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Обзор литературы / Review article

Targeting the feminized nature of prostate cancer exploring estrogen-driven metabolic reprogramming and its therapeutic intervention: A narrative review

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Abstract

AbstractProstate cancer (PCa) has long been classified as an androgen-driven malignancy; however, mounting evidence underscores the pivotal role of estrogen in its initiation, progression, and therapeutic resistance. This review establishes that PCa exhibits intrinsic estrogen dependence through intratumoral aromatization, positioning it within the spectrum of estrogen-driven malignancies. Through integrative molecular analyses, we elucidate how estrogen orchestrates metabolic reprogramming, shifting prostate tumors toward enhanced lipid oxidation and glucose uptake a hallmark of glucolipotoxicity. Mechanistically, estrogen signaling, primarily via the PI3K/AKT pathway, drives the upregulation of carnitine palmitoyltransferase 1 and glucose transporter 1, fueling a metabolic storm characterized by oxidative stress, mitochondrial dysfunction, and chronic inflammatory signaling. This metabolic adaptation enables androgen-independent survival, presenting a critical vulnerability overlooked by conventional androgen-targeted therapies. Our findings necessitate a paradigm shift in the classification and treatment of PCa, advocating for a novel therapeutic framework targeting the estrogen–metabolic axis. We propose a precision strategy integrating aromatase inhibition, estrogen receptor blockade, and metabolic stress modulation to counteract castration-resistant disease. Recognizing PCa as an estrogen-driven, metabolically adaptive malignancy transforms its clinical understanding and therapeutic approach, demanding urgent reconsideration of current oncologic paradigms.

Key words: prostate cancer, estrogen signaling, metabolic reprogramming, glucolipotoxicity, therapeutic resistance.

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Целевая терапия феминизированной природы рака предстательной железы: изучение эстроген-зависимой метаболической перепрограммировки и ее терапевтического вмешательства: нарративный обзор

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Резюме

Рак предстательной железы (РПЖ) традиционно рассматривается как андроген-зависимое злокачественное новообразование. Однако накапливающиеся данные подчеркивают ключевую роль эстрогенов в его инициации, прогрессии и резистентности к терапии. Данный обзор устанавливает, что РПЖ обладает внутренней эстрогеновой зависимостью за счет интраопухолевой ароматизации, что позволяет рассматривать его в спектре эстроген-зависимых новообразований. Путем интегративного молекулярного анализа мы демонстрируем, как эстрогены регулируют метаболическую перепрограммировку, смещая опухоли предстательной железы к усиленному окислению липидов и захвату глюкозы признакам глюколипотоксичности. Механистически эстрогеновая сигнализация, преимущественно через путь PI3K/AKT, способствует повышенной экспрессии карнитинпальмитоилтрансферазы-1 и транспортера глюкозы-1, что запускает метаболическую бурю, характеризующуюся окислительным стрессом, митохондриальной дисфункцией и хроническим воспалительным сигналингом. Эта метаболическая адаптация позволяет опухолевым клеткам выживать независимо от андрогенов, создавая критическую уязвимость, которую игнорируют традиционные методы андроген-таргетной терапии. Наши выводы требуют пересмотра классификации и лечения РПЖ, предлагая новый терапевтический подход, нацеленный на ось «эстроген–метаболизм». Мы предлагаем точечную стратегию, включающую ингибирование ароматазы, блокаду эстрогеновых рецепторов и модуляцию метаболического стресса для борьбы с кастрационно-резистентной формой заболевания. Признание РПЖ как эстроген-зависимой метаболически адаптивной злокачественности изменяет его клиническое понимание и терапевтический подход, требуя срочного пересмотра существующих онкологических парадигм.

Ключевые слова: рак предстательной железы, эстрогеновая сигнализация, метаболическое перепрограммирование, глюколипотоксичность, терапевтическая резистентность.

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Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder characterized by the selective destruction of pancreatic beta cells, resulting in absolute insulin deficiency. Predominantly affecting children and young adults, T1DM manifests with hallmark symptoms such as polyuria, polydipsia, and weight loss, necessitating lifelong insulin therapy [1]. Despite extensive research, the precise mechanisms driving beta-cell autoimmunity remain incompletely elucidated [2]. The prevailing autoimmune hypothesis posits that genetic predisposition, coupled with environmental triggers, precipitates an aberrant immune response targeting beta-cell antigens. However, this model fails to fully account for the variability in disease progression, the presence of autoantibodies in non-progressors, and the localized patterns of beta-cell loss, underscoring critical gaps in our understanding of T1DM pathogenesis. We propose a novel paradigm, the peritoneal protection hypothesis (PPH), which suggests that structural defects in the peritoneal membrane enveloping the pancreatic tail may serve as a critical initiator of autoimmune activation in T1DM. Unlike other pancreatic regions, the tail is uniquely intraperitoneal, rendering its beta-cell-rich microenvironment vulnerable to immune infiltration if the peritoneal barrier is compromised. This hypothesis reframes T1DM as a condition influenced not solely by systemic immune dysregulation but also by localized anatomical vulnerabilities that facilitate immune access to beta cells. The objectives of this narrative review are threefold: first, to critically reassess the traditional autoimmune hypothesis of T1DM in light of emerging anatomical and immunological insights; second, to synthesize evidence supporting the role of peritoneal membrane defects in beta-cell vulnerability; and third, to explore therapeutic interventions, particularly those leveraging pharmacological agents such as GLP-1 receptor agonists and ultra-long-acting insulins, that may restore peritoneal integrity and preserve beta-cell function. By integrating these perspectives, this study aims to redefine the etiological landscape of T1DM and propose innovative strategies for its prevention and management.

Methodology

This narrative review synthesized multidisciplinary evidence to explore the role of peritoneal membrane defects in triggering autoimmune beta-cell destruction in T1DM. The review encompassed anatomical, immunological, and therapeutic dimensions, with particular emphasis on interventions capable of restoring mesothelial integrity. A structured literature search was conducted using PubMed, Scopus, and Web of Science databases, covering the period from 2000 to 2024. Search terms included "type 1 diabetes mellitus", "pancreatic tail", "peritoneal membrane", "mesothelial cells", "GLP-1 receptor agonists", "degludec insulin", "mesenchymal stem cells", "hydrogels", and "anti-TNF therapies", combined using Boolean operators. Inclusion criteria focused on English-language peer-reviewed studies, including experimental models, clinical trials, and reviews that addressed the anatomical properties of the peritoneal membrane, its immunological role in T1DM, and the therapeutic modulation of peritoneal function. Articles lacking full-text access, written in other languages, or failing to address the core hypothesis were excluded. After initial retrieval of 612 articles, 137 duplicates were removed.

Abstract screening excluded 356 irrelevant studies, and full-text review of 119 articles led to the inclusion of 44 studies deemed methodologically robust, as assessed using the SANRA checklist (minimum score: 9/12). Particular focus was given to studies evaluating therapeutic agents such as GLP-1 receptor agonists, ultra-long-acting insulin (degludec), mesenchymal stem cells, anti-inflammatory biomaterials (hydrogels), and immunomodulatory monoclonal antibodies and their capacity to reinforce peritoneal integrity. These findings were thematically analyzed to construct a unified pathophysiological model linking anatomical disruption to immune-mediated beta-cell destruction and to outline promising therapeutic strategies grounded in the restoration of peritoneal barrier function.

Anatomical and immunological background

The pancreatic tail, a slender, intraperitoneal segment of the pancreas situated adjacent to the spleen within the splenorenal ligament, is distinguished by its unique anatomical and immunological properties [3]. Constituting approximately 15–20 % of the pancreatic mass, the tail harbors a disproportionately high density of islets of Langerhans, with 25–30 % of the pancreas's insulin-producing beta cells and an elevated expression of glucagon-like peptide-1 (GLP-1) receptors, which enhance insulin secretion and beta-cell proliferation [4]. Enveloping this region is the peritoneal membrane, a serous layer of mesothelial cells that forms a selective barrier within the intraperitoneal space [5]. Anatomically, this membrane shields the pancreatic tail from external stressors, while immunologically, it maintains an anti-inflammatory microenvironment through the secretion of cytokines such as IL-10 and TGF-β [6]. These cytokines, alongside major histocompatibility complex (MHC) molecules expressed by mesothelial cells, regulate immune cell trafficking and promote immune tolerance, safeguarding beta cells from autoreactive infiltration [7]. Disruption of this peritoneal barrier, whether through structural defects or inflammatory insults, may expose the beta-cell-rich tail to immune-mediated damage, positioning it as a critical nexus in the pathogenesis of T1DM.

The hypothesis and proposed mechanisms

The PPH posits that structural and functional defects in the peritoneal membrane enveloping the pancreatic tail precipitate immune-mediated beta-cell destruction in T1DM, challenging the conventional view of T1DM as solely an immune-driven disorder. The peritoneal membrane, a mesothelial barrier, normally restricts immune cell access to the beta-cell-rich pancreatic tail. Compromise of this barrier whether through congenital anomalies, inflammatory damage, or environmental insults renders beta cells vulnerable to autoreactive immune infiltration, initiating or amplifying autoimmune cascades. Under physiological conditions, mesothelial cells maintain barrier integrity via tight junctions and secrete anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which suppress immune activation. Defects in this membrane, such as thinning or fibrosis, disrupt these junctions, increasing permeability [8].

This allows peritoneal macrophages and dendritic cells to access beta-cell antigens, processing them via MHC class II molecules for presentation to CD4+ T-helper cells. Activated CD4+ T cells orchestrate cytotoxic CD8+ T-cell recruitment, which directly mediate beta-cell apoptosis through perforin-granzyme pathways [9, 10]. Concurrently, peritoneal B cells may produce autoantibodies (e.g., anti-GAD, anti-IA-2), triggering complement activation and amplifying beta-cell lysis, further accelerating autoimmune progression [11]. We propose three novel mechanisms that may contribute to peritoneal membrane dysfunction, expanding the hypothesis's scope. First, dysbiosis of the gut microbiome may exacerbate peritoneal vulnerability. Reduced populations of bacteria producing short-chain fatty acids, such as Faecalibacterium prausnitzii, diminish its levels (e.g., butyrate), which normally enhance mesothelial IL-10 production and barrier integrity [12, 13]. This dysbiotic state fosters a

pro-inflammatory peritoneal microenvironment, upregulating cytokines like TNF-α and IL-6, which impair mesothelial tight junction proteins (e.g., zonula occludens-1 (ZO-1), occludin), facilitating immune cell ingress [14, 15]. Second, mechanical stress on the peritoneal membrane, potentially induced by microtrauma from abdominal surgeries, infections, or visceral fat accumulation, may compromise its structural integrity [16]. Such stress activates mechanotransduction pathways, including integrin-mediated focal adhesion kinase signaling, leading to mesothelial apoptosis and extracellular matrix (ECM) remodeling, which weakens the barrier and permits immune cell transmigration [17]. Third, lymphatic interactions may amplify immune activation. The pancreatic tail's proximity to peritoneal lymphatic vessels enables antigen-presenting cells that have engulfed beta-cell antigens to migrate to regional lymph nodes, such as the pancreaticoduodenal nodes [18].

Here, antigen-presenting cells present antigens to naïve T cells, initiating clonal expansion of autoreactive T-cell populations that recirculate to the pancreatic tail, perpetuating beta-cell destruction [19]. Inflammation and oxidative stress play pivotal roles in exacerbating peritoneal defects, though their discussion is herein focused on their direct effects on the membrane (Fig.). Chronic inflammation, driven by elevated TNF-α, IL-1β, and IL-6, disrupts mesothelial homeostasis by activating nuclear factor-kappa B (NF-κB) signaling, which downregulates anti-inflammatory cytokine production and compromises tight junction integrity [20]. Simultaneously, oxidative stress, characterized by reactive oxygen species accumulation, induces lipid peroxidation and protein oxidation in mesothelial cells, triggering apoptosis and ECM degradation. These processes collectively enhance peritoneal permeability, enabling immune cell infiltration and antigen exposure, thus linking structural defects to autoimmune activation [21].

Supporting evidence

The PPH posits that an intact peritoneal membrane safeguards pancreatic beta cells from autoimmune destruction in T1DM, and its compromise precipitates immune-mediated beta-cell loss. Here, we synthesize existing evidence from clinical and imaging studies that support this paradigm, with a focus on the peritoneal membrane's protective role, and propose novel investigative approaches to further validate this hypothesis.

Current evidence underscores the interplay between peritoneal integrity and beta-cell preservation. A pivotal clinical study investigated semaglutide, a GLP-1 receptor agonist, in 10 newly diagnosed T1DM patients aged 21–39. Initiated within three months of diagnosis, semaglutide treatment enabled all patients to discontinue prandial insulin within three months, with seven discontinuing basal insulin within six months. Glycated hemoglobin (HbA1c) decreased from 11.7 % to 5.7 % over 12 months, accompanied by increased fasting C-peptide levels, indicating enhanced endogenous insulin secretion. These findings suggest that GLP-1 agonists may mitigate beta-cell stress, potentially by stabilizing peritoneal membrane function through anti-inflammatory effects, as GLP-1 receptors are densely expressed in the pancreatic tail. Although the study did not directly assess peritoneal integrity, its outcomes align with the hypothesis that preserving the peritoneal microenvironment enhances beta-cell resilience during the critical "honeymoon phase" of T1DM [22]. Imaging studies further corroborate the hypothesis by revealing structural alterations in the pancreatic tail of T1DM patients conducted a case-control ultrasonographic study comparing pancreatic morphology in T1DM patients and healthy controls. Their findings demonstrated a significant reduction in pancreatic tail diameter in T1DM patients ($p < 0.001$), alongside increased echogenicity with disease duration ($p = 0.015$), indicative of chronic remodeling and immune infiltration [23].

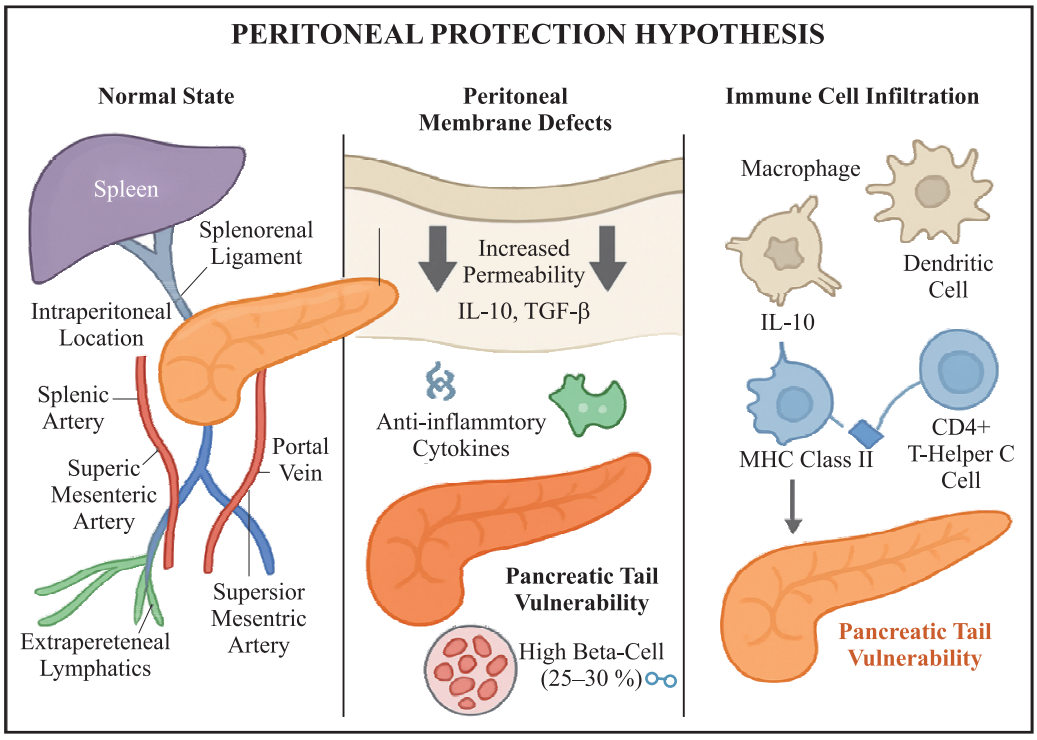
These changes suggest that the pancreatic tail, enveloped by the peritoneal membrane, is disproportionately affected in T1DM, potentially due to compromised peritoneal protection allowing localized immune access. While ultrasonography lacks the resolution to directly visualize peritoneal defects, these observations support the notion that anatomical vulnerabilities in the tail contribute to beta-cell loss [23]. To strengthen this evidence base, we propose two innovative investigative strategies. First, advanced imaging techniques, such as high-resolution MRI with contrast-enhanced sequences or positron emission tomography targeting mesothelial markers, could non-invasively assess peritoneal membrane thickness, integrity, and inflammatory status in T1DM patients versus controls.

Such modalities, increasingly utilized in peritoneal metastasis research, offer superior resolution to detect subtle defects or fibrosis, providing direct evidence of the membrane's role in beta-cell protection. Second, genomic analysis, specifically genome-wide association studies, could identify genetic variants associated with peritoneal membrane dysfunction. Polymorphisms in genes regulating ECM components (e.g., collagen, fibronectin) or inflammatory pathways (e.g., IL-6, NOD2) may predispose individuals to peritoneal permeability, correlating with T1DM susceptibility. Recent genome-wide association studies studies have linked T1DM risk to immune-regulatory genes, but none have explored peritoneal-specific loci,

presenting a novel research frontier [24]. Additional indirect evidence supports the peritoneal membrane's protective function. Experimental models, such as peritoneal islet transplantation in diabetic rodents, demonstrate that the peritoneal cavity provides an immunologically privileged environment, with encapsulated islets achieving sustained glycemic control. These findings, while not directly addressing T1DM autoimmunity, highlight the membrane's capacity to shield beta cells from immune attack when intact. Collectively, these clinical, imaging, and experimental observations, alongside proposed advanced methodologies, provide a compelling foundation for the PPH, emphasizing the peritoneal membrane as a critical determinant of beta-cell survival in T1DM [25].

Therapeutic interventions

GLP-1 receptor agonists enhance beta-cell function and exert potent anti-inflammatory effects, potentially reinforcing peritoneal integrity. By binding to GLP-1 receptors highly expressed on pancreatic tail beta cells, these agents stimulate cAMP signaling, activating protein kinase A [26]. This cascade upregulates anti-apoptotic proteins (e.g., Bcl-2), reducing beta-cell death under autoimmune stress [27]. Immunologically, GLP-1 agonists suppress peritoneal inflammation by inhibiting NF-κB activation in mesothelial cells, decreasing pro-inflammatory cytokine production (e.g., tumor necrosis factor-alpha TNF-α, interleukin-6 IL-6) and enhancing interleukin-10 (IL-10) secretion [28]. This fosters a tolerogenic microenvironment, limiting antigen-pre-



Overview of the PPH in T1DM. In the normal state, the peritoneal membrane surrounds the pancreatic tail, maintaining an anti-inflammatory microenvironment (IL-10, TGF-β) to prevent immune cell infiltration; peritoneal membrane defects increase permeability, disrupting this protective barrier; immune cell infiltration, involving macrophages, dendritic cells, and CD4+ T-helper cells via MHC class II antigen presentation, leads to beta-cell destruction, emphasizing the pancreatic tail's vulnerability due to its intraperitoneal location and high beta-cell density (25–30 %)

Обзор гипотезы перитонеальной защиты при СД1. В нормальном состоянии брюшинная оболочка окружает хвост поджелудочной железы, поддерживая противовоспалительную микросреду (IL-10, TGF-β), которая препятствует проникновению иммунных клеток; дефекты брюшинной оболочки увеличивают ее проницаемость, нарушая защитный барьер; инфильтрация иммунных клеток, включая макрофаги, дендритные клетки и Т-хелперы CD4+ через презентацию антигенов с участием молекул MHC класса II, приводит к разрушению бета-клеток, что подчеркивает уязвимость хвоста поджелудочной железы, обусловленную его внутрибрюшинным расположением и высокой плотностью бета-клеток (25–30 %)

senting cell activation and T-cell infiltration, thereby protecting beta cells from cytotoxic $CD8^+$ T-cell attack via perforin-granzyme pathways [29]. As an ultra-long-acting insulin, degludec provides stable glycemic control, mitigating metabolic stressors that exacerbate peritoneal damage [30]. By maintaining euglycemia, degludec reduces hyperglycemia-induced reactive oxygen species generation in mesothelial cells, which otherwise triggers lipid peroxidation and apoptosis through caspase-3 activation. This preserves mesothelial tight junction proteins (e.g., ZO-1, occludin), preventing immune cell transmigration.

Additionally, degludec's glucotoxicity reduction stabilizes beta-cell endoplasmic reticulum homeostasis, downregulating MHC class I overexpression, which curtails autoreactive T-cell recognition and complement-mediated lysis, indirectly supporting peritoneal barrier function [31]. Mesenchymal stem cells offer regenerative potential to repair peritoneal defects. MSCs secrete trophic factors, including vascular endothelial growth factor and TGF-β, which activate PI3K-Akt signaling in mesothelial cells, promoting proliferation and ECM synthesis (e.g., collagen, fibronectin). This restores membrane thickness and barrier integrity [32]. Immunologically, MSCs induce regulatory T-cell (Treg) differentiation via IL-10 and indoleamine 2,3-dioxygenase, suppressing effector $CD4^+$ T-cell proliferation and cytokine release (e.g., IFN-γ). This dual regenerative-immunomodulatory action reduces peritoneal permeability, shielding beta cells from autoimmune attack [33].

Hydrogels embedded with anti-inflammatory agents provide targeted peritoneal reinforcement. These biomaterials, designed to adhere to mesothelial surfaces, release IL-10 and dexamethasone, which inhibit NF-κB and STAT3 pathways in macrophages, reducing IL-1β and TNF-α secretion [34]. This dampens local inflammation, stabilizing tight junction proteins (ZO-1, occludin) and ECM components [35]. Mechanically, hydrogels enhance mesothelial resilience by mimicking ECM structure, preventing stress-induced apoptosis via integrin-mediated focal adhesion kinase signaling. By blocking immune cell access, hydrogels maintain beta-cell immunological privilege within the peritoneal cavity [36]. Targeted delivery of monoclonal antibodies against pro-inflammatory cytokines (e.g., anti-TNF-α) or immune checkpoint modulators (e.g., anti-PD-1) suppresses peritoneal immune activation [37]. Anti-TNF-α antibodies neutralize TNF-α, inhibiting NF-κB-driven inflammation and mesothelial apoptosis, preserving barrier function [38]. Anti-PD-1 modulators enhance programmed cell death protein-1 (PD-1) signaling, attenuating $CD8^+$ T-cell effector functions and promoting Treg expansion via IL-2 signaling. This localized approach minimizes systemic immunosuppression, reducing autoreactive T-cell infiltration and beta-cell destruction while maintaining peritoneal integrity [39].

Hypothesis validation plan

We propose a case-control study to compare peritoneal membrane characteristics in T1DM patients and non-diabetic controls. The study will enroll 50 T1DM patients (aged 18–40, diagnosed within 5 years to capture early disease dynamics) and 50 age- and sex-matched controls undergoing elective abdominal surgeries (e.g., cholecystectomy, appendectomy) where peritoneal sampling is feasible. Peritoneal biopsies (~1 cm^2) will be collected from the region overlying the pancreatic tail during surgery, ensuring minimal additional risk. Samples will undergo histological analysis to assess mesothelial thickness, collagen deposition, and tight junction integrity (e.g., ZO-1, occludin expression via immunohistochemistry). Immunological profiling will quantify inflammatory infiltrates (e.g., CD4+ T cells, macrophages) and cytokine expression (e.g., IL-6, TNF-α, IL-10) using flow cytometry and ELISA. Ultrastructural examination via transmission electron microscopy will evaluate mesothelial cell morphology and ECM disruptions. Primary endpoints include significant differences in peritoneal thickness and inflammatory cell density between groups, with a power calculation indicating 80 % power to detect a 20 % difference at $\alpha = 0.05$. Secondary endpoints will explore correlations between peritoneal defects and clinical markers (e.g., HbA1c, C-peptide content). Statistical analysis will employ unpaired t-tests for continuous variables and chi-square tests for categorical data, adjusted for confounders (e.g., body mass index, smoking status).

A primary challenge is the limited availability of peritoneal samples from T1DM patients, as pancreatic tail biopsies are not clinically indicated in early disease. To overcome this, we propose collaborations with tertiary surgical centers specializing in abdominal procedures, leveraging existing protocols for incidental peritoneal sampling during unrelated surgeries. Ethical considerations, including informed consent and minimal risk assurance, will be addressed through institutional review board approval, emphasizing the scientific value of opportunistic sampling. Another challenge is sample heterogeneity due to surgical or inflammatory variability. This will be mitigated by standardizing biopsy sites (pancreatic tail region) and excluding patients with confounding conditions (e.g., peritoneal infections, malignancies). Technical limitations in histological analysis, such as fixation artifacts, will be addressed by employing cryopreservation techniques and validating findings

with multiple staining methods (e.g., hematoxylin and eosin, Masson's trichrome). These solutions ensure robust data collection while prioritizing patient safety and scientific integrity. To capture the temporal dynamics of peritoneal defects, we propose a prospective cohort study tracking 100 at-risk individuals (e.g., first-degree relatives of T1DM patients with positive autoantibodies, aged 10–30) over 5 years. Non-invasive imaging, such as high-resolution MRI with gadolinium-enhanced sequences, will monitor peritoneal thickness and inflammatory markers in the pancreatic tail region annually. Blood samples will assess autoantibody profiles (e.g., anti-GAD, anti-IA-2) and systemic cytokines, correlating these with imaging findings. Incident T1DM cases will be analyzed for associations between baseline peritoneal abnormalities and disease onset, using Cox proportional hazards models to estimate hazard ratios.

This longitudinal approach will elucidate whether peritoneal defects precede or accelerate autoimmune progression, providing critical insights into causality. Current T1DM models, such as non-obese diabetic mice, do not specifically address peritoneal membrane dysfunction. We propose developing a novel transgenic mouse model with targeted peritoneal defects in the pancreatic tail region. This could involve conditional knockout of genes encoding mesothelial tight junction proteins (e.g., ZO-1, claudin-1) or ECM components (e.g., collagen type I) using Cre-LoxP recombination, driven by a mesothelium-specific promoter (e.g., mesothelin). These mice would be crossed with non-obese diabetic mice backgrounds to assess whether peritoneal compromise accelerates autoimmune beta-cell loss, monitored via glycemic profiles, histological analysis, and immune cell infiltration ($CD8^+$ T cells, macrophages). Pharmacological interventions (e.g., GLP-1 agonists, anti-TNF-α antibodies) could be tested to evaluate their efficacy in restoring peritoneal integrity, with endpoints including beta-cell mass and insulitis scores. This model would provide mechanistic clarity on the interplay between peritoneal defects and T1DM onset, overcoming limitations of streptozotocin-based models that lack autoimmune specificity.

This multifaceted validation plan integrates immediate, feasible studies with long-term and experimental approaches, addressing the PPH through rigorous anatomical, immunological, and clinical lenses. By overcoming logistical and technical challenges, these strategies pave the way for confirming the peritoneal membrane's role as a novel therapeutic target in T1DM.

Discussion

The PPH offers a transformative perspective on T1DM pathogenesis by implicating structural defects in the peritoneal membrane surrounding the pancreatic tail as a critical trigger for autoimmune beta-cell destruction. This section compares the hypothesis with the conventional autoimmune model, evaluates its implications for T1DM prevention and treatment, and explores its broader applicability to other autoimmune disorders, underscoring its potential to reshape therapeutic paradigms. The prevailing autoimmune model of T1DM posits that genetic predisposition, combined with environmental triggers (e.g., viral infections, dietary factors), initiates systemic immune dysregulation, leading to autoreactive T-cell activation and beta-cell destruction [40]. This model emphasizes immune-mediated pathways, such as MHC class II presentation of beta-cell antigens and cytotoxic $CD8^+$ T-cell effector functions, supported by autoantibodies (e.g., anti-GAD, anti-IA-2) [41]. However, it inadequately explains the localized pattern of beta-cell loss, the variable progression among genetically susceptible individuals, and the presence of autoantibodies in non-progressors.

In contrast, the PPH integrates anatomical vulnerability with immunological dysregulation, proposing that peritoneal membrane defects enable localized immune cell infiltration into the beta-cell-rich pancreatic tail. Unlike the systemic focus of the traditional model, this hypothesis highlights a specific anatomical nexus compromised mesothelial tight junctions and increased permeability that facilitates antigen-presenting cell access to beta cells, amplifying MHC-driven T-cell responses. By situating the initiation of autoimmunity within a defined microenvironment, the hypothesis offers a mechanistic bridge between genetic, environmental, and anatomical factors, addressing gaps in the conventional paradigm while complementing its immunological insights.

The hypothesis has profound implications for T1DM management, particularly in early-stage intervention and prevention. For prevention, identifying peritoneal membrane defects in at-risk populations (e.g., first-degree relatives with positive autoantibodies) could enable preemptive strategies. Non-invasive imaging, such as high-resolution MRI, could detect early peritoneal abnormalities, guiding risk stratification and monitoring. Pharmacological interventions, such as GLP-1 receptor agonists,

which reduce inflammation and enhance beta-cell resilience, could be initiated prophylactically to stabilize the peritoneal microenvironment, potentially delaying or preventing disease onset. For treatment, the hypothesis underscores the therapeutic potential of restoring peritoneal integrity. Clinical evidence from semaglutide trials demonstrates improved glycemic control and beta-cell function, suggesting that targeting peritoneal inflammation may extend the "honeymoon phase" in newly diagnosed patients. Novel therapies, including mesothelial stem cell transplantation to repair membrane defects, biomaterials to reinforce barrier function, and localized immunomodulation to suppress autoreactive responses, offer transformative possibilities. These approaches could reduce reliance on exogenous insulin and mitigate long-term complications, reshaping T1DM care by addressing a previously unrecognized anatomical driver [31].

The PPH has broader implications beyond T1DM, offering insights into autoimmune diseases involving serosal membranes or organ-specific immune dysregulation. In systemic lupus erythematosus, peritoneal inflammation (serositis) is a recognized feature, and defects in mesothelial barriers may exacerbate immune complex deposition, suggesting parallels with T1DM's peritoneal vulnerability [42]. Similarly, in autoimmune hepatitis, where immune attack targets hepatocytes within a peritoneal-adjacent microenvironment, compromised serosal integrity could facilitate immune cell access, warranting investigation of peritoneal-specific therapies [43].

Inflammatory bowel diseases, such as Crohn's disease, also involve peritoneal complications (e.g., adhesions, fistulae), and microbiome-driven inflammation a proposed mechanism in our hypothesis may disrupt mesothelial homeostasis, amplifying mucosal autoimmunity [44]. Therapies targeting peritoneal repair, such as biomaterials or localized anti-TNF-α antibodies, could be adapted for these conditions, leveraging shared pathways (e.g., IL-6, NF-κB signaling). By highlighting the role of anatomical barriers in modulating immune responses, the hypothesis provides a framework for cross-disciplinary research, potentially unifying mechanistic insights across serosal-associated autoimmune disorders.

Conclusions

In summary, the PPH challenges the traditional autoimmune model by integrating anatomical and immunological perspectives, offering a nuanced understanding of T1DM pathogenesis. Its implications for prevention and treatment ranging from early detection to innovative therapies promise to enhance clinical outcomes, while its applicability to other autoimmune diseases underscores its transformative potential. Further research is warranted to validate these concepts, paving the way for precision medicine approaches targeting serosal barriers in autoimmunity.

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