of *S. zooepidemicus* and its other endogenous genes involved in the HA biosynthetic pathway [58]. The fermentation medium contained glycerol as the carbon and energy source, H_3PO_4 as the phosphate source, NH_4OH as the nitrogen source, $MgSO_4$ as the Mg^{2+} donor and sulfur source, and finally KOH to buffer the pH [58]. Hence, the obtained HA yield was comparable with the streptococcal one [58].

Thus, all mentioned works allowed us to understand that the strain, exogenous genes, and fermentation conditions (i.e., soil composition, temperature, pH, concentration of the gene expression inductor, and agitation speed) are fundamental parameters that affect HA yield. The optimization of these parameters is fundamental for obtaining the highest HA amount from bacterial fermentation.

4. HA as a Powerful Bioactive Molecule

HA has been used for both medical and commercial applications thanks to its biocompatibility, biodegradability, and non-immunogenicity. Therefore, several HA-based products have been developed and are currently available on the market. HA showed its major potential for aesthetic applications but also was revealed to be promising in other biomedical fields. This is due to the fact that HA was revealed to be a versatile biomaterial with tunable properties that allowed the development of different kinds of devices (i.e., injectable formulations, gels, nanoparticles,

sponges, and hydrogels) according to the injured tissue's specific requirements. The main applications of HA as a powerful bioactive molecule are summarized in **Figure 3**.

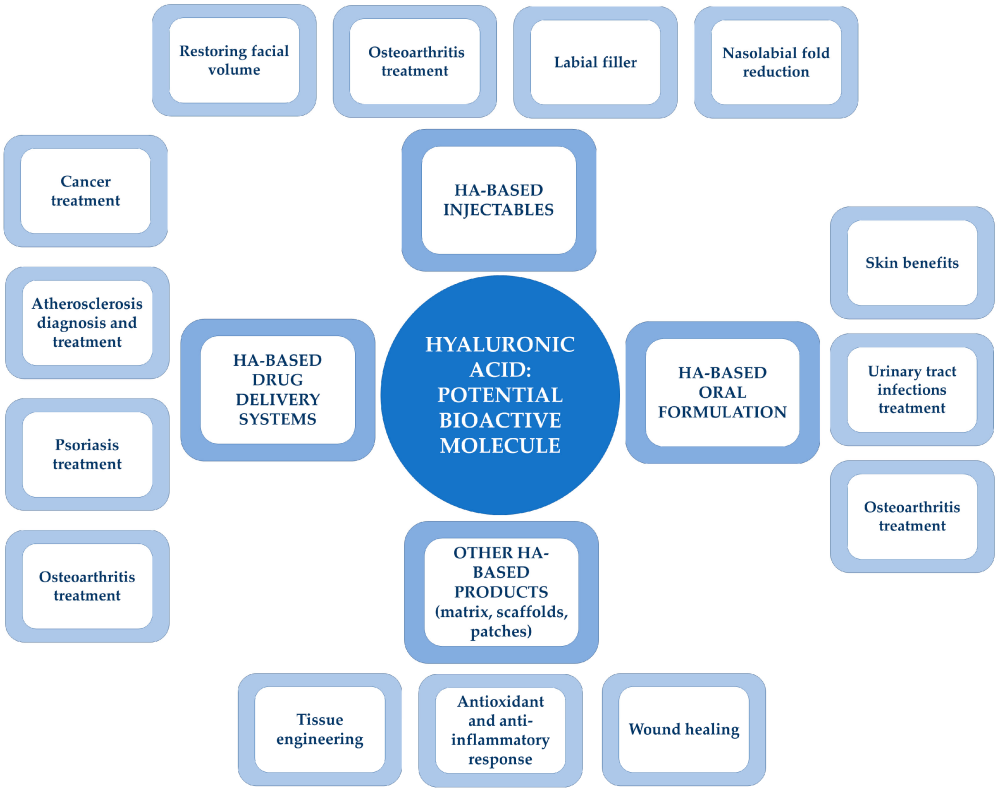


Figure 3. HA: a powerful bioactive molecule. Schematical representation of the most important HA applications in the health-related sector.

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