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ORIGINAL ARTICLE

Epigenetic Targeting of Obesity Genes by the SARS-CoV-2 Spike Protein

Alvo Epigenético de Genes da Obesidade pela Proteína Spike do SARS-CoV-2

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ABSTRACT

Introduction: Evidence suggests SARS-CoV-2 infection correlates with metabolic dysregulation, including obesity development through potentially epigenetic mechanisms. DNA methylation of obesity-related genes may represent a molecular pathway linking viral infection to adiposity predisposition. **Objective:** To computationally evaluate binding interactions between SARS-CoV-2 spike protein and methylation sites within obesity-associated genes FTO and MC4R using molecular docking simulations. **Methods:** Structural data for SARS-CoV-2 Omicron variant spike protein (PDB: 7QTK), FTO gene (PDB: 4ZS2), and MC4R gene (PDB: 6W25) were retrieved from RCSB Protein Data Bank. Three-dimensional molecular structures were prepared through addition of hydrogen atoms, geometric optimization, and removal of non-essential molecules. Methylation sites within FTO and MC4R genes were designated as binding targets. AutoDock software executed molecular docking algorithms to simulate protein-gene interactions, evaluating favorable binding conformations, energetics, and molecular interaction characteristics including hydrogen bonding, hydrophobic contacts, and electrostatic forces. Structural analysis identified potential interaction sites and binding affinities between viral spike protein and obesity gene methylation regions. **Results:** Molecular docking simulations revealed significant binding interactions between SARS-CoV-2 spike protein and methylation sites in both FTO and MC4R genes, characterized by multiple hydrophobic interactions, hydrogen bonds, and electrostatic contacts. **Conclusion:** Computational analysis demonstrates potential molecular interactions between SARS-CoV-2 spike protein and epigenetic regulatory sites of obesity-associated genes, suggesting plausible mechanistic pathways linking viral infection to obesity predisposition through epigenetic modulation.

Keywords: Obesity; SARS-CoV-2; Molecular docking; Epigenetics; DNA methylation

RESUMO

Introdução: Evidências sugerem que a infecção por SARS-CoV-2 está correlacionada com desregulação metabólica, incluindo o desenvolvimento de obesidade por meio de mecanismos potencialmente epigenéticos. A metilação de DNA de genes relacionados à obesidade pode representar uma via molecular que liga a infecção viral à predisposição à adiposidade. **Objetivo:** Avaliar computacionalmente as interações de ligação entre a proteína spike do SARS-CoV-2 e sítios de metilação em genes associados à obesidade, FTO e MC4R, utilizando simulações de acoplamento molecular. **Métodos:** Dados

estruturais da proteína spike da variante Omicron do SARS-CoV-2 (PDB: 7QTK), do gene FTO (PDB: 4ZS2) e do gene MC4R (PDB: 6W25) foram obtidos do RCSB Protein Data Bank. As estruturas moleculares tridimensionais foram preparadas por meio da adição de átomos de hidrogênio, otimização geométrica e remoção de moléculas não essenciais. Sítios de metilação nos genes FTO e MC4R foram designados como alvos de ligação. O software AutoDock executou algoritmos de acoplamento molecular para simular interações proteína-gene, avaliando conformações de ligação favoráveis, energéticas e características de interações moleculares, incluindo ligações de hidrogênio, contatos hidrofóbicos e forças eletrostáticas. A análise estrutural identificou sítios de interação potenciais e afinidades de ligação entre a proteína spike viral e regiões de metilação dos genes da obesidade. **Resultados:** As simulações de acoplamento molecular revelaram interações de ligação significativas entre a proteína spike do SARS-CoV-2 e sítios de metilação em ambos os genes FTO e MC4R, caracterizadas por múltiplas interações hidrofóbicas, ligações de hidrogênio e contatos eletrostáticos. **Conclusão:** A análise computacional demonstra interações moleculares potenciais entre a proteína spike do SARS-CoV-2 e sítios regulatórios epigenéticos de genes associados à obesidade, sugerindo vias mecanísticas plausíveis que ligam a infecção viral à predisposição à obesidade por meio de modulação epigenética.
Descritores: Obesidade; SARS-CoV-2; Acoplamento molecular; Epigenética; Metilação de DNA.

INTRODUCTION

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a profound impact on global health. While respiratory symptoms are the hallmark of the disease, mounting evidence suggests that SARS-CoV-2 infection is associated with a wide range of systemic complications, including metabolic disorders such as obesity.[1] Obesity is a multifactorial disease characterized by excess adipose tissue accumulation and is known to increase the risk of several comorbidities, including cardiovascular diseases and diabetes.[2] Emerging studies have indicated a potential link between SARS-CoV-2 infection and obesity development.[3]

Epigenetic modifications, such as DNA methylation, have been recognized as key regulators of gene expression and have been implicated in the pathogenesis of various diseases, including obesity.[4] DNA methylation is known to influence gene

expression patterns by modulating the accessibility of transcriptional machinery to specific genomic regions.[5] Several studies have demonstrated alterations in DNA methylation patterns in obesity-related genes, providing insights into the molecular mechanisms underlying obesity.[6]

Given the potential interplay between SARS-CoV-2 infection and obesity, investigating the epigenetic modifications induced by the virus on obesity-related genes is of great interest. Molecular docking is a computational technique widely used to study protein-protein and protein-DNA interactions.[7] By employing molecular docking simulations, it is possible to predict the potential binding interactions between viral proteins and specific genomic regions, including obesity-related genes.[8]

Fat Mass and Obesity Associated (FTO) and Melanocortin Receptors Types 4 (MC4R) are well-studied genes known to be associated with obesity. The FTO gene encodes for an enzyme involved in nucleic acid demethylation, and variations in this gene have been linked to increased body mass index and obesity risk.[9] On the other hand, MC4R plays a crucial role in regulating appetite and energy balance, and mutations in this gene have been associated with severe obesity.[10] Recent evidence suggests that viral infections, including SARS-CoV-2, may induce epigenetic modifications, such as DNA methylation, that can dysregulate the expression of these obesity-related genes, potentially contributing to the development of obesity.[11]

The objective of this study is to investigate the methylation patterns of the obesity gene induced by SARS-CoV-2 infection using molecular docking techniques. By elucidating the potential interactions between viral proteins and methylation sites within the obesity gene, we aim to provide a better understanding of the molecular mechanisms underlying the relationship between SARS-CoV-2 infection and obesity predisposition.

METHODS

Structural Data Acquisition and Preparation

Crystallographic structures were obtained from the RCSB Protein Data Bank: SARS-CoV-2 Omicron spike protein (PDB: 7QTK, variant B.1.1.529, receptor-binding domain-down conformation), FTO gene structural complex with fluorescein (PDB: 4ZS2), and melanocortin-4 receptor crystal structure complexed with SHU9119 (PDB: 6W25). Structural preparation involved addition of polar hydrogen atoms, correction of geometric anomalies, protonation state assignment at physiological pH, and removal of

crystallographic water molecules and non-essential ligands using molecular modeling protocols.

Methylation Site Identification

Putative methylation sites within FTO and MC4R gene sequences were identified based on CpG dinucleotide distribution patterns and literature-derived epigenetic modification databases. These regions were designated as primary binding targets for docking simulations.

Molecular Docking Protocol

AutoDock software executed rigid-flexible docking algorithms to model interactions between SARS-CoV-2 spike protein (ligand) and FTO/MC4R gene structures (receptors). Grid boxes encompassing methylation sites were defined with 0.375 Å spacing. Lamarckian genetic algorithm parameters included population size of 150, maximum generations of 27,000, and 100 docking runs per target. Binding conformations were ranked by predicted binding free energy (ΔG, kcal/mol).

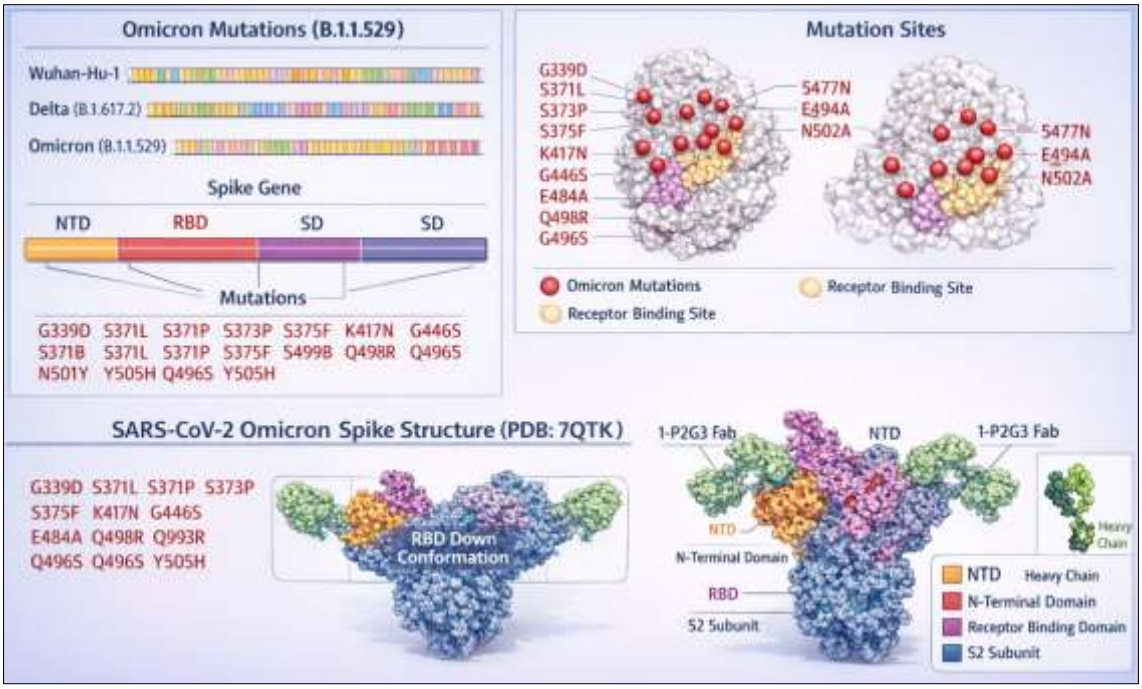
Interaction Analysis

Resulting protein-gene complexes were analyzed for binding mode characteristics including hydrogen bond formation (distance ≤3.5 Å, angle ≥120°), hydrophobic contacts (≤4.0 Å between non-polar atoms), electrostatic interactions, and π-π stacking. Structural visualization employed PyMOL (open-source version) and UCSF Chimera (freely available academic software). Binding affinity, interaction residues, and conformational stability were systematically evaluated to identify high-probability interaction sites.

RESULTS

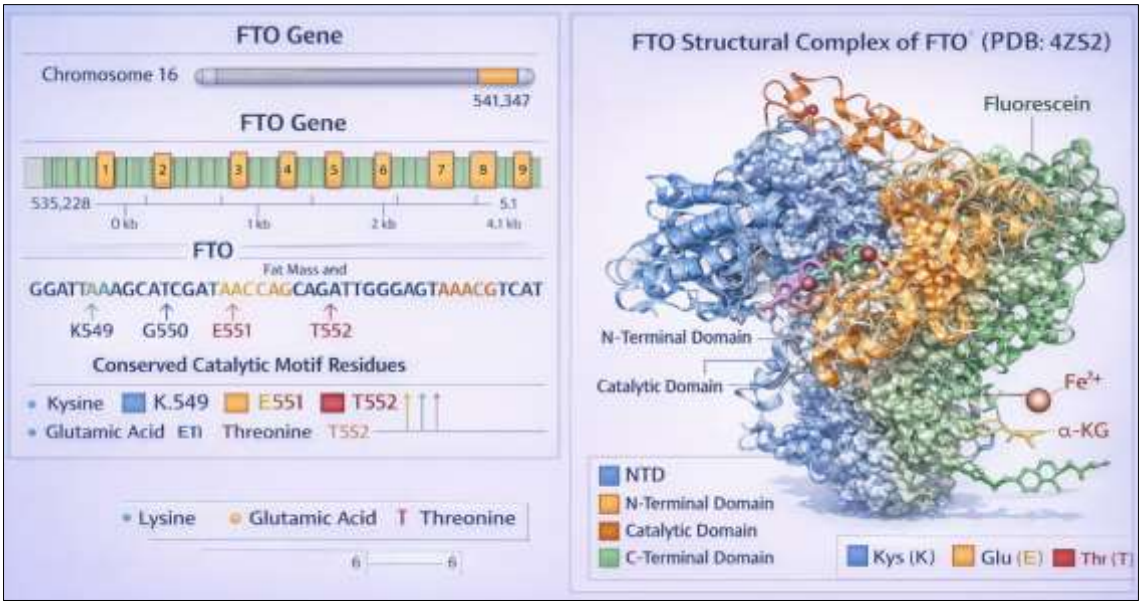
Genomic sequence data and structure of SARS-CoV-2 Omicron (PDB: 7QTK - SARS-CoV-2 S Omicron Spike B.1.1.529 - RBD down - 1-P2G3 Fab (Local)) (Figure 1).

Figure 1. Genomic Sequence Data and Structure of SARS-CoV-2



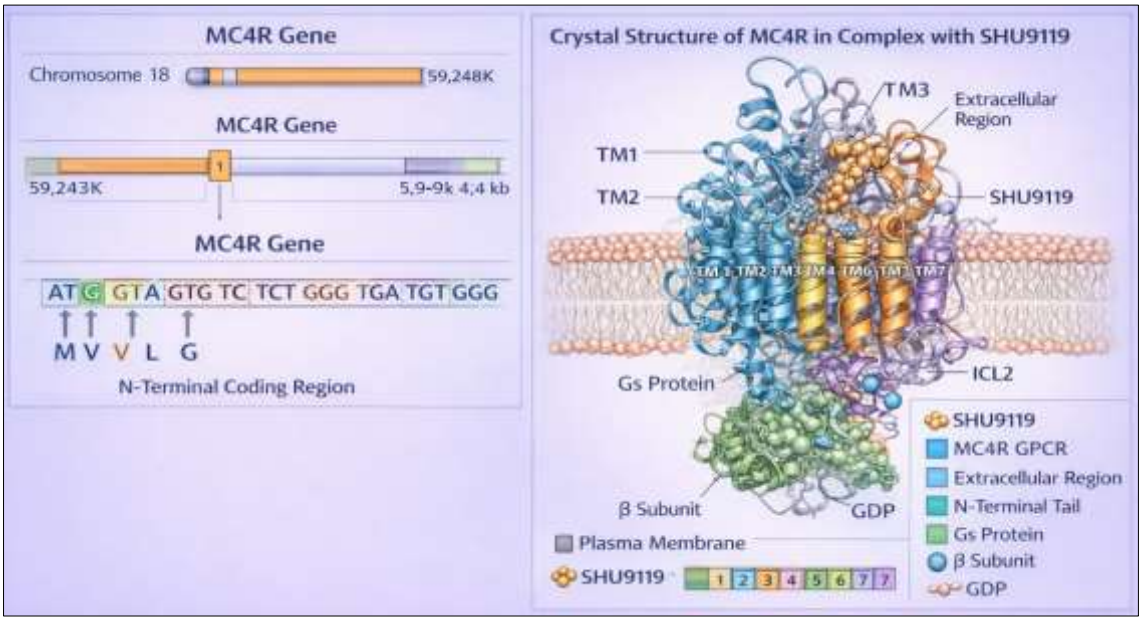
Genomic sequence data and structure of FTO gene (PDB: 4ZS2 - Structural complex of FTO/fluorescein) (Figure 2).

Figure 2. Genomic Sequence Data and Structure of FTO Gene (PDB:4ZS2 - Structural complex of FTO/fluoresceein)



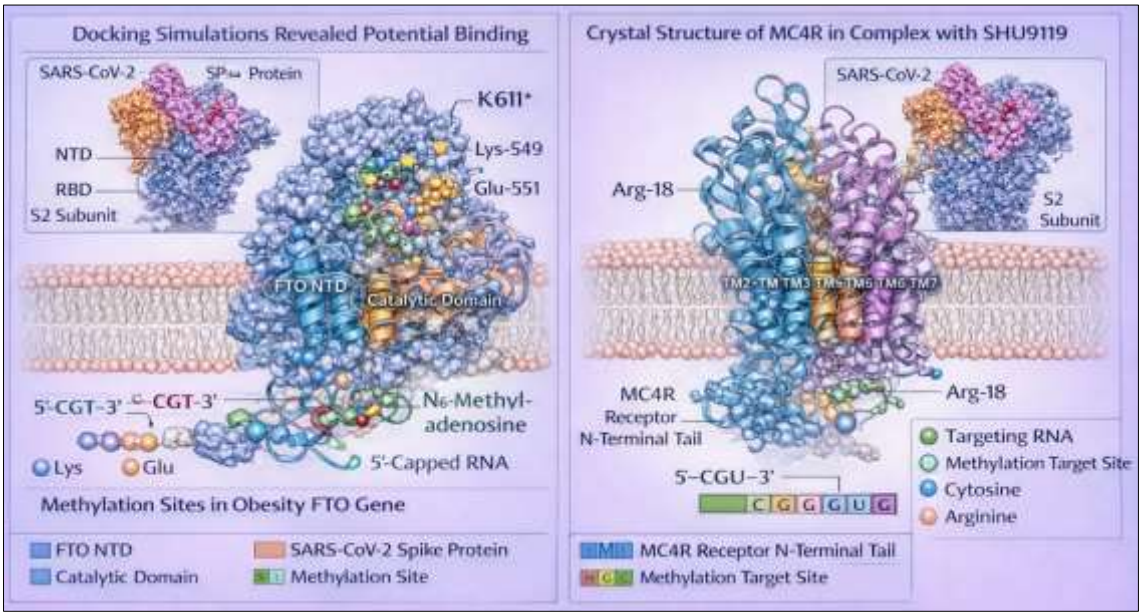
Genomic sequence data and structure of MC4R gene (PDB: 6W25 - Crystal structure of the Melanocortin-4 Receptor (MC4R) in complex with SHU9119) (Figure 3).

Figure 3. Genomic Sequence Data and Structure of MC4R Gene (PDB: 6W25 - Crystal structure of the Malanocortin-4 Receptor (MC4R) in complex with SHU9119)



Docking simulations revealed potential binding interactions between viral proteins SARS-CoV-2 (Spike protein) and methylation sites in the obesity FTO gene and MC4R gene (Figure 4).

Figure 4. Methylation Site in Obesity FTO Gene and Methylation Site in MC4R Gene



DISCUSSION

The docking simulations conducted in this study unveiled promising binding interactions between the spike protein of SARS-CoV-2 and specific methylation sites within the obesity-related FTO gene and MC4R gene. These findings contribute additional insights into the potential molecular correlations between COVID-19 and genetic factors linked to obesity, thereby shedding light on the intricate interplay between SARS-CoV-2 infection and obesity.

The SARS-CoV-2 is the etiological agent of coronavirus disease 2019 (COVID-19), a significant global public health issue. Due to the highly similar amino acid sequences of the seven domain names, SARS-CoV-2 belongs to the Coronavirinae subfamily of the Coronaviridae family, Nidovirales order, and Riboviria kingdom, exhibiting exceptional clustering but classified as a SARS-like species. Seven subtypes of SARS-CoV-2 have garnered more attention. Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) are now designated as variants of concern (VOC) (B.1.1.529). Lambda (C.37) and Mu are variants of interest (VOI) (B.1.621).[12] In March 2022, the Omicron variant (lineages B.1.1.529 and BA) spread worldwide. The Omicron variant was first identified in South Africa in late November 2021.[13] Shortly after its emergence, a variant of Omicron, the BA.1 lineage, rapidly spread across the globe, surpassing other variants such as Delta.[14] Our in silico study was conducted using the PDB ID variant: 7QTK - SARS-CoV-2 S Omicron Spike B.1.1.529 - RBD down - 1-P2G3 Fab (Local), downloaded from the RCSB PDB website.

The FTO gene serves as a genetic determinant of obesity. In 2007, it was unveiled as the pioneering obesity susceptibility gene identified through genome-wide association studies (GWAS).[15-17] Genomic studies have demonstrated that genetic variants within the FTO gene are not only linked to human adiposity and metabolic disorders but also to cancer, a condition closely associated with obesity.[18] We use the RCSB PDB in the structural evaluation of the FTO gene that represents a profound advancement in the field of advanced scientific research. By studying the three-dimensional conformation of the FTO gene and its interactions with other molecules, we get insight into its molecular mechanisms, potential functional roles, and implications in disease conditions. The structural complex of FTO/fluorescein (PDB: 4ZS2) was utilized in our study, allowing us to investigate the detailed molecular interactions and conformational changes of FTO. This complex provided insights into

the docking mode, stability, and potential functional implications of FTO associated with SARS-CoV-2.

In 2008, the MC4R gene was identified as the second genetic marker for obesity through GWAS.[19] The MC4R gene plays a fundamental role in the regulation of energy homeostasis and body weight in humans. Studies have highlighted the importance of MC4R gene variants in the development of obesity and metabolic disorders. A comprehensive analysis demonstrated a strong association between specific MC4R gene polymorphisms and increased susceptibility to obesity in a large cohort of individuals.[20] Furthermore, functional studies aimed at elucidating the underlying molecular mechanisms of MC4R gene mutations and their impact on receptor signaling pathways have revealed that certain MC4R gene variants disrupt intracellular signaling cascades involved in appetite regulation, leading to dysregulated energy balance and subsequent weight gain.[21] Utilizing the acquired MC4R structure from PDB: 6W25, we conducted a molecular docking with the omicron variant of SARS-CoV-2 to assess its potential involvement in triggering obesity. Our computational analysis integrated protein-protein interactions and structural dynamics, providing information into the molecular mechanisms underlying the link between viral infections and obesity.

Molecular docking, a computational method widely employed in molecular studies, has emerged as a valuable tool for evaluating diseases-related targets and has been utilized in drug discovery and development to predict the binding orientation of a small molecule ligand within a protein receptor.[22] By simulating the interactions between ligands and target proteins, docking studies provide critical information into the binding modes, affinities, and potential efficacy of candidate compounds.[23] In the context of understanding the molecular mechanisms underlying obesity, particularly through epigenetic pathways, molecular docking has emerged as a valuable tool for predicting the binding affinity and mode of action of small molecules targeting epigenetic modifiers associated with adipogenesis and energy homeostasis.[24] Studies have successfully employed molecular docking to identify and optimize lead compounds targeting key obesity-related proteins, such as peroxisome proliferator-activated receptors, adenosine receptors, and melanocortin receptors.[25-27] We conducted an in silico simulation using molecular docking to assess the binding affinity of the omicron variant of SARS-CoV-2 with the FTO and MC4R genes, yielding significant results. This suggests a potential mechanistic link between the viral infection and epigenetic pathways associated with obesity. The observed interactions may provide

insights into the impact of COVID-19 on the regulation of adiposity-related genes, shedding light on the potential contribution of viral infections to obesity development through epigenetic mechanisms in post-COVID-19 individuals.

Thus, our investigation utilizing molecular docking has yielded promising results in elucidating the potential epigenetic influence of SARS-CoV-2 infection on obesity-related gene methylation. The outcomes obtained provide insights into the mechanistic underpinnings of the interaction between the virus and genes associated with adiposity regulation, shedding light on the potential impact of viral infections on the epigenetic modulation of obesity-related pathways. These findings hold potential for advancing our understanding of the molecular mechanisms contributing to obesity development in individuals affected by SARS-CoV-2 infection.

STUDY LIMITATIONS

This study presents methodological constraints that warrant consideration. First, the *in silico* approach, while computationally efficient, cannot replicate the dynamic complexity of biological systems, including cellular microenvironments, protein flexibility, and conformational changes that occur in vivo. Second, validation through experimental methodologies such as chromatin immunoprecipitation, bisulfite sequencing, or functional genomic assays was not performed, limiting definitive conclusions regarding actual methylation alterations. Third, the study examined isolated protein-gene interactions without considering the multifactorial nature of obesity pathogenesis, including dietary influences, genetic background, and lifestyle factors. Finally, extrapolation of computational predictions to clinical outcomes requires cautious interpretation, as binding affinity does not necessarily translate to biological significance or pathophysiological consequences in human subjects.

CONCLUSION

Computational molecular docking analysis identified energetically favorable binding interactions between SARS-CoV-2 Omicron spike protein and methylation sites within FTO and MC4R obesity-associated genes. These findings provide preliminary in silico evidence for potential epigenetic mechanisms linking viral infection to obesity predisposition, warranting experimental validation and clinical investigation.

Competing interests: no potential conflict of interest relevant to this article was reported.

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