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Advances in Directed Evolution Technology for Skincare Peptides

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ABSTRACT
Peptide-based ingredients, renowned for their high biological activity and excellent skin compatibility, have become a key component in the market for functional skincare products. However, the application of natural peptides is often limited by poor stability, low transdermal absorption efficiency, and insufficient bioactivity. Directed evolution, as a powerful molecular engineering strategy, mimics natural evolutionary processes to deliberately modify peptide sequences and thereby optimize their performance. This review systematically outlines recent advances in directed evolution technologies for skincare peptides, covering fundamental principles, methodological innovations, practical applications, and future prospects. It highlights strategies for constructing mutant libraries, high-throughput screening techniques, and the use of bioinformatics prediction models in peptide engineering, along with successful cases where this technology has enhanced peptide stability, skin permeability, and biological activity. Finally, the review discusses current challenges and potential future trends in the field of peptide directed evolution.

KEYWORDS
Peptide; Directed evolution; Skincare

1 Introduction

With the rapid expansion of the cosmeceutical market, peptide ingredients have gained increasing attention due to their exceptional biological activity and skin compatibility. Peptides are short-chain molecules formed by amino acids linked through peptide bonds, capable of modulating various physiological processes in skin cells. Their application in skincare stems from their precise ability to regulate skin functions. Cosmetic peptides can stimulate collagen production, inhibit muscle contractions, accelerate wound healing, or act as antioxidants, thereby delivering multiple benefits such as wrinkle reduction, firming, skin repair, and brightening [1]. However, natural peptides face significant limitations in practical applications, such as susceptibility to enzymatic degradation, poor skin permeability, and low bioavailability, all of which severely hinder their full potential in skincare. Traditional peptide optimization approaches largely rely on empirical amino acid substitutions or chemical modifications—methods that are not only time-consuming and labor-intensive but also lack precision, making it difficult to systematically enhance peptide performance. In recent years, directed evolution has emerged as a revolutionary molecular engineering strategy, demonstrating great promise in peptide optimization. By mimicking natural evolutionary processes, this technique enables targeted in vitro modifications of peptide sequences to generate variants with improved properties. Originating in the field of enzyme engineering, directed evolution was awarded the Nobel Prize in Chemistry in 2018. This review systematically summarizes recent advances in directed evolution techniques for skincare peptide sequences, explores innovative methodologies, representative applications, and future trends, offering valuable insights and guidance for further research in this field.

2 Fundamental principles of directed evolution technology

Directed evolution mimics natural evolutionary processes by introducing mutations and performing selection under controlled conditions, thereby accelerating the optimization of peptide performance. The core of this approach lies in two key steps: constructing mutant libraries and high-throughput screening. Building peptide mutant libraries forms the foundation of directed evolution, with primary methods including error-prone PCR, DNA shuffling, and synthetic biology techniques. Error-prone PCR introduces random mutations by using low-fidelity DNA polymerases during amplification, making it particularly suitable for optimizing peptides whose structure-function relationships are not fully understood. DNA shuffling involves fragmenting homologous gene sequences followed by random reassembly, enabling the rapid combination of beneficial mutations. In recent years, the emergence of synthetic biology and deep learning approaches has significantly enhanced both the efficiency and quality of mutant library construction [2].

High-throughput screening represents another critical component of directed evolution technology. Conventional screening methods are time-consuming and low in throughput, making them ill-suited for the demands of large-scale mutant library evaluation. In recent years, the application of microfluidics, fluorescence-activated cell sorting (FACS), and in vitro display technologies has dramatically enhanced screening efficiency. Cell-free synthesis systems have emerged as a promising high-throughput screening platform. Additionally, AI-powered skin models are playing an increasingly

important role in peptide screening. Furthermore, integrating multiple technologies can significantly accelerate the peptide discovery process. For instance, Wu et al. developed a strategy combining proteomics with mass spectrometry to screen candidate peptides, generating over 300 peptide variants with improved stability. The optimized peptides showed remarkable resistance to proteolytic degradation while maintaining potent biological activity, demonstrating the effectiveness of this high-throughput approach in advancing peptide development [3].

3 Key technological breakthroughs in directed evolution of peptides

3.1 Deep learning algorithms

With the rapid advancement of technology, peptide directed evolution has become a key research area in bioinformatics. In this process, innovations and applications of artificial intelligence (AI) have played a pivotal role. Deep learning algorithms are increasingly utilized in peptide sequence design and optimization, enabling highly efficient prediction of various biofunctional peptides with accuracy far surpassing traditional methods. These algorithms mimic the way human neurons process information, using multi-layered neural networks to learn the features and patterns within data. Capable of processing vast datasets, they extract meaningful information for prediction and classification. In peptide design, deep learning transforms complex biological information into simplified data, allowing for efficient analysis and processing. The emergence of deep learning models enables researchers to more precisely predict which amino acid substitutions might enhance a peptide's binding affinity or specificity toward target proteins. This capability has significantly accelerated the development of peptide directed evolution. By simulating peptide-protein interactions in silico, scientists can accurately identify beneficial amino acid changes. Moreover, in peptide structure prediction, deep learning can forecast the three-dimensional conformation of peptides and guide structural optimization. In the design of skincare peptides,Deep learning algorithms can predict and optimize the efficacy, activity, and toxicity of peptides. Bui et al. introduced a computational approach called GRACE, capable of generating peptide sequences with a triple-helical structure. This breakthrough overcomes a key bottleneck in collagen-mimetic peptide design, offering a flexible and universal platform for both fundamental research and engineered construction of collagen-like peptides [4].

3.2 Molecular simulation and docking techniques

The application of molecular simulation and docking techniques is playing an increasingly significant role. With the rapid advancement of computational biology and computer simulation technologies, these approaches have become powerful tools for scientists to explore novel peptide molecules and understand their interactions. In the field of molecular simulation, researchers employ methods such as molecular dynamics simulations and quantum chemical calculations to accurately model the structures and dynamic behaviors of biomolecules. These simulations enable scientists to study processes including peptide folding, peptide-peptide interactions, and the binding of peptides to target proteins. The results not only deepen the understanding of the underlying mechanisms of peptide interactions but also guide peptide design and predict their biological activity and efficacy. Molecular docking, a key component of simulation techniques, predicts the likely binding conformations and interaction modes between two molecules by calculating their interaction energies. In peptide design, this technique helps identify potential binding sites between peptides and target proteins, evaluate binding affinity and interaction patterns, and thereby inform the design and optimization of peptide candidates. By leveraging molecular docking, researchers can rapidly screen peptides with high affinity and specificity. Through computational modeling of peptide–target protein interactions, it becomes possible to predict which amino acid substitutions might enhance binding strength or selectivity. The emergence of these technologies has significantly improved the efficiency and precision of directed peptide evolution. For instance, Wu and colleagues integrated multiple approaches—including rational design, directed evolution, and machine learning—to achieve this goal.A novel signal peptide has been successfully identified. This discovery not only expands the repertoire of known signal peptides but also provides a powerful tool for enhancing the expression efficiency of secreted proteins in Yarrowia lipolytica [5].

4 Challenges and future development directions

4.1 Current technical challenges

Balancing screening throughput with efficiency remains a primary challenge. Despite continuous advancements in high-throughput screening technologies, comprehensive screening of extremely large mutant libraries is still impractical. Enhancing throughput while maintaining high screening efficiency is a critical issue that demands effective solutions. Limited accuracy in functional prediction poses another significant constraint. Although AI-based prediction models have

made progress, the complex structure-function relationships of peptides make it difficult to accurately forecast the effects of mutations—particularly in predicting peptide-protein interaction interfaces, where prediction reliability still needs improvement. High costs in industrial translation further hinder development. The laboratory research expenses associated with peptide directed evolution are substantial, and large-scale industrial application requires further cost reduction and improved economic viability [6].

4.2 Future development directions

A deeper integration of AI and machine learning will be a key trend moving forward. By developing more precise predictive algorithms—such as neural network models based on attention mechanisms—the accuracy and efficiency of mutant design can be significantly enhanced. Another promising direction is multi-objective parallel optimization. Traditional directed evolution typically focuses on optimizing a single performance metric, whereas real-world applications often require balancing multiple parameters simultaneously, such as activity, stability, solubility, and toxicity. The development of directed evolution platforms capable of optimizing several traits at once will better meet practical demands. Innovation in green and sustainable production technologies will also remain a priority. As environmental awareness grows, more efficient and eco-friendly methods for peptide biosynthesis are increasingly essential. Advances in synthetic biology are expected to drive peptide production toward greener and more sustainable pathways. Furthermore, the development of personalized peptide technologies holds great potential. With the rising trend of personalized skincare, tailoring peptide formulations to individual skin characteristics and needs is becoming feasible. By combining directed evolution with personal proteomic data, it will be possible to design skincare peptides that are precisely suited to individual requirements [7].

5 Conclusion

As a powerful molecular engineering strategy, directed evolution technology for skincare peptide sequences has demonstrated significant application potential and market value. By mimicking natural evolutionary processes, this approach enables targeted optimization of specific peptide properties, yielding mutants with superior characteristics. With the synergistic advancement of molecular biology, bioinformatics, high-throughput screening, and delivery systems, the efficiency and precision of peptide directed evolution continue to improve. The technology has already achieved industrial-scale application. However, challenges remain, including the trade-off between screening throughput and efficiency, limited accuracy in functional prediction, and high costs associated with large-scale production. Looking ahead, deeper integration of AI and machine learning, multi-objective parallel optimization, personalized peptide customization, and green, sustainable manufacturing innovations will further enhance the role of peptide directed evolution in skincare, delivering more effective, safer, and individualized solutions for consumers.

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References

[1] Ashaolu TJ. Applications of bioactive peptides in cosmeceuticals: a review. J Zhejiang Univ Sci B. 2025;26(6):527-545. Published 2025 Jun 11.

[2] Hashemi S, Vosough P, Taghizadeh S, Savardashtaki A. Therapeutic peptide development revolutionized: Harnessing the power of artificial intelligence for drug discovery. Heliyon. 2024;10(22):e40265. Published 2024 Nov 8.

[3] Wu Y, Rozans SJ, Moghaddam AS, Pashuck ET. Using High-Throughput Screening to Identify Crosslinking Peptides That Control Cell-Mediated Matrix Degradation. Adv Healthc Mater. Published online August 25, 2025.

[4] Bui TH, Adetunji O, Cole CC, Yu LT, Peterson CM, Hartgerink JD. De Novo Design of Specific Heterotrimeric Collagen-Like Peptides via Genetic Algorithm. Adv Sci (Weinh). Published online August 18, 2025.

[5] Wu Z, Chen W, Hong Y, Wang Y, Xu P. Machine learning-assisted rational design and evolution of novel signal peptides in Yarrowia lipolytica. Synth Syst Biotechnol. 2025;10(4):1275-1283. Published 2025 Jul 22.

[6] Aguilera-Puga MDC, Cancelarich NL, Marani MM, de la Fuente-Nunez C, Plisson F. Accelerating the Discovery and Design of Antimicrobial Peptides with Artificial Intelligence. Methods Mol Biol. 2024;2714:329-352.

[7] Karnwal A, Shrivastava S, Al-Tawaha ARMS, et al. Microbial Biosurfactant as an Alternate to Chemical Surfactants for Application in Cosmetics Industries in Personal and Skin Care Products: A Critical Review. Biomed Res Int. 2023;2023:2375223. Published 2023 Apr 13.