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Study on the Difference of Intestinal Barrier Function and Homeostasis Regulation by Different Vectors-Mediated Probiotics Delivery

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Abstract: This study investigates the differential regulatory mechanisms of polysaccharide-based, protein-based, and liposome-mediated probiotic delivery systems in maintaining intestinal barrier homeostasis. By analyzing the physicochemical properties of these three carrier types and their interactions with probiotics, the research reveals how carrier materials influence barrier function through molecular pathways including regulation of tight junction protein expression, activation of goblet cells, and polarization of immune cells. Polysaccharide carriers demonstrate sustained release and immune modulation effects, protein-based carriers enhance microbial colonization through targeted release, while liposomes prioritize activation of epithelial repair signaling. The synergistic interaction between carrier degradation products and microbial metabolites further optimizes the intestinal microenvironment. Future delivery system design should integrate material properties with host-microbiota interaction networks to achieve precise and long-term regulation of intestinal barriers.

1. Introduction

Intestinal barrier homeostasis serves as the cornerstone of host health maintenance, with its imbalance being closely associated with various metabolic and inflammatory bowel diseases. Probiotics, as key therapeutic agents for regulating gut microbiota balance, demonstrate highly dependent delivery efficiency and targeting capabilities on vector system design. Currently, polysaccharide-based vectors, protein-based vectors, and liposome vectors exhibit distinct biological effects in probiotic encapsulation, intestinal colonization, and barrier function regulation due to their varying physicochemical properties. This study systematically analyzes the delivery characteristics of these three types of vectors, exploring their differential impacts on tight junction protein expression, mucus layer secretion, and immune regulatory pathways. The findings aim to provide theoretical foundations for optimizing probiotic delivery systems.

2. Relationship between carrier type and probiotic delivery efficiency

2.1 Slow release characteristics and intestinal adhesion mechanism of polysaccharide-based carriers

Polysaccharide-based carriers have become pivotal in probiotic delivery systems due to their exceptional biocompatibility and biodegradability. Their sustained-release properties stem from the physical encapsulation capacity of polysaccharide molecular chains and pH/enzyme-responsive degradation mechanisms. Natural polysaccharides like sodium alginate and chitosan form three-dimensional networks through ionic gelation or electrostatic interactions, effectively protecting probiotics from gastric acid and bile salt degradation while enabling controlled release of active strains in intestinal environments. Moreover, the adhesion properties of polysaccharides significantly influence probiotic colonization efficiency. Certain polysaccharides can establish hydrogen bonds or hydrophobic interactions with mucin in the intestinal mucus layer, prolonging carrier retention time on intestinal epithelial cells and enhancing local microbial concentration. Additionally, specific polysaccharides may activate downstream signaling pathways by modulating surface receptors on intestinal immune cells, thereby indirectly improving colonization stability. However, optimizing mechanical strength and degradation rates remains crucial to prevent premature disintegration or excessive slow-release that could compromise microbial viability. Future research should focus on chemical modification strategies and composite carrier approaches to further enhance delivery precision[1].

2.2 pH responsiveness and targeted release behavior of protein-based carriers

Protein-based carriers demonstrate remarkable pH-responsive characteristics in probiotic delivery systems due to their unique structural tunability and biological functionality, enabling targeted intestinal release. Unlike polysaccharide carriers, proteins 'conformational changes are highly dependent on environmental pH levels, maintaining stability under low gastric pH conditions while undergoing depolymerization or swelling in the intestinal neutral or slightly alkaline environment, thus precisely controlling the release site of probiotics. For instance, whey protein forms a dense structure through hydrophobic interactions and disulfide bond cross-linking in gastric acid, effectively protecting encapsulated probiotics. When entering the intestinal tract, increased pH levels cause protein deprotonation and enhanced intermolecular electrostatic repulsion, leading to structural relaxation and release of live bacteria[2]. Additionally, certain proteins bind to specific receptors on intestinal epithelial cell surfaces, further enhancing the delivery system's targeting efficiency. This pH-dependent release mechanism not only improves probiotic survival rates but also optimizes colonization efficiency in specific intestinal regions. However, the mechanical strength and thermal stability of protein carriers still require improvement. Future strategies may involve combining with other biopolymers or genetically modifying protein structures to balance pH sensitivity with controlled delivery, thereby achieving more precise regulation of probiotic release kinetics.

2.3 Transmembrane transport capacity and biofilm compatibility of liposome carriers

Liposomes, as a class of nanoscale delivery systems composed of phospholipid bilayers, demonstrate unique transmembrane transport advantages and excellent biofilm compatibility in probiotic delivery. Their structural characteristics enable effective penetration through the intestinal epithelial cell barrier via endocytosis or membrane fusion mechanisms, primarily relying on biomimetic properties derived from phospholipid composition similar to cell membranes.

Compared with polysaccharide and protein carriers, liposomes' bilayer structure not only effectively encapsulates probiotic active components but also precisely controls membrane fluidity and stability by adjusting proportions of phosphatidylcholine, cholesterol, and other components, thereby adapting to varying physicochemical environments across gastrointestinal segments. In terms of biocompatibility, liposomes utilize human-derived phospholipids whose degradation products are non-immunogenic and directly metabolized by intestinal cells. Notably, surface ligand modification can further enhance active targeting interactions between liposomes and specific intestinal epithelial cells, providing novel approaches for modulating the local intestinal immune microenvironment[3]. However, challenges remain in controlling encapsulation efficiency during large-scale production and maintaining long-term storage stability. Future research may explore optimized cryoprotectants or solid lipid nanoparticles (SLNs) to balance delivery efficacy with industrial production feasibility.

3. Differences in the regulation of intestinal barrier structure by delivery systems

3.1 Expression regulation of tight junction proteins

The regulatory effects of probiotic delivery systems on intestinal barrier function are primarily manifested through their direct impact on the expression of tight junction proteins. As critical structural components maintaining the integrity of intestinal epithelial cell barriers, the expression levels and distribution patterns of these proteins directly determine gut permeability[4]. Different vector-mediated probiotic delivery systems can modulate protein expression through multiple molecular mechanisms: Polysaccharide-based vectors typically activate the TLR4/MyD88 signaling pathway to promote ZO-1 transcription, while protein-based vectors may enhance occludin's membrane localization stability by regulating intracellular calcium ion signals. Liposome vectors, owing to their excellent membrane fusion properties, can directly deliver probiotic metabolites to epithelial cells, thereby upregulating tight junction-related gene expression by inhibiting histone deacetylase activity. Notably, the physicochemical properties of vector materials themselves influence this process: positively charged vectors may temporarily disrupt tight junctions through electrostatic interactions, whereas neutral or negatively charged vectors tend to maintain barrier homeostasis[5]. Additionally, the synergistic interaction between probiotics and vectors should not be overlooked: extracellular polysaccharides secreted by certain strains can form complexes with vector materials, further enhancing their regulatory effects on tight junction proteins. Future research should focus on deciphering the spatiotemporal dynamic characteristics of interactions among vectors, microbial communities, and hosts to optimize the precision of delivery systems in regulating intestinal barrier functions[6].

3.2 Effects of goblet cell activity on mucus layer thickness

The regulatory effects of probiotic delivery systems on intestinal mucus barriers primarily manifest through dynamic influences on goblet cell activity and mucus secretion. As specialized secretory cells in the intestinal epithelium, goblet cells directly determine the thickness and composition of the mucus layer. Different vector-mediated probiotic delivery systems can modulate this process through distinct mechanisms[7]. Polysaccharide-based vectors (e.g., hyaluronic acid) not only act as physical barriers protecting goblet cells from inflammatory stimuli but also promote MUC2 transcription and secretion by activating CD44 receptors. Protein-based vectors reduce oxidative stress through iron ion chelation, indirectly maintaining normal goblet cell differentiation cycles. Their enzymatic breakdown products may directly act as signaling molecules regulating mucus secretion-related gene expression. Liposome vectors efficiently deliver lipophilic probiotic

metabolites, enhancing goblet cells' energy metabolism and secretory functions via the PPARγ pathway[8]. Notably, synergistic effects between vector materials and probiotics are crucial—specifically, surface proteins of certain strains can form biofilm-like structures with vectors, providing physical support for the mucus layer while continuously stimulating goblet cell activity through quorum sensing. This multi-level regulatory mechanism suggests that future vector design should comprehensively consider material properties and strain functionality compatibility to achieve spatiotemporal-specific repair of mucus barriers, which holds significant value for interventions in mucin-deficient diseases like inflammatory bowel disease[9].

3.3 Carrier-mediated immune cell polarization effect

The polarization state of intestinal immune cells plays a central role in maintaining the homeostasis of the intestinal barrier. Different vector-mediated probiotic delivery systems can achieve precise intervention in the gut microenvironment by regulating the phenotypic transformation of key immune cells such as macrophages. Polysaccharide-based vectors, due to their molecular patterns being specifically recognized by macrophage surface pattern recognition receptors, tend to induce M2-type anti-inflammatory polarization. This is achieved by upregulating arginase-1 (Arg-1) and IL-10 expression, thereby promoting tissue repair and inhibiting excessive inflammatory responses. Protein-based vectors regulate intracellular reactive oxygen species levels in macrophages through their iron-binding capacity. Their enzymatic degradation products activate the PPARγ pathway, synergizing with probiotic metabolites to promote M2 polarization and enhance immune tolerance of the intestinal barrier[10]. Liposome vectors, with their bilayer structure similar to cell membranes, not only efficiently deliver probiotic-derived signaling molecules but also target macrophage surface C-type lectin receptors through surface modification, enabling directional regulation of the M1/M2 balance. Notably, the physical properties of vector materials significantly influence immune recognition-nanocarriers are more easily internalized by macrophages, while neutral or mildly negatively charged surfaces reduce nonspecific inflammatory activation. These multi-level immune regulatory mechanisms suggest that ideal delivery systems require a tripartite interaction network among vectors, microbiota, and immune cells. Future research should focus on developing "smart vectors" with immune programming capabilities to achieve precise regulation of intestinal inflammatory diseases[11].

4. Functionally stable state optimization pathway of carrier-probiotic interaction

4.1 Synergistic effect of metabolites

The interaction between carriers and probiotics demonstrates significant synergistic effects in optimizing intestinal barrier homeostasis by regulating the synthesis and distribution of short-chain fatty acids (SCFAs). Different carrier systems influence probiotic metabolic activity through distinct mechanisms: Polysaccharide-based carriers not only serve as physical protective matrices but also release degradation products that act as substrates for probiotic fermentation, promoting the production of SCFAs such as acetic acid, propionic acid, and butyric acid. Enzymatic degradation products from protein-based carriers regulate intestinal pH levels, thereby optimizing the microenvironment for SCFAs-producing bacterial colonization. Liposome carriers encapsulate lipophilic SCFAs precursors via their hydrophobic cores, enabling targeted delivery and sustained release. The biological effects of SCFAs exhibit multi-dimensional regulatory features: Butyric acid, serving as the primary energy source for intestinal epithelial cells, enhances tight junction protein assembly through activation of the AMPK/mTOR signaling pathway; Propionic acid modulates goblet cell mucus secretion by binding to GPR43 receptors; Acetic acid exerts epigenetic regulation

through histone deacetylase inhibition. Notably, the synergistic interaction between carrier materials and SCFAs forms a positive feedback loop: Certain cationic polysaccharides adsorb anionic SCFAs via electrostatic interactions, prolonging their local action duration, while SCFAs in turn promote the proliferation of carrier-degrading bacteria. This dynamic interaction network suggests that future vector design should comprehensively consider the matching degree between material metabolic characteristics and microbial metabolic spectrum. By precisely regulating the spatial and temporal distribution of SCFAs, systematic optimization of intestinal barrier function can be achieved, which has important translational value for the intervention of diseases related to SCFAs deficiency such as metabolic syndrome and inflammatory bowel disease.

4.2 Potential effects of carrier degradation products on intestinal microenvironment

The degradation process of carrier materials not only affects the release kinetics of probiotics, but the metabolic products they generate also deeply participate in the homeostatic regulation of the intestinal microenvironment. The enzymatic degradation products of polysaccharide-based carriers can selectively promote the proliferation of specific symbiotic bacteria, regulating bile acid metabolism and immune tolerance through the microbiota-host co-metabolic network. Meanwhile, bioactive peptides generated from protein-based carrier degradation may directly act on calcium adhesion proteins in intestinal epithelial cells to enhance intercellular junction stability. Notably, phospholipid molecules released from liposome carriers after degradation can be metabolized by gut microbiota to produce anti-inflammatory mediators, while also serving as surfactants to improve the rheological properties of mucus layers. These degradation products and probiotic metabolites form a complex regulatory network: certain cationic polysaccharide degradation fragments can neutralize the negative charges of pathogenic lipopolysaccharides through electrostatic interactions, thereby reducing inflammatory responses. Specific amino acid sequences in protein hydrolysates competitively inhibit the binding of pathogenic adhesins to intestinal epithelial receptors. This dual regulatory mechanism suggests that carrier degradation is not merely a simple material decomposition process, but a significant biological event in shaping intestinal ecology. Future carrier design should systematically evaluate dose-response relationships of degradation products to avoid ecological imbalance caused by excessive accumulation, while developing intelligent carriers with pre-digestive characteristics to create spatiotemporal coupling synergies between degradation products and probiotic interventions, thereby achieving precise remodeling of the intestinal microenvironment.

4.3 Adaptive regulation of barrier function under long-term delivery

During long-term probiotic administration, the dynamic interactions between carrier systems and intestinal barrier function exhibit significant adaptive regulatory characteristics. This regulation manifests not only as short-term physiological responses but also reflects systematic remodeling of the host-microbiome interaction network. Polysaccharide-based carriers, leveraging their sustained-release properties and dual functions as microbial fermentation substrates, promote ecological succession in gut microbiota structure during long-term interventions. They particularly increase the relative abundance of short-chain fatty acid-producing bacteria, thereby enhancing intestinal epithelial barrier function through epigenetic regulatory mechanisms. Protein-based carriers, due to their amino acid composition differences, may establish more robust barrier structures by influencing host protein synthesis metabolism, regulating intestinal epithelial cell renewal cycles, and modulating the turnover rate of tight junction proteins during continuous delivery. Notably, liposome carriers demonstrate unique membrane-stabilizing effects in prolonged applications. Their phospholipid degradation products can integrate into intestinal epithelial cell

membranes, altering membrane fluidity and signal transduction efficiency to enhance environmental adaptability of barrier functions. This adaptive regulation also involves immune system participation: long-term carrier-probiotic complexes stimulate regulatory T cell maturation, fostering immune tolerance to symbiotic flora while maintaining pathogen defense capabilities. From a molecular mechanism perspective, sustained delivery alters the intestinal stem cell microenvironment to influence epithelial regeneration patterns and may regulate systemic metabolic states through the microbiota-gut-brain axis. Future research should prioritize understanding the cumulative effects of carrier materials and balancing host feedback regulation. Developing intelligent delivery systems with dose-responsive characteristics will enable precise long-term modulation of intestinal barrier function, which is crucial for managing and preventing chronic intestinal diseases. Carrier design must also account for individual factors such as host genetic background and baseline microbiota composition to optimize the efficacy-to-risk ratio and safety profile of long-term interventions.

5. Conclusions

This study demonstrates that polysaccharide-based, protein-based, and liposome carriers significantly influence probiotic intestinal colonization efficiency and barrier function regulation through distinct physical encapsulation mechanisms and chemical release strategies. Polysaccharide carriers enhance microbial survival by improving mucus permeability, protein-based carriers deliver active strains via localized pH-responsive release, while liposomes preferentially activate epithelial immune signaling pathways. Future research should integrate controllable modification of carrier materials with multi-omics analysis to further elucidate the molecular network of interactions among delivery systems, microbial communities, and host mechanisms. This will advance the clinical translation of targeted probiotic formulations.

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