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Induced Pluripotent Stem Cell Treatment for Type 2 Diabetes Mellitus

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Abstract. Awareness of adipose tissue dysfunction as the underlying pathway for major metabolic diseases has been rising as research on inflammation and lipotoxicity makes progress. Adipose storage capacity is a tenuous boundary that results in surplus free fatty acids spilling into the circulation and deposit ectopically in the liver, skeletal muscle, and pancreas when surpassed. Existing pharmacological agents are efficient in accounting for downstream effects of lipid spillover but lack the capability of restoring the body's intrinsic lipid-buffering capacity, posing disease recurrence as a reverberating effect of these approaches. This paper proposes a novel therapeutic approach based on the concept of transplantation of autologous induced pluripotent stem cells (iPSC)-derived adipocytes as bioengineered lipid sinks that can intercept excess circulating lipids prior to ectopic disposition. This paper addresses the pathophysiologic basis of lipid spillover and lipotoxicity, discusses the current state of iPSC-to-adipocyte differentiation, presents the mechanistic rationale for this strategy and summarizes and critiques the translational barriers that remain from the development of this work toward preclinical validation.

Keywords: Adipocytes, Lipotoxicity, iPSCs, Spillover, Metabolism

1. Introduction

Type II Diabetes Mellitus (T2DM) has become one of the leading degenerative diseases in the 21st century, affecting a population of more than 500 million people and predicted to surpass 780 million by 2045 [1]. With the total cost of diabetes diagnosis summing up to $412.9 billion in 2022, including $306.6 billion in direct medical costs and $106.3 billion in indirect medical costs, the financial burden for this disease is staggering. Diving deeper into the income distribution in this patient population, a disproportionate rise in T2DM is observed among low-income Americans, a trend strongly linked to higher obesity rates in these communities due to limited access to nutritious food and barriers to preventative healthcare [2]. Despite policies made worldwide to remedy this phenomenon, pharmaceutical approaches must be undertaken alongside these efforts to minimize the long-term impact of T2DM on global health.

T2DM differs from Type I Diabetes Mellitus as it it retains the body's intrinsic insulin production abilities but has defects in the insulin signal transduction pathway in skeletal muscle and adipose tissue, resulting in hyperglycemia and ultimately leading to macrovascular (e.g., cardiovascular disease) and microvascular complications (neuropathy, nephropathy, and retinopathy) over time.

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Insulin resistance, being the predominant feature of T2DM, stems from the disruption of an intricate series of interrelated circuits of signaling cascades, rather than the failure of defective insulin receptors. In particular, pathophysiological stressors from metabolic events (endoplasmic reticulum stress, chronic inflammation, and lipotoxicity) induce inhibitory serine phosphorylation of insulin receptor substrate (IRS) proteins, which suppress active PI3K and prevent the translocation of GLUT4-bearing vesicles to the site of the cell surface. Furthermore, IRS-2 signaling in pancreatic beta cells is compromised, leading to the progressive beta-cell failure, further lowering the overall insulin output of the pancreas and hyperglycemia in the patient.

Rather than fault in the insulin signaling pathway as the trigger of chronic inflammation and ER stress that drive IRS serine phosphorylation, it is postulated that it is actually the adipose tissue dysfunction that generates a chronic pro-inflammatory environment, which in turn leads to a dysfunctional insulin signal transduction.

Breakthroughs in metabolic syndrome studies have consistently provided evidence that nuances the well established epidemiological correlation between obesity and T2DM, providing insight into a more complex association between the two. Counterintuitive statistics that either display normal insulin sensitivity and glucose homeostasis under high-BMI conditions or lean individuals that present with frank metabolic syndrome offer a redirection of focus from adipose mass to adipose function as the main factor impacting metabolic health.

The expandability hypothesis offers an explanation for the circumstances described above. The hypothesis posits that metabolic health is mediated by the capacity of adipose tissue to safely increase or reduce fat content under a fixed cell number; exceeding the cell's buffering capacity, either from chronic caloric overload, genetic predisposition, or age-related decline in adipogenesis, leads to free fatty acids (FFAs) leakage from dysfunctional adipocytes into the systemic circulation [3]. Subsequently, these lipids target non-adipose organs, such as the liver, skeletal muscle, heart, and pancreatic beta cells for ectopic deposition; this initiates multiple lipotoxic pathways, leading to ceramide accumulation, ER stress, mitochondrial dysfunction, inflammasome activation, and further cellular damage. Accordingly, T2DM develops from the resulting chronic low-grade inflammation and insulin resistance [4].

Though current treatments demonstrate effort and success at targeting the aspects of this cascade, they are ultimately unable to radically address the foundational cause of T2DM. Some therapies that target aspects of this cascade include Bariatric surgery, which dramatically improves metabolic parameters but is invasive, irreversible, and inaccessible to the majority; GLP-1 receptor agonists which reduce body weight and improve glycemia but do not directly restore adipose buffering capacity; metformin and Thiazolidinediones (TZDs) that target PPARγ to enhance adipocyte function, at the expense of weight gain, fluid retention, and bone loss [5]; A therapy that reconstitutes the body's ability to safely sequester excess circulating lipids remains a fundamental unmet need.

By augmenting the body's endogenous lipid storage capacity with transplanted, fully functional fat cells derived from patient-specific induced pluripotent stem cells (iPSCs), the approach this paper proposes should effectively prevent and curb the lipid spillover cascade at its roots, prevent ectopic deposition, inhibit lipotoxic inflammation, and also maintain insulin sensitivity. We review the scientific foundations supporting this concept, evaluate its feasibility given current iPSC technology, and identify the critical challenges that must be addressed to advance this idea of bioengineered lipid sinks from theory to therapy.

DOI: 10.54254/2753-8818/2026.37085

2. Lipid spillover, lipotoxicity, and the pathogenesis of T2DM

2.1. A metabolic buffer in adipose tissue

Perinatal and Pre-puberty l white adipose tissue mediates caloric surplus in healthy individuals through adipogenesis, which recruits preadipocytes differentiated from mesenchymal progenitor pools to yield small adipocytes. Until the end of puberty, individuals benefit greatly from WAT hyperplastic potential, which can foster insulin sensitivity, lipid uptake and transport capability, as well as a healthy adipokine profile [6]. As the end of puberty sets the individual's adipogenic ability, the body loses its incipient potential of adipogenic expansion, thus shifting to hypertrophic expansion of existing adipocytes rather than quantity, upregulating progressive dysfunctionality in the form of hypoxia due to inadequate vascularization; hypoxia-inducible factor 1α (HIF-1α) signaling; fibrotic pathways; and shifting of their secretome toward a pro-inflammatory profile dominated by tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) [7].

2.2. Ectopic lipid deposition and organ-specific lipotoxicity

The development of T2DM from lipid spillover mainly results from the ectopic deposition of free fatty acids in the liver, skeletal muscle, and pancreas. Lipids accumulate in the liver from de novo lipogenesis and subsequent triglyceride deposition, which activates Kupffer cells, stimulates stellate cell fibrogenesis, and impairs hepatic glucose output suppression, contributing to fasting hyperglycemia [8]. Intramyocellular lipid accumulation in skeletal muscle activates protein kinase C (PKC), which directly phosphorylates insulin receptor substrate-1 (IRS-1) at inhibitory serine residues, thus blunting insulin-stimulated glucose uptake [9]. In the pancreas, lipid deposition in and around beta cells impairs glucose-stimulated insulin secretion through ER stress and oxidative damage, accelerating the transition from insulin resistance to overt diabetes [10].

2.3. Inflammatory amplification

Inflammatory signals wrought by lipotoxicity include an external and an internal trigger. The external trigger, in which saturated fatty acids serve as ligands for Toll-like receptor 4 (TLR4) on macrophages and adipocytes, activates inflammatory mechanisms that include NF-κB and, more essentially, the NOD-like receptor protein 3 (NLRP3) [11]. NLRP3 activation induces caspase-1-dependent maturation of critical pro-inflammatory cytokines IL-1β and IL-18 that also hinder insulin signaling. Conversely, the internal trigger consists of damage-associated molecular patterns (DAMPs) released by lipid-laden hypertrophic adipocytes dying by necrotic cell death, which recruit and polarize adipose tissue macrophages toward the classically activated M1 phenotype, inducing the formation of a characteristic of inflamed dysfunctional adipose tissue: crown-like structures of macrophages surrounding dead adipocytes [12]. The pro-inflammatory milieu increases JNK and IKKβ pathways within insulin-responsive sites and systems leading to systemic insulin resistance (the hallmark of T2DM) [13]. This pathophysiologic narrative of lipid spillover, ectopic tissue buildup, lipotoxicity, inflammation, and insulin resistance signals a clear therapeutic aim: re-establishing the body's ability to safely sequester circulating lipids before they enter sensitive organs.

Indeed, this concept has already been demonstrated in mouse models…..

DOI: 10.54254/2753-8818/2026.37085

3. IPSC-derived adipocytes

3.1. Differentiation protocols

Several protocols have been reported for yielding functional adipocytes through the differentiation of human iPSCs. While many of these follow a sequence of events that recapitulates developmental adipogenesis, some employ more artificial or accelerated routes that do not strictly adhere to this developmental sequence. A standard protocol for adipocyte derivation from iPSCs includes a three-step process as shown below.

Step 1: the generation of mesenchymal progenitor cells (MPC) from differentiated iPSCs procured from the patient, this step is usually conducted by directed monolayer differentiation.

Step 2: expansion of MPCs under conditions that preserve their adipogenic capacity.

Step 3: the terminal adipogenic differentiation using cocktails that contain insulin, dexamethasone, 3-isobutyl-1-methylxanthine (IBMX), rosiglitazone (or another TZD), and indomethacin [14].

Ahfeldt et al. [14] proved that iPSC-based adipocytes possessed canonical adipocyte markers such as PPARγ, C/EBPα, FABP4, and adiponectin, which, along with the formation of lipid droplets similar to human primary adipocytes and an enrichment of 85-90%, bolster the phenotypic credibility of the generated cells [15]. Subsequently, Mohsen-Kanson et al. [15] improved protocols for generating adipocytes capable of engaging in insulin-stimulated glucose uptake and lipolytic responses to β-adrenergic stimulation. Recently, approaches involved genetic engineering to overexpress transcription factors, especially PPARγ2, and boost the efficiency of differentiation, curtailing the conversion duration within 14-21 days [16].

3.2. Functional characterization

Several prerequisites have to be satisfied in order for iPSC-derived adipocytes to clinically perform as lipid sinks, requiring strict adherence to the molecular, structural, morphological, and functional (metabolic) components and activity of mature white adipocytes. Critical parameters must entail the five hallmarks below to ensure adequacy for clinical application:

(1)Lipid uptake, expression and activity of LPL, CD36/FAT, and FATP family members;

(2)Lipid storage, formation of unilocular lipid droplets coated with perilipin proteins;

(3)Insulin responsiveness with GLUT4 translocation and suppression of lipolysis; as well as catecholamine-induced lipolysis.

(4)Appropriate endocrine function, specifically the secretion of adiponectin (insulin-sensitizing) with low levels of pro-inflammatory cytokines.

(5)Lipid handling under metabolic stress without activating apoptotic pathways.

The latest evidence indicates that iPSC-derived cells reach profound but incomplete functional maturity in comparison to primary cells. Though PPARγ, GLUT4, and adiponectin are reliably expressed from these cells and show insulin-dependent glucose uptake as well, unilocular lipid droplet morphology associated with fully mature adipocytes is still needed [17], and their lipolytic regulation and adipokine secretion profiles may not completely mimic in vivo adipocyte behaviour. Despite these limitations, the path of enhancement for differentiation procedures in the past ten years indicates that these limitations are within their control.

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3.3. White, brown and beige: selecting the best phenotype

Selecting the appropriate adipocyte subtype for iPSC differentiation is an essential feature to the lipid sink concept that directly impacts the buffering potential per cell. White adipocytes convert lipids to triglyceride and essentially serve as energy stores, whereas brown and beige adipocytes provide heat-generating non-shivering thermogenesis via the expression of uncoupling protein 1 (UCP1) to dissipate the proton gradient as heat. Though white adipocytes provide the direct solution to lipid sequestration with the greatest buffering potential per cell, a combined approach based on beige adipocyte could offer a complementary strategy by integrating lipid storage and active lipid disposal through thermogenesis; differentiation protocols for iPSC [18, 19] are available to produce both white and brown/beige adipocytes, allowing for potential titration of therapeutic products for individual patient requirements [20].

4. The therapeutic concept: lipid sinks using transplanted iPSC-adipocytes

4.1. Mechanistic rationale

The essence of this hypothesis revolves around a simple notion: excess circulating FFAs can be intercepted via an increased adipose capacity achieved by transplanted functional adipocytes, such that they can be safely sequestered before they reach ectopic sites. The transplanted cells establish a metabolic buffer that mitigates postprandial lipids by capturing triglycerides as metabolically inert lipid droplets and releasing FFAs in a regulated manner in response to fasting-state hormonal cues. Thus, they focus directly on the upstream driver lipotoxicity instead of addressing its downstream inflammatory and metabolic consequences.

Rodent adipose tissue transplantation studies have shown increased glucose tolerance in metabolically impaired recipients after a healthy subcutaneous adipose tissue transplantation, along with an alleviated hepatic steatosis and reinstated circulating adipokine profile [21, 22]. Further demonstrating that metabolic dysfunction can be relieved through lipid restoration, studies on lipodystrophic mice undergo severe insulin resistance, hepatic steatosis, and diabetes that can be saved with adipose tissue transplantation or leptin [23].

4.2. Proposed implementation

The translational pathway for iPSC-derived adipocyte therapy involves a multi-step process as proposed below:

1. Obtain somatic cells via a skin biopsy or blood draw and, using non-integrating methods (e.g., Sendai virus or mRNA reprogramming) to reprogram these cells into induced pluripotent stem cells (iPSCs), thus minimizing the risk of insertional mutagenesis [24].

Perform rigorous quality control checks to screen for acquired mutations: karyotyping, pluripotency validation, and whole-genome sequencing [25].

2. Execute the optimized adipogenic protocol to expand and differentiate validated iPSCs into mature adipocytes [26].

3. Thoroughly characterize the resulting adipocytes to verify lipid uptake capacity, insulin sensitivity, adipokine secretion, and absence of residual undifferentiated cells [27].

4. Deliver adipose tissue through subcutaneous transplantation compared to visceral depots, subcutaneous implantation possesses a more favorable metabolic profile and is less prone to metabolic diseases [21].

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5. Transplantation delivery through direct injection, Scaffold-based implantation, or Macro-encapsulation [14].

4.3. Anticipated therapeutic outcomes

Success iPSC-adipose tissue transplantation should be evident with multiple relevant metabolic changes, ranging from mitigated hepatic lipotoxicity and systemic inflammation, to improved insulin sensitivity and protected β-cell function. First, magnetic resonance spectroscopy could assess changes in intrahepatic triglyceride content to determine whether transplanted adipocytes reduce ectopic hepatic lipid deposition through enhanced uptake and storage of excess circulating FFAs. Second, Hyperinsulinemic-euglycemic clamp measurements and HOMA-IR indices could be used to assess improvements in whole-body insulin sensitivity, providing a readout of the therapeutic efficacy of this approach. Third, circulating inflammatory markers, including CRP, IL-6, TNF-α, and MCP-1, could be assessed to determine whether the intervention attenuates systemic inflammation associated with metabolic dysfunction. Fourth, adiponectin-secreting transplanted adipocytes could increase insulin sensitivity, potentially through the activation of AMPK and fatty acid oxidation in target tissues. Last, lowered lipotoxic stress to the pancreatic β-cells could enhance insulin secretory capacity, which may result in the delay or prevention of prediabetes to overt T2DM.

4.4. Comparison to current therapeutic strategies

Current therapeutic approaches for T2DM remain insufficient, as many primarily target the downstream consequences of metabolic dysfunction rather than restoring healthy adipose tissue function and preventing ectopic lipid accumulation. Bariatric surgery can produce profound and sustained improvements in glycemic control and metabolic health; however, it is a highly invasive intervention associated with potential complications, including nutritional deficiencies, gastrointestinal disturbances, surgical risks, and the need for lifelong monitoring. Pharmacological therapies, including incretin-based therapies such as GLP-1 receptor agonists and DPP-4 inhibitors, improve glycemic regulation through enhanced incretin signaling. GLP-1 receptor agonists additionally promote substantial weight loss, which can reduce adipose tissue inflammation and improve metabolic health; however, their use may be limited by gastrointestinal adverse effects, gallbladder disease, and loss of lean body mass. DPP-4 inhibitors generally have more modest effects on weight and primarily improve glucose control. Thiazolidinedione (TZD)-based therapies improve insulin sensitivity through activation of peroxisome proliferator-activated receptor gamma (PPARγ), promoting adipocyte differentiation and lipid storage capacity; however, their clinical use is constrained by adverse effects, including weight gain, fluid retention, and increased risk of heart failure. An emerging therapeutic strategy that may overcome some limitations of current approaches is the transplantation of functional adipose tissue as a metabolic "sink" to restore lipid homeostasis through endocrine signaling and lipid-buffering mechanisms. In particular, induced pluripotent stem cell (iPSC)-derived adipocyte transplantation represents a promising approach to replenish healthy adipose tissue, enhance lipid storage capacity, reduce ectopic fat accumulation, and improve systemic metabolic homeostasis.

DOI: 10.54254/2753-8818/2026.37085

5. Challenges and limitations

5.1. Manufacturing and scalability

Scale is among the most challenging limitations for iPSC-mediated adipocyte transplantation, as a functional adipose tissue has about 1-2 million adipocytes per gram. With approximately tens to hundreds of grams of transplantation to be metabolically significant clinically, the treatment would require billions of mature adipocytes per patient. The transition from laboratory-scale iPSC differentiation protocols to clinical-grade, GMP-compatible manufacturing at a commercial scale presents a prominent bioengineering challenge. Remediation can be achieved via improvements in bioreactor technology such as stirred tank as well as perfusion systems for three-dimensional adipocyte culture [28].

5.2. In vivo survival and vascularization

Transplanted adipocytes require adequate vascularization to survive and engage in endothelial cross-talk for metabolic signaling and lipid transmission. Transplanted cell populations of more than about 200 micrometers in diameter are central hypoxic and necrotic due to menial access in circulation. Potential remedies are co-transplantation with endothelial cells or endothelial progenitors, pre-vascularization of scaffolds, pro-angiogenic-induced factors like vascular endothelial growth factor (VEGF), and porous scaffold architectures permitting host vascular ingrowth [29].

5.3. Safety concerns

IPSC-derived products to date bear tumorigenic hazards under a clinical context. Specifically, teratomas, a population tumor resulting from undifferentiated iPSC residuals in the transplanted population, remain a well-characterized safety obstacle to clinical translation. Thus, stringent purification is crucial, involving negative selection against pluripotency markers (e.g. TRA-1-60, SSEA-4) and using metabolic selection based on differences in metabolic needs in iPSCs and adipocytes. Furthermore, a pharmacological fail safe can be implemented through the addition of inducible suicide gene systems like herpes simplex virus thymidine kinase (HSV-TK) or inducible caspase-9 (iCasp9), eliminating transplanted cells in case of adverse events [30].

5.4. Functional integration and regulation

Transplanted adipocytes must integrate into systemic metabolic regulation in order to be effective metabolic buffers; this includes acting in response to insulin by inhibiting lipolysis, favouring lipid uptake, and responding to catecholamines during fasting by mobilizing stored fatty acids and secreting adipokines in physiologically appropriate amounts.while many of these characteristics have been addressed in vitro (see aforementioned citations), they remain to be demonstrated in vivo. Apart from the unknown hormone integration of graft/iPSC adipocytes, the inadequate restoration of adipose tissue innervation also remains an unresolved limitation for optimal metabolic response.

5.5. Addressing root causes

Transplanting additional lipid storage does not overshadow the upstream cause of energy surplu Absent of concurrent dietary and lifestyle modification, transplanted adipocytes would only serve as temporary relievers of metabolic stress, eventually becoming hypertrophic and dysfunctional

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themselves. Thus, this therapy shouldn't be conceptualized as a standalone cure but a component of a multimodal strategy that includes caloric management, physical activity, and potentially pharmacological support.

6. Future directions

6.1. Genetic enhancement of transplanted adipocytes

The adoption of iPSC enables the future potential of a variety of optimizations via genetic engineering of adipocytes prior to transplantation. For instance, overexpression of CD36 or FATP1 could enhance per cell lipid sequestration efficiency. Other potential genetic modifications include:

1. Constitutive or inducible expression of adiponectin to amplify the insulin-sensitizing paracrine effects of the graft [31].
2. Creating engineered beige adipocytes via introduction of UCP1 or other thermogenic factors to actively metabolize stored lipid, providing a dual mechanism of lipid removal [32].
3. Knockout of pro-inflammatory pathway components (e.g., NLRP3, TLR4) via CRISPR to protect transplanted adipocytes against inflammatory activation even under lipotoxic stress, ensuring they remain metabolically healthy under adverse conditions [4].

6.2. Biomaterial and encapsulation strategies

Advances in biomaterial engineering offer promising solutions to engraftment and immune isolation challenges [33]. Hydrogen-based scaffolds composed of a decellularized adipose tissue extracellular matrix can mimic an authentic biochemical environment to support adipocyte survival and function [34]. Three-dimensional bioprinting could fabricate well defined vascular network architecture [35]; and Macro-encapsulation in immunoprotective devices could enable universal donation of iPSC-derived adipocytes, eliminating the onerous necessity of patient-specific reprogramming [33]

6.3. Preclinical validation

The immediate priority is establishing preclinical proof of concept, which most informative initial experiments are represented by studies in diet-induced obese (DIO) mouse models. Human iPSC-derived adipocytes (or murine iPSC-derived adipocytes for syngeneic studies) would be transplanted subcutaneously into DIO mice, with endpoints below [36]:

1. Intrahepatic and intramyocellular lipid content by magnetic resonance spectroscopy
2. Glucose tolerance and insulin sensitivity by GTT, ITT, and hyperinsulinemic-euglycemic clamp
3. Circulating inflammatory biomarker profiles
4. Adipokine levels
5. Histological assessment of graft survival, vascularization, and lipid accumulation.

Lipodystrophic mouse models (e.g., A-ZIP/F-1 fatless mice) would provide an additional model in which the contribution of restored lipid storage capacity can be assessed in isolation from endogenous adipose confounders.

6.4. Personalized medicine applications

Beyond the therapeutic concept, iPSC's nature allows the derived adipocytes to serve as personalized metabolic medicine. Specifically, patient-derived iPSC-adipocytes can serve as in vitro

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models of individual lipid handling capacity, identifying patients with intrinsically low adipogenic potential or accelerated adipocyte dysfunction as most beneficial from the therapy.

6.5. Patent law

As of 2026, Kyoto University's twenty-year iPSCs patent family spanning thirty-three countries and one special administrative region (Hong Kong) will have expired. Prospective pharmaceutical firms and institutions would, as a result, populate the market, increasing the supply of clinical iPSC cell lines and reducing access difficulty of this treatment. Given the disproportionate rise in T2DM is observed among the low-income population, the expiration of this patent could remedy the global health of T2DM at a scale larger than if the treatment would've been accessible exclusively to the high-income classes.

7. Conclusion

Lipid mismanagement is the pathological basis to T2DM, triggering lipid spillover and a trailing cascade of ectopic deposition, inflammation and progressive insulin resistance. Though current therapeutic strategies managing the consequences of this cascade exist, such treatments do not restore the missing metabolic capacity. Lipid sinks achieved through iPSC-derived adipocytes may serve as a compelling strategy to address this deficit directly, introducing functional autologous cells to potentially enhance lipid storage capacity. While substantial challenges remain in manufacturing scale, in vivo engraftment, safety assurance, and functional integration, translational feasibility is imminent given the convergence of advancements in iPSC biology, adipocyte differentiation, biomaterials engineering, and genome editing. The next step would be preclinical proof-of-concept studies, which their success in execution would establish a new paradigm in the treatment of T2DM that not merely manages the consequences of adipose failure, but rebuilding the metabolic buffer itself.

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