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Hydrophobicity in Guiding Biological Interactions and Related Applications

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Abstract. Hydrophobicity is a universal phenomenon in nature with profound effects on the structure and function of biological macromolecules, which holds great promise for biomedical applications. Therefore, this paper reviews recent research advances in hydrophobicity in guiding biological interactions and their applications, pointing out that the folding and aggregation of biomolecules, such as proteins and lipids, in water is greatly influenced by hydrophobicity, and that the repulsive force of hydrophobic groups leads to the formation of stable spatial structures of biomolecules, maintaining their biological activity. Furthermore, modulation of hydrophobicity has been widely used to enhance the ability of the materials to disrupt cell membranes, and to improve antimicrobial properties while taking biocompatibility into account. The optimization of the hydrophobic group structure has led to significant advances in the development of antimicrobial polymers for medical implant applications. These advances have been achieved through the implementation of efficient and safe material design strategies. In addition, the equilibrium between hydrophilicity and hydrophobicity is critical in gene delivery. A moderate augmentation of hydrophobicity can help improve delivery efficiency and cellular uptake. It has been shown that adjusting the hydrophobicity of the nanoparticle surface can significantly influence the activity of immune cells, thus providing a new pathway for immune modulation. As such, the paper also investigates the potential applications of hydrophobicity in biomaterials design and proposes future directions, which includes standardized analytical approaches, and multidimensional experimental design. These approaches are intended to facilitate the advancement and utilization of functional materials based on hydrophobicity in biomedical fields.

Keywords: Hydrophobicity, Polymer, Biological Interactions, Nanoparticles.

1. Introduction

The role of hydrophobicity in regulating the structure and function of biological molecules is of particular significance, particularly with regard to the spatial conformation of proteins and lipids. In recent years, with the rapid development of the biomedical field, there has been an increasing amount of research on the application of hydrophobicity in antimicrobial polymers and gene delivery systems. Nevertheless, current research often focuses on the hydrophobicity regulation of specific polymers, lacking systematic reviews and standardized evaluation methods. Therefore, the paper aims to explore the mechanisms of hydrophobicity in guiding biological interactions and related applications, with a focus on its application in antimicrobial materials, gene delivery, and immune responses. Through a systematic literature review, it summarizes the current status of hydrophobicity in these areas, explores

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the effect of hydrophobicity on antimicrobial properties, gene delivery efficiency, and immune cell activation mechanisms through modulation of the polymer structure, and evaluates the limitations of the existing research approaches. This paper provides a theoretical foundation for the design of future biomaterials and proposes standardized evaluation methods to address the challenges faced by hydrophobicity in biomedical applications.

2. The Role of Hydrophobicity in Polymer Systems

2.1. Basics of Hydrophobic Effects

The hydrophobic effect characterizes the behavior of nonpolar molecules in water; these nonpolar molecules are unable to interact with water molecules through hydrogen bonding. As a result, water molecules form an ordered repulsive structure around these nonpolar molecules, which reduces the entropy of the system. When two hydrophobic molecules are in close proximity, the nonpolar surface area exposed to water decreases, which decreases the degree of ordering of the water molecules and thus increases the entropy of the system. The spontaneity of this process is driven by an increase in entropy, i.e., the aggregation of hydrophobic molecules helps to reduce the ordering of the water molecules on the nonpolar surface, decreasing the overall free energy of the system. This mechanism explains why hydrophobic molecules tend to form aggregates or micelles in the aqueous phase, thereby affecting their function in organisms [1]. As shown in Figure 1, water molecules form an ordered structure around a single hydrophobic molecule [2].

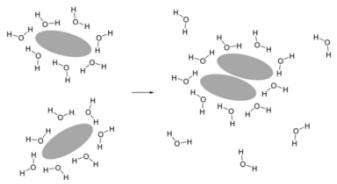

Figure 1. Water Molecules Forming an Ordered Structure around a Single Hydrophobic Molecule

2.2. Hydrophobic Aggregation Behavior in Polymers

In polymer systems, the presence of hydrophobic groups greatly affects the self-assembly behavior and function of the polymer. Hydrophobic groups in polymers drive these molecules to form ordered hydrophobic aggregates in water, a phenomenon that plays a key role in many biomedical applications. For example, in antimicrobial polymers, by adjusting the types and lengths of hydrophobic groups, their ability to penetrate bacterial membranes can be optimized, thus enhancing antimicrobial efficacy. Specifically, hydrophobic polymers can insert into bacterial membranes and disrupt their structure, leading to membrane leakage and cell death. Additionally, hydrophobic polymers also affect their adsorption and uptake on cell membranes. Higher hydrophobicity generally improves the affinity of the polymer for the membrane, which is particularly important for gene delivery systems, as it can enhance gene transfection efficiency and drug delivery effectiveness within cells. Such regulation not only impacts the biological performance of the materials but also optimizes their application in the biomedical field [3].

3. Applications of Hydrophobic Polymers in Biomedical Fields

3.1. Design and Mechanisms of Antimicrobial Polymers

The use of hydrophobicity in antimicrobial polymers has been widely recognized. Early studies of host defense peptides as alternatives to conventional small molecule antibiotics revealed their antimicrobial mechanisms [4]. These peptides contain cationic groups and regularly distributed hydrophobic side chains that form amphipathic helical structures that disrupt the integrity of bacterial membranes, thus leading to membrane leakage and cell death. Further studies optimized this selective toxicity by adjusting the position and chemical nature of the hydrophobic side chains. The synthesis of

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amphipathic polymethyl methacrylate derivatives and their hemolytic activity (HC50) against red blood cells are shown in Figure 2 [5]. The research results showed that the hemolytic activity was mainly influenced by the total hydrophobicity (∑logP) rather than the specific chemical properties of the hydrophobic moietys. Despite the crucial role of cationic segments in antimicrobial activity, hydrophobicity remains the key factor in membrane binding and pore formation. And the design of amphipathic cationic-hydrophobic block copolymers represents a pivotal approach in the advancement of antimicrobial polymers. By modifying the hydrophobicity of these polymers, it is possible to enhance their antimicrobial efficacy and biocompatibility, thereby developing more effective and safer antimicrobial materials.

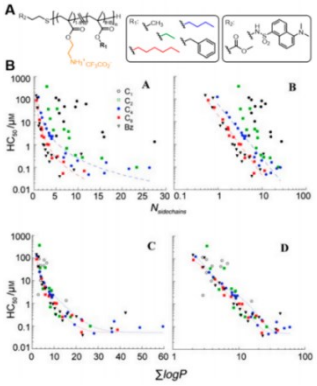

Figure 2. Synthesis of Amphipathic PMMA Derivatives and Their Hemolytic Activity (HC50)

3.2. Antimicrobial Polymers Containing Amino Guanine

In-depth studies have been conducted on the antimicrobial properties of hydrophobic amino guanine polymers. The left side of Figure 3 shows the chemical structure of polymers based on amino guanine salts (PGXs), which are synthesized by selecting different hydrophobic groups (such as PGE, PGO, PGC, etc.). Different hydrophobic groups can adjust the hydrophobicity of the polymers, thus affecting their antimicrobial properties. The central part of the figure shows the state of PGXs in solution; these polymers can be synthesized and dissolved in solution or coated on surfaces to form antimicrobial coatings. The right side of the figure displays the biological activity of PGXs, including their bactericidal effects, ability to inhibit bacterial biofilm formation, and ability to provide persistent antimicrobial effects after implantation. By modifying the configuration of the hydrophobic groups, researchers have devised novel, highly efficacious antimicrobial materials and medical implants. PGXs exhibit remarkable antimicrobial efficacy in both solution and on coated surfaces, suggesting a vast array of potential applications [6].

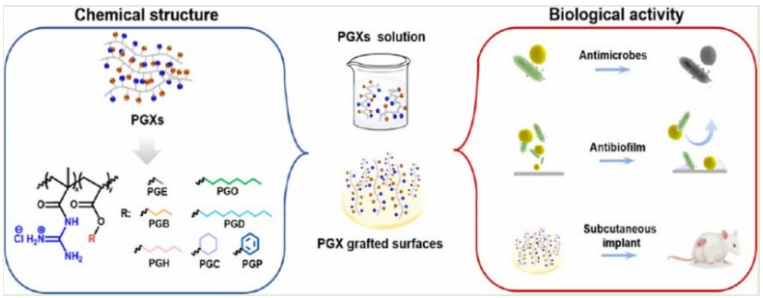

Figure 3. Hemolytic Activity and Gene Transfection Efficiency of Different Polymers

3.3. Hydrophobicity Regulation in Gene Delivery Systems

Gene delivery represents a promising therapeutic approach for the treatment of a wide range of clinical diseases, including cancer, cardiovascular diseases, neurological disorders, and viral infections [7].

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Thus, the balance between hydrophobicity and hydrophilicity of polymers is of critical importance in the gene delivery process. It has been demonstrated that augmenting the hydrophobicity of antimicrobial polymer systems (either through the direct introduction of hydrophobic groups or the utilisation of a high ionic capacity) typically enhances membrane interactions, cellular uptake and delivery efficiency. Experiments analyzed the effects of different branching hydrophobicities on gene transfection. The lower left side of Figure 4 shows the hemolytic activity curves of different polymers, with results indicating that increased branching hydrophobicity significantly enhances the polymer's hemolytic activity [8]. The bar chart on the lower right of Figure 4 shows gene transfection efficiency, where polymer b exhibited the best transfection efficiency at higher N/P ratios [8], while polymer d, despite having the highest hydrophobicity, did not show ideal transfection efficiency due to its higher cytotoxicity. These results suggest that moderate hydrophobicity (such as hexyl and 4-methylbenzyl) can significantly enhance gene transfection efficiency while maintaining low toxicity.

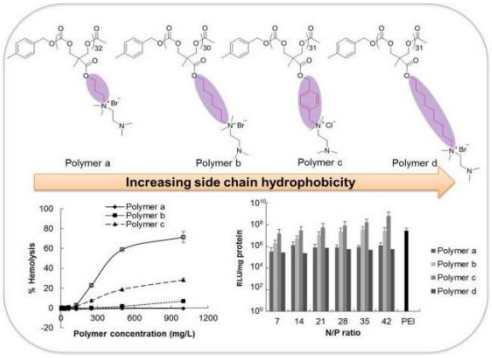

Figure 4. Gene Transfection Efficiency of Different Polymers

4. Interaction of Hydrophobicity on Immune Responses and Proteins

Research indicates that the hydrophobicity of polymers plays a significant role in interactions with cells and proteins. In vivo, numerous proteins with hydrophobic regions are distributed throughout the blood and cell membranes, and these proteins are crucial for immune responses, cell growth, and cell adhesion [9]. When polymer materials enter the body, they must navigate various potential interactions while avoiding disruptions to cell behavior and function. Rotello and colleagues demonstrated how polymer hydrophobicity directly affects immune responses in spleen cells using a set of engineered gold nanoparticles with tunable hydrophobicity. The researchers constructed a series of nanoparticles that differed only in their surface ligand head groups and calculated their logP values to rank them by hydrophobicity. Figure 5(A) indicates gold nanoparticles protected by a monolayer, with adjustable surface functional groups (R groups) [5]. By altering the chemical properties of these functional groups, the hydrophobicity (logP value) of the particles can be controlled. For example, the head groups of NP1 to NP9 range from relatively hydrophilic (e.g., the amine group of NP1) to highly hydrophobic (e.g., the phenyl group of NP8), with logP values increasing from 0.63 to 5.35. Figure 5(B) illustrates the relationship between the logP values of the nanoparticle head groups and the gene expression of the pro-inflammatory cytokine TNF and the anti-inflammatory cytokine IL-10. The upper part of the figure shows that as the logP value increases (indicating greater particle hydrophobicity), the gene expression of TNF also increases, suggesting that more hydrophobic nanoparticles may more strongly activate pro-inflammatory immune responses. The lower part of the Figure shows that IL-10 gene expression varies less with different logP values, but there is a slight trend of increasing expression for more hydrophobic nanoparticles (e.g. NP8). This may indicate that more hydrophobic nanoparticles can also enhance anti-inflammatory responses under certain conditions. Both in vitro and in vivo studies (in mouse models) show a linear increase in immune activity with increased hydrophobicity, providing important insights into the molecular mechanisms of

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immune cell activation, particularly the role of hydrophobicity in guiding immune responses in biological systems.

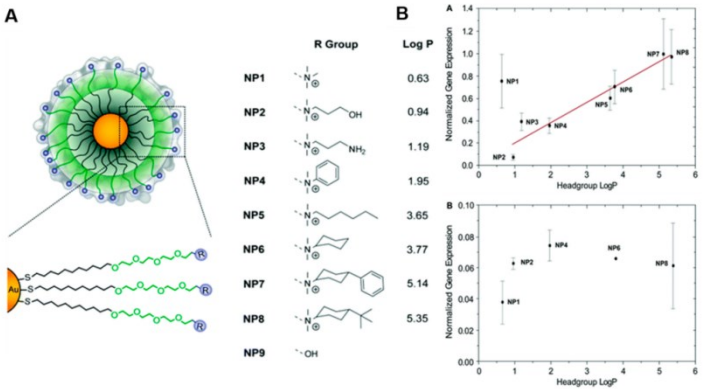

Figure 5. Effect of Hydrophobicity on Immune Response: (A) Surface Functional Groups and LogP Values of Gold Nanoparticles; (B) Gene Expression of TNF and IL-10

5. Conclusion

The attainment of an equilibrium between hydrophobic and hydrophilic characteristics in polymeric biomaterials is essential for the optimal functioning of these materials within biological systems. The results indicate that this equilibrium not only affects the interactions between polymers and biological membranes but also determines their biocompatibility and therapeutic efficacy. Therefore, in the field of antimicrobial polymers, it is essential that the design of the material ensures effective interactions with bacterial membranes while avoiding toxicity to mammalian cells. In terms of tissue engineering, the binding of target cell types to scaffolds or implants is a crucial step in the process of healing and regeneration. Importantly, non-specific protein attachment should be avoided to prevent an immune response. For drug delivery, nanomedicines are intended to evade interactions with serum proteins and blood cells during circulation, in order to prevent premature clearance. However, this may also have an impact on the internalization efficiency by target cells. Despite the existence of numerous studies aimed at elucidating the physicochemical properties of polymers, there is a lack of standardized and consistent analytical methodologies for the evaluation of these properties in specific applications. The implementation of standardized processes and consistent analytical methods, including computational models and statistical approaches, will facilitate future experimental design, result interpretation, and a comprehensive understanding of the role of chemistry and hydrophobicity in guiding biological interactions. The majority of studies employ the partition coefficient (logP) as a quantitative measure of hydrophobicity. However, the predictive power of logP is diminished when applied to larger polymer systems. Mathers and colleagues put forth the solubility parameter logP/SA, which considers the number of repeat units and polymer surface area, and has been demonstrated to yield more meaningful correlations. The combination of computational models with experimental validation, particularly for synthetic polymers, using UV or fluorescently labeled materials, enables the sensitive and quantitative characterization of water/oil biphasic models. These methods will facilitate the accelerated development of novel functional and efficient biomaterials, thereby advancing their translational applications in the biomedical field.

References

[1] Chandler, D. (2005) Interfaces and the driving force of hydrophobic assembly. Nature. 437(7059): 640-647.

[2] Jonsson, A.L., Roberts, M.AJ., Kiappes, J.L., Scott, K.A. (2017) Essential chemistry for biochemists. Essays Biochem. 61(4): 401-427.

DOI: 10.54254/2753-8818/64/2024.18019

[3] Ghezzi, M., et al. (2021). Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. Journal of controlled release : official journal of the Controlled Release Society.

[4] Timofeeva, L. and Kleshcheva, N. (2011) Antimicrobial polymers: mechanism of action, factors of activity, and applications. Appl Microbiol Biotechnol 89, 475-492.

[5] Pearce, A.K. and O'Reilly R.K. (2021) Polymers for Biomedical Applications: The Importance of Hydrophobicity in Directing Biological Interactions and Application Efficacy. Biomacromolecules. 22(11): 4459-4469.

[6] Rao, Y, et al. (2024) Regulation of Hydrophobic Structures of Antibacterial Guanidinium-Based Amphiphilic Polymers for Subcutaneous Implant Applications. Biomacromolecules. 25(1): 89-103.

[7] Yadav, K.S., et al. (2023). Biomedical applications of nanomaterials in the advancement of nucleic acid therapy: Mechanistic challenges, delivery strategies, and therapeutic applications. International journal of biological macromolecules, 124582 .

[8] Ong, Z.Y., et al. (2017) Biodegradable cationic poly (carbonates): Effect of varying side chain hydrophobicity on key aspects of gene transfection. Acta Biomater. 54: 201-211.

[9] Vinderola, C., et al. (2004) Relationship between interaction sites in the gut, hydrophobicity, mucosal immunomodulating capacities and cell wall protein profiles in indigenous and exogenous bacteria. J Appl Microbiol. 96(2): 230-243.