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Antimicrobial Role of Glycosaminoglycans: Beyond Bacterial Adhesion to Host Cell †

Zannat Urbi [1], Nina Suhaity Azmi [1,*] and Md. Sanower Hossain [2,*]

1 Department of Industrial Biotechnology, Biotechnology, Faculty of Industrial Science and Technology, Universiti Malaysia Pahang, 26300 Kuantan, Malaysia; urbi.zannat@gmail.com (Z.U.); nina@ump.edu.my (N.S.A.)

2 Department of Biomedical Science, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, 25200 Kuantan, Malaysia; mshossainbge@gmail.com

* Correspondence: nina@ump.edu.my (N.S.A.); Tel: +6095492404 (N.S.A.); mshossainbge@gmail.com (M.S.H.); Tel.: +601169609649 (M.S.H.)

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Abstract: Glycosaminoglycans (GAGs) are complex unbranched polysaccharides widely found in intracellular compartments, at the cell surface, and in the extracellular environment in living organisms. This availability facilitates attachment of a wide variety of microbial pathogens, including viruses, bacteria, parasites, and fungi, to the host cells and invasion or evasion of host defence mechanisms. There are no doubt GAGs has a potential role in pathogenesis in infectious diseases, and at the same time, GAGs have multiple applications in the medical, veterinary, pharmaceutical, and cosmetic fields. However, little is known about the mechanistic role of GAGs as therapeutic agents, particularly antimicrobial agents. Several documented literature reported primary findings of the antibacterial, antiviral and antiparasitic role of GAGs in controlling infections. Heparin, one kind of GAGs, can prevent biofilm formation for a more extended period in ureteral stents. Desulfated heparins also reduced bacterial adhesion to different extents depending on the bacterium and the sulfated residue. Are GAGs valuable agents for the treatment of infectious diseases or only facilitator of the pathogenesis of infections? This prospective study aimed to discuss the current understanding of how microbes co-opt GAGs activities to bypass host defence mechanisms and to propose the reverse role of GAGS as antimicrobial agents for the inhibition of infections or treatment of infectious diseases by considering the contributing mechanisms to the anti-infective pharmacology of GAGs alone or GAGs-based experimental studies.

Keywords: antibiotics; heparin; hyaluronic acid; receptors

1. Introduction

Infectious diseases (IDs) are the top 10 leading causes of death worldwide [1]. IDs remained unresolved yet for many factors, including changes in the environment, inadequate preventive measurement, unrestricted travel and global trade, importantly host susceptibility changes, and microorganisms themselves grow resistance through altering their genetic makeup [2]. Emerging and re-emerging infections are added a high death toll to the IDs list. Currently, coronavirus disease 19 (covid-19) is one of the best examples of an emerging infectious disease that has already killed about 3.2 million (worldometers.info, access on 30 April 2021). The increasing prevalence of antibiotic resistance (ABR) makes IDs eradication more complicated [3,4], and an urgent alternative is crucial to resolve IDs health problems.

Glycosaminoglycans (GAGs) are long unbranched polysaccharides covalently attached to a wide variety of core proteins. GAGs display remarkable structural diversity, which enables them to fulfil numerous functions, such as in anticoagulation of blood, inhibition of tumour growth and metastasis, but also to control of inflammatory processes [5-8]. However, GAGs have a role in pathogenesis, particularly in bacterial infections. GAGs facilitate pathogen attachment, invasion, or evasion of host defence mechanisms [9]. On the contrary, at a specific concentration, GAGS, particularly heparin sulfate, one of the GAGs classes, capable of inhibiting bacterial adhesion to the cells [10]. So, a question may arise, are GAGs valuable agents for treating IDs or only facilitator of the pathogenesis of infections? Therefore, this prospective study aimed to discuss the current understanding of how microbes co-opt GAGs activities to bypass host defence mechanisms and to propose the reverse role of GAGS as antimicrobial agents for the inhibition of infections or treatment of infectious diseases by considering the contributing mechanisms to the anti-infective pharmacology of GAGs alone or GAGs-based experimental studies.

2. Role of GAGs in Infections

As GAGs have the diversity of their core proteins, especially patterns of composition, and nature of sulfation in saccharide chains, modification of GAGs chain produces specific binding motifs for many ligands, which become facilitators for bacterial adhesion to the cells [10]. Therefore, different types of invasive microbes such as a broad spectrum of viruses, bacteria and parasites can recognize GAGs as cell surface receptors, and through this process, microbes bypass host defence mechanisms and infect host cells. In addition to infection progression, Nelson, *et al.* [11] reported that the GAGs inhibited the endogenous antibacterial activity of plasma and isolated antimicrobial peptides. They also reported that the GAGs in relevant concentrations neutralize antimicrobial peptides in plasma.

3. Antimicrobial Role of GAGs

The concept of GAGs use for infections was drawn in 1968 by Filkins and Di Luzio [12]. They tested heparin for the ability to influence shock induced by lipopolysaccharide in a rat model. Lipopolysaccharide was extracted from *Salmonella enteritidis*, *S. typhimurium*, and *Escherichia coli* to mimic the sepsis shock conditions. Heparin significantly lowers the lethality compared to the untreated group; however, it was ineffective after 180 minutes of shock induction. Additionally, heparin pretreatment maintained normal leukocyte levels after endotoxin treatment. They suggested the role of heparin in the physiological defence against endotoxemia.

Heparin was tested in *Pseudomonas pneumonia* induced acute lung injury in sheep, and inhalation of heparin attenuates acute lung injury, but it was intravenous administration of heparin not effective [13]. Their data suggested that nebulized inhaled heparin is a beneficial therapy for sepsis-induced acute lung injury.

Biofilm formation on the prosthetic devices and developing ABR by bacteria have complicated IDs management like osteomyelitis. Uses of heparin can alleviate biofilm formation and control infections. Tenke, *et al*. [14] used a heparin-coated urinary catheter to resist encrustation by crystalline *Proteus mirabilis* biofilm. The heparinized nephrostomy tubes remained unaffected for the whole 6–8 weeks indwelling periods, whereas uncoated tubes got obstructed within 2–3 weeks. This pilot study showed that no biofilms were detectable on heparin-coated stents, whereas significant biofilms were demonstrated in 33% of uncoated stents. However, mild incrustation was observed in 10% of heparin stents, whereas a significantly higher incrustation (50%) was on the uncoated stents.

Like bacteria, viruses are also received advantages in terms of attachment to the host cell surface because of the presence of GAGs and invade host cells. Heparan sulfate (HS) facilitates the binding of viruses to the cell. However, heparin, an analogue of HS, has the potentiality to inhibit viral attachment, for example, Dengue-2 virus (DENV-2) [15]. This in vitro study demonstrated that heparin could compete with the HS on the cell membrane for binding viruses, and heparin showed superiority on HS; therefore, heparin inhibits replication of DENV-2 and Japanese encephalitis viruses in hepatoma and BHK-21 cells, respectively [15]. GAGs have been shown to be effective to

prevent infections caused by the measles virus [16], influenza virus, strain H5N1 [17], Zika virus infections [18]. Knowledge about the role of GAGs against parasite has known very little. However, GAGs also accelerate the infections caused by the parasites. Similarly, heparin determined as a potential inhibitor of parasitic infections through altering the activity of a cysteine protease and accelerating the degradation of proteins in the parasite [19,20].

4. Conclusions

In general, the role of GAGs in pathogenesis is widely discussed in all levels of studies. Recent extensive research revealed the reverse role of GAGs in inhibiting the invasive microbes' attachment to the cell surface and their replication in the infected cells. Heparin is one of the potential GAGs that can compete with other GAGs to inhibit microbial binding and progression. Further studies are required to validate the target-specific inhibiting role of GAGs against infectious microbial agents.

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