Hypothesis

The Energy-Deficit Hypothesis of Autism: TNF-α-Mediated Mitochondrial Dysfunction as a Common Pathway from Parental Immune Dysregulation to Offspring Autism Risk

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The Energy-Deficit Hypothesis of Autism: TNF-α-Mediated Mitochondrial Dysfunction as a Common Pathway from Parental Immune Dysregulation to Offspring Autism Risk

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Abstract

Background: Autism spectrum disorder (ASD) affects approximately 1-2% of children worldwide, yet its etiology remains incompletely understood. Emerging evidence suggests that offspring of parents with autoimmune diseases show elevated autism prevalence. Notably, children of parents with psoriasis (OR 1.59), type 1 diabetes (OR 1.49-2.36), and rheumatoid arthritis (OR 1.51) demonstrate particularly strong associations. **Hypothesis:** I propose that autism may be conceptualized as an immune-metabolic disorder in which TNF-α-mediated mitochondrial dysfunction contributes to cerebral energy deficiency. This energy deficit may impair three critical processes: (1) synaptic pruning during neurodevelopment, (2) real-time social cognition including gaze processing and emotion recognition, and (3) protein synthesis of critical synaptic scaffolding molecules. The proposed mechanism is TNF-α pathway dysregulation arising from inherited inflammatory susceptibility and/or direct fetal exposure to elevated maternal TNF-α during pregnancy. I further propose that the well-documented "firstborn effect" in autism reflects maternal immune maladaptation during primigravid pregnancies. Additionally, for cases without parental autoimmune history, a speculative secondary mechanism is proposed: mitonuclear immune conflict, where paternal immune genes may partially recognize maternal mitochondria as non-self, generating endogenous TNF-α.

Implications: This framework may provide an integrative account of disparate observations about autism pathophysiology and suggests that TNF-α-related pathways merit further investigation for potential risk modification, particularly in pregnancies identified as high-risk through parental autoimmune or inflammatory disease.

Keywords: autism spectrum disorder; TNF-α; mitochondrial dysfunction; synaptic pruning; protein synthesis; SHANK3; birth order; maternal immune tolerance; energy metabolism; normal-tension glaucoma; psoriasis; type 1 diabetes; neuroinflammation; eye contact avoidance; tissue-specific vulnerability; hypotonia; hyperlactatemia

Lay Summary

Children of parents with certain immune-related conditions—such as psoriasis, type 1 diabetes, and rheumatoid arthritis—have a higher chance of being autistic. These conditions share a common feature: overactivity of an immune signaling molecule called TNF-α. This paper proposes that TNF-α may damage the energy-producing structures inside brain cells (mitochondria), creating an energy shortage in the developing brain. Because the brain requires enormous amounts of energy—especially during early childhood—this shortage may disrupt processes critical for typical neurodevelopment, including the refinement of brain connections and real-time social processing

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such as eye contact. The paper also predicts that a specific eye condition called normal-tension glaucoma, which is driven by the same TNF-α pathway but has never been studied in relation to autism, should be associated with elevated autism rates in offspring. If confirmed, this framework could help identify pregnancies at higher risk and guide future research into potential preventive strategies.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in social communication and interaction, restricted interests, and repetitive behaviors. Despite decades of research, the fundamental biological mechanisms underlying autism remain elusive. While genetic factors contribute substantially to autism risk, environmental and immunological factors increasingly appear to play critical roles [1].

A growing body of evidence indicates that offspring of parents with autoimmune diseases show elevated autism prevalence. Meta-analyses have demonstrated that family history of autoimmune disease is associated with a 28-50% higher autism prevalence. Importantly, specific autoimmune conditions mediated by tumor necrosis factor-alpha (TNF-α) show particularly robust associations with offspring autism.

In this paper, I propose that autism may be conceptualized as an **immune-metabolic disorder** in which TNF-α-mediated mitochondrial dysfunction contributes to cerebral energy deficiency, impairing three critical processes: synaptic pruning during neurodevelopment, real-time social cognitive processing, and protein synthesis of synaptic scaffolding molecules. This framework may help explain core autism symptoms from a unified energetic perspective and generates testable predictions.

A central tenet of this hypothesis is that autism-related neural circuit abnormalities are established **prenatally**, during in utero brain development, rather than arising de novo after birth. In this view, the autistic brain is not a typically developed brain that subsequently malfunctions; it is a brain whose foundational architecture—synaptic density, connectivity patterns, and microglial programming—has been shaped by an adverse intrauterine inflammatory and metabolic environment. The clinical manifestations observed postnatally represent the downstream expression of developmental trajectories that were altered before birth.

A central implication of the present hypothesis is that ASD may arise not only from overt maternal inflammatory disease, but also from a *"clinically silent, chronic low-to-intermediate pro-inflammatory cytokine state"* that is insufficient to endanger maternal or fetal survival, yet sufficient to disrupt fetal brain development during sensitive gestational windows.

2. Epidemiological Evidence: Parental Autoimmune Diseases and Autism Risk

2.1. Large-Scale Studies

Multiple large-scale epidemiological studies have established associations between parental autoimmune diseases and offspring autism risk. Table 1 summarizes key findings from major studies.

Table 1. Parental Autoimmune Disease and Offspring Autism Risk.

Parental Disease	Odds Ratio	95% CI	Key Reference
Psoriasis	**1.59**	1.21-2.10	Wu et al. (2015) [2]
Type 1 Diabetes (T1D)	**1.49-2.36**	1.21-4.12	Xiang et al. (2018); Persson et al. (2023) [3,4]
Rheumatoid Arthritis	**1.51**	1.14-2.00	Keil et al. (2010) [5]

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Hypothyroidism	**1.64**	1.16-2.32	Atladóttir et al. (2009) [6]
Any Autoimmune Disease	**1.28-1.50**	1.11-1.75	Wu et al. (2015) [2]

Note: All listed conditions involve inflammatory pathways in which TNF-α has been implicated. CI = Confidence Interval.

2.2. The TNF-α Common Denominator

A critical observation is that the parental diseases most strongly associated with offspring autism risk involve a common inflammatory mediator: TNF-α signaling. TNF-α is a master pro-inflammatory cytokine that has been implicated in:

- **Psoriasis:** TNF-α drives keratinocyte proliferation and inflammatory cascade; anti-TNF biologics are first-line therapy [2]
- **Type 1 Diabetes:** TNF-α directly induces β-cell apoptosis and promotes autoimmune destruction of pancreatic islets [7]
- **Rheumatoid Arthritis:** TNF-α orchestrates synovial inflammation and joint destruction; anti-TNF therapy revolutionized treatment [5]
- **Normal-Tension Glaucoma:** TNF-α has been implicated in NTG pathogenesis, and experimental glaucoma models support a TNF-α-mediated mechanism of retinal ganglion cell loss [8]

3. Sources of TNF-α Exposure

Multiple pathways can lead to elevated TNF-α exposure during critical periods of neurodevelopment. This section examines four distinct sources: parental autoimmune diseases, maternal obesity, maternal immune maladaptation during first pregnancies, and endogenous mitonuclear immune conflict.

3.1. Parental Autoimmune Diseases

As detailed in Section 2, offspring of parents with autoimmune diseases including psoriasis, type 1 diabetes, and rheumatoid arthritis show elevated autism prevalence. These conditions share TNF-α pathway dysregulation as a common pathogenic mechanism. Children may be exposed to elevated TNF-α through genetic inheritance of inflammatory gene variants and/or direct fetal exposure to maternal TNF-α during pregnancy.

3.2. Maternal Obesity: An Additional Source of Prenatal TNF-α Exposure

Beyond parental autoimmune diseases, maternal obesity represents another condition associated with elevated offspring autism prevalence. Multiple large-scale epidemiological studies have consistently demonstrated that children of obese mothers show higher autism rates.

3.2.1. Epidemiological Evidence

Meta-analyses reveal that maternal obesity (BMI ≥30) is associated with a 41–47% increased risk of offspring autism (OR 1.41–1.47) [9,10]. Importantly, the risk increases in a dose-dependent manner with maternal BMI, suggesting a biological gradient rather than confounding [10].

3.2.2. Obesity as a Chronic Inflammatory State

Obesity is fundamentally a state of chronic low-grade inflammation [11]. Adipose tissue is not merely an energy storage organ but an active endocrine tissue that produces pro-inflammatory cytokines:

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- Adipose tissue is a major source of TNF-α production; obese individuals express approximately 2.5-fold more TNF-α mRNA in adipose tissue than lean controls [12]
- TNF-α protein production is elevated both locally in adipose tissue and systemically, though circulating levels are lower than in catabolic diseases [11,12]
- Other inflammatory markers (IL-6, CRP, leptin) are also elevated
- Inflammation correlates with degree of adiposity [11]

3.2.3. Mechanism of Fetal Exposure

During pregnancy, maternal obesity creates multiple pathways for fetal TNF-α exposure [13]:

- **Transplacental passage:** Maternal TNF-α can cross the placenta and directly affect fetal brain development
- **Placental inflammation:** The placenta itself becomes inflamed in obese pregnancies, producing additional local cytokines
- **Metabolic stress:** Maternal hyperglycemia and insulin resistance further compromise fetal mitochondrial function
- **Oxidative stress:** Obesity-associated oxidative stress damages both maternal and fetal mitochondria

3.2.4. Convergence with the Energy-Deficit Model

Maternal obesity thus represents another route to the same pathogenic endpoint: TNF-α-mediated mitochondrial dysfunction in the developing fetal brain. Whether TNF-α elevation originates from parental autoimmune disease, maternal obesity, or both, the downstream consequences—impaired synaptic pruning, compromised social cognition, and protein synthesis deficits—may remain the same. I propose that this convergence may explain why maternal obesity and parental autoimmune conditions show similar effect sizes for autism risk and could have additive effects when co-occurring.

3.3. The Birth Order Effect: Maternal Immune Maladaptation

Epidemiological studies consistently demonstrate that firstborn children have significantly elevated autism risk compared to later-born siblings. This "firstborn effect" has been dismissed as reproductive stoppage (parents not having more children after an autistic child), but this explanation conflates correlation with causation.

3.3.1. Epidemiological Evidence for the Firstborn Effect

Table 2. Birth Order and Autism Risk: Evidence Summary.

Finding	Effect Size	Reference
Firstborn autism risk (Utah)	**OR 1.8**	Bilder et al. (2009) [14]
Short interpregnancy interval (<12 mo)	**OR 3.39**	Cheslack-Postava et al. (2011) [15]
Preeclampsia in nulliparous women	**Significantly higher**	Robillard et al. (1994) [16]
Partner change resets preeclampsia risk	**Returns to primigravid**	Dekker & Robillard (2007) [17]

Note: OR = Odds Ratio. Preeclampsia data included as parallel evidence for primigravid immune maladaptation.

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3.3.2. Primigravid Immune Maladaptation Mechanism

The maternal immune system must achieve tolerance to semi-allogeneic fetal antigens. This tolerance develops progressively across the first pregnancy as paternal antigen-specific regulatory T cells (Tregs) expand [16,17]. During the first pregnancy, the maternal immune system encounters paternal antigens for the first time, resulting in a Th1-dominant response with elevated pro-inflammatory cytokines including TNF-α. Subsequent pregnancies (with the same partner) benefit from immunological memory, with rapid Treg expansion providing enhanced tolerance [17].

3.3.3. Preeclampsia as Parallel Paradigm

Preeclampsia—characterized by placental inflammation and TNF-α elevation—has been called "the disease of primigravidae" since 1902. Nulliparous women have significantly higher preeclampsia risk than multiparous women, and critically, this protective effect is lost when women change partners [16]. Prior abortion with the same partner reduces preeclampsia risk by half (OR 0.54), but abortion with a different partner confers no protection [16]. These findings demonstrate that paternal antigen-specific tolerance develops during first pregnancy and provides lasting protection [17]—precisely the mechanism I propose underlies the autism birth order effect.

3.4. Mitonuclear Immune Conflict: An Endogenous Source of TNF-α

While the preceding sections describe how TNF-α-mediated mitochondrial dysfunction leads to autism, an important question remains: what about cases where parents have no autoimmune disease? I propose that mitonuclear immune conflict may represent an endogenous source of TNF-α that activates the same pathogenic pathway. *This mechanism remains highly speculative and is presented as a hypothesis-generating extension of the TNF-α framework; it requires independent empirical validation.*

3.4.1. The Gap in the TNF-α Hypothesis

The TNF-α energy deficit hypothesis explains autism risk in offspring of parents with autoimmune diseases such as psoriasis, type 1 diabetes, and rheumatoid arthritis. However, autism also occurs in families with no history of autoimmune disease. Additionally, studies show that a substantial proportion of autistic individuals exhibit mitochondrial dysfunction biomarkers without carrying classical mitochondrial disease mutations.

This raises a critical question: if TNF-α-mediated mitochondrial dysfunction is central to autism pathophysiology, what is the source of TNF-α in cases without parental autoimmune disease?

3.4.2. The Unique Inheritance Pattern of Mitochondria

Mitochondria possess a unique inheritance pattern. Mitochondrial DNA (mtDNA) is inherited exclusively from the mother—paternal mitochondria are actively eliminated from the fertilized egg. Every mitochondrion in an individual's body carries only maternal genetic information.

In contrast, the nuclear genome—including genes governing immune function and self/non-self recognition—is inherited from both parents. This creates an asymmetry: the immune system is shaped by both parental genomes, but the mitochondria it must tolerate are exclusively maternal.

3.4.3. The Conflict Hypothesis: Paternal Immune Genes vs. Maternal Mitochondria

I hypothesize that in some individuals, paternally inherited immune genes may fail to fully recognize maternal mitochondria as "self." This could result in:

- **Immune misrecognition:** The paternal contribution to immune recognition machinery (HLA genes, innate immune pathways) may be calibrated to recognize mitochondrial signatures that differ from those inherited from the mother.
- **Chronic immune attack:** The immune system may mount persistent inflammatory responses against the individual's own mitochondria, treating them as partially foreign.

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- **Endogenous TNF-α production:** This chronic immune activation would result in sustained TNF-α release—activating the same pathogenic cascade described in previous sections, even without external TNF-α exposure from parental autoimmune disease.

The biological plausibility of this mechanism is supported by two established principles. First, mitochondria retain their bacterial ancestry and, when damaged or released extracellularly, their components—including mtDNA, cardiolipin, and formyl peptides—function as damage-associated molecular patterns (DAMPs) that potently activate innate immune receptors, particularly Toll-like receptor 9 (TLR9) and formyl peptide receptors [18]. Second, mitochondrial stress is known to activate NF-κB signaling, which in turn promotes production of pro-inflammatory cytokines including TNF-α, while released mtDNA can also activate the NLRP3 inflammasome [19]. Thus, even partial immune misrecognition of mitochondrial components could initiate a self-amplifying cycle: immune-mediated mitochondrial damage releases DAMPs, which activate NF-κB, which drives further TNF-α production, which causes additional mitochondrial dysfunction.

3.4.4. Two Pathways to the Same Outcome

The mitonuclear immune conflict hypothesis does not replace the parental autoimmune disease hypothesis—it complements it by providing a second pathway to TNF-α-mediated mitochondrial dysfunction:

Table 3. Two Pathways to TNF-α-Mediated Mitochondrial Dysfunction.

	Pathway 1: External	Pathway 2: Internal
Source of TNF-α	Parental autoimmune disease	Mitonuclear immune conflict
Mechanism	Genetic inheritance + fetal exposure during pregnancy	Paternal immune attack on maternal mitochondria
Parental disease required?	Yes	No
Final common pathway	**TNF-α elevation → Mitochondrial dysfunction → Energy deficit → Autism**	

Note: Both pathways converge on the same final mechanism of TNF-α-mediated mitochondrial dysfunction.

This framework is consistent with the following observations:

- Parental autoimmune disease is associated with elevated autism prevalence (Pathway 1)
- Autism also occurs without parental autoimmune disease (Pathway 2)
- Only a subset of children with autoimmune parents develop autism (variable mitonuclear compatibility may be protective or additive)

3.4.5. Testable Predictions and Preliminary Evidence

The mitonuclear immune conflict hypothesis generates testable predictions:

- Anti-mitochondrial antibodies or mitochondria-targeted immune markers may be elevated in autistic individuals without parental autoimmune history
- Inflammatory cytokines including TNF-α may be elevated even in autism cases without parental autoimmune disease
- Specific HLA haplotype combinations from parents may show associations with autism risk

Notably, the first prediction has already received preliminary support. Zhang et al. [20] reported that serum from young autistic children contains significantly elevated levels of anti-mitochondrial

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antibody Type 2 (AMA-M2; p = 0.001) and extracellular mitochondrial DNA (cytochrome B, p = 0.0002) compared to neurotypical controls. The authors noted that AMA-M2 had previously been detected clinically only in primary biliary cholangitis (PBC)—an autoimmune disease characterized by immune-mediated destruction of mitochondria-rich biliary epithelial cells. The presence of this antibody in autistic children is consistent with the possibility that the immune system can mount responses against mitochondrial components in autism, aligning with the mitonuclear immune conflict mechanism proposed here. Whether parental PBC is associated with elevated offspring autism risk remains untested and represents an additional testable prediction of this hypothesis.

3.5. The Decidual-Placental Transmission Pathway: How TNF-α Reaches the Fetal Brain

The preceding sections have identified multiple sources of TNF-α elevation relevant to autism risk. However, a critical spatial question remains insufficiently addressed: through what anatomical pathway does maternal or endogenous TNF-α reach the developing fetal brain? I propose that the decidua basalis—the specialized maternal tissue forming the immunological core of the placenta—represents a key intermediate locus in this transmission chain.

3.5.1. The Decidual Immune Tolerance Circuit

The decidua basalis harbors a uniquely high density of immune cells, including uterine natural killer cells (uNK, ~50–70% of decidual leukocytes), decidual macrophages (~20–25%), and regulatory T cells (Tregs) [21]. In normal pregnancy, these populations maintain a coordinated tolerogenic circuit: Tregs suppress maternal immune responses against paternally derived fetal antigens, macrophages adopt an anti-inflammatory M2 phenotype producing IL-10 and TGF-β, and uNK cells promote spiral artery remodeling through controlled IFN-γ secretion rather than cytotoxic activity [22]. This circuit ensures that the local immune environment at the maternal-fetal interface remains anti-inflammatory and supportive of placental development.

3.5.2. Disruption of the Tolerogenic Circuit

I hypothesize that in mothers with autoimmune disease, chronic inflammation, or other predisposing conditions described in Sections 3.1–3.4, this tolerogenic circuit may become dysregulated through three converging mechanisms: (1) Treg insufficiency, leading to inadequate suppression of pro-inflammatory responses at the maternal-fetal interface; (2) macrophage polarization shift from M2 (anti-inflammatory) toward M1 (pro-inflammatory), increasing local TNF-α, IL-6, IL-1β, and IFN-γ production; and (3) uNK cell dysfunction, shifting from controlled IFN-γ-mediated vascular remodeling toward excessive pro-inflammatory cytokine release, impairing spiral artery remodeling and contributing to chronic placental hypoperfusion [21,22]. These mechanisms are not independent but mutually reinforcing: Treg insufficiency promotes macrophage M1 polarization, which further destabilizes the local immune environment.

3.5.3. Placental Amplification and Fetal Exposure

A critical feature of this pathway is that the placenta does not function as a passive filter. Placental trophoblast cells express receptors for TNF-α and IL-6, and respond actively to inflammatory stimulation by increasing their own cytokine production [23]. This means that a relatively modest inflammatory signal originating in the decidual compartment can be amplified through placental relay, resulting in disproportionate cytokine exposure at the fetal level. This amplification mechanism may explain a clinically important observation: why ASD occurs in offspring of mothers who appear outwardly healthy during pregnancy.

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3.5.4. Subclinical Decidual Inflammation: Why Healthy-Appearing Mothers Can Have Affected Offspring

A central implication of this model is that clinically significant immune dysregulation at the decidual level need not manifest as overt maternal illness. The decidual immune environment is relatively compartmentalized from the systemic maternal circulation [21,22]; its immune cell composition and cytokine profile are shaped by local factors including progesterone signaling, trophoblast-derived HLA-G molecules, and paracrine interactions among resident immune cells. Consequently, a mother may exhibit normal or subclinical systemic inflammatory markers while harboring a substantially dysregulated immune environment at the decidual level. This dissociation between systemic and local immune states is fundamentally different from conditions such as preeclampsia or cytokine storm, in which maternal systemic inflammation is clinically apparent. The present model proposes that even this "quiet" decidual inflammation—operating below the threshold of clinical detection—may generate sufficient TNF-α signaling, amplified through placental relay, to impair fetal brain mitochondrial function during critical developmental windows. Although immune dysregulation at the decidual-placental interface may exert effects throughout gestation, the second trimester may represent a particularly important convergence window, as this period coincides with the peak of microglial colonization of the fetal brain, the maturation of placental transport function, active synaptogenesis and early circuit formation, and the height of decidual immune activity [21–23]. However, the precise gestational timing of maximal vulnerability likely varies across individuals and may depend on the nature, severity, and duration of the maternal immune perturbation.

This framework helps resolve a persistent puzzle in autism epidemiology: why the majority of mothers who deliver autistic children have unremarkable pregnancy histories. If the operative locus of immune dysregulation is the decidua rather than the systemic maternal compartment, then conventional prenatal screening—which relies on systemic markers—would be expected to miss these cases.

3.5.5. Microglial Reprogramming: The Bridge from Placental Inflammation to Aberrant Synaptic Pruning

The pathway from decidual-placental inflammation to disrupted fetal brain development requires a cellular intermediary within the fetal brain itself. Microglia—the resident immune cells of the central nervous system—serve this role. During normal fetal development, microglia originating from the yolk sac colonize the brain primarily during the second trimester, where they perform essential functions including synaptic pruning, neuronal circuit refinement, and clearance of apoptotic cells [24,25]. These functions are activity-dependent and energetically costly, requiring precise calibration of microglial activation state.

When the placental relay transmits elevated TNF-α and other pro-inflammatory cytokines to the fetal compartment, fetal microglia may undergo functional reprogramming toward a chronically activated, pro-inflammatory phenotype [24,25]. This reprogramming has two consequences directly relevant to autism: first, chronically activated microglia may execute synaptic pruning aberrantly—either excessively or insufficiently—disrupting the normal refinement of neural circuits during critical developmental windows. This aligns with the excess synaptic density observed in postmortem autism brain tissue (Section 5.1). Second, activated microglia increase local TNF-α production within the fetal brain itself, potentially creating a self-sustaining neuroinflammatory loop that persists beyond the initial prenatal insult. This mechanism provides a cellular explanation for how a transient gestational exposure can produce permanent alterations in brain architecture—the microglia are reprogrammed during a critical window, and their altered pruning behavior shapes the synaptic landscape of the developing brain irreversibly.

This intermediate range of immune dysregulation—below the clinical threshold of conditions such as preeclampsia or cytokine storm, yet above the level compatible with normal fetal neurodevelopment—may define an "autism-risk immune activation zone" in which clinically silent

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decidual inflammation remains biologically consequential for fetal neurodevelopment. The precise immunological parameters defining this zone, including cytokine thresholds, Treg counts, and decidual macrophage polarization ratios, remain to be established through future investigation.

4. TNF-α and Mitochondrial Dysfunction: The Mechanistic Link

Before detailing the mechanisms by which TNF-α impairs mitochondrial function, it is important to note that TNF-α elevation in autism is not merely hypothetical—it is an empirically supported finding. Vargas et al. [26] demonstrated active neuroinflammation in postmortem brain tissue from autistic individuals, with marked activation of microglia and astroglia and elevated pro-inflammatory cytokine profiles including TNF-α in both brain parenchyma and cerebrospinal fluid. Li et al. [27] independently confirmed elevated immune responses in the brains of autistic patients, reporting increased expression of pro-inflammatory cytokines in frontal cortex tissue. At the peripheral level, Ashwood et al. [28] and Xie et al. [29] identified TNF-α as a key cytokine significantly elevated in the plasma of autistic children compared to typically developing controls, with higher TNF-α levels correlating with greater behavioral symptom severity. These converging lines of evidence—from postmortem brain tissue, cortical immune profiling, and peripheral blood—suggest that TNF-α elevation is a reproducible feature of autism [30], providing an empirical basis for the mechanistic model that follows.

An important caveat is warranted: the cross-sectional nature of existing cytokine studies cannot establish whether TNF-α elevation is a cause of autistic neurodevelopment, a consequence of ongoing neuroinflammatory processes, or both. The present hypothesis proposes a causal role for TNF-α based on three lines of reasoning: (1) parental autoimmune diseases characterized by TNF-α dysregulation precede and predict offspring autism risk, establishing temporal precedence; (2) TNF-α has well-characterized, direct inhibitory effects on mitochondrial function (detailed below), providing mechanistic plausibility; and (3) the anti-TNF biologic golimumab has demonstrated disease-modifying effects in a TNF-α-mediated condition (type 1 diabetes [7]), establishing that the pathway is amenable to intervention. Nevertheless, definitive causal evidence would require prospective longitudinal studies tracking prenatal TNF-α levels and subsequent neurodevelopmental outcomes.

4.1. Direct Effects of TNF-α on Mitochondrial Function

TNF-α exerts profound inhibitory effects on mitochondrial function through multiple mechanisms. Table 4 summarizes the key pathways by which TNF-α impairs cellular energy production.

Table 4. TNF-α Effects on Mitochondrial Function.

Mechanism	Effect on Energy Metabolism
ETC Complex I Inhibition	Blocks electron transfer at the first step of oxidative phosphorylation
ETC Complex III Inhibition	Disrupts cytochrome bc1 complex function
Cytochrome c Oxidase (COX)	Reduces terminal electron transfer and oxygen consumption
Membrane Depolarization	Collapses mitochondrial membrane potential (ΔΨm), halting ATP synthesis
PDH Suppression	Inhibits pyruvate dehydrogenase, blocking glucose entry into TCA cycle

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ROS Overproduction	Increases reactive oxygen species, causing oxidative damage to mitochondrial components
Warburg Effect Induction	Shifts metabolism to inefficient aerobic glycolysis (2 vs 36 ATP per glucose)

Note: ETC = Electron Transport Chain; PDH = Pyruvate Dehydrogenase; TCA = Tricarboxylic Acid Cycle; ROS = Reactive Oxygen Species.

4.2. Rapid Neurotoxicity of TNF-α

Critically, TNF-α-induced mitochondrial dysfunction occurs rapidly in neurons. Studies using pathophysiologically relevant concentrations demonstrate [31]:

- Reduction in mitochondrial basal respiration within **1.5 hours** of TNF-α exposure
- Decreased ATP production preceding neuronal cell death
- Effects mediated specifically through TNF-R1 receptor signaling
- Cascade involving caspase-8 activation, membrane potential collapse, and cytochrome c release

4.3. Tissue-Specific Vulnerability: Why the Brain Bears the Burden

A potential objection to the energy-deficit hypothesis is the clinical observation that many autistic individuals exhibit normal or even exceptional physical strength. If mitochondrial dysfunction is central to autism pathophysiology, why does skeletal muscle appear largely unaffected? The answer lies in the fundamentally different energy metabolic profiles of these tissues, and closer examination reveals that muscle is not entirely spared.

4.3.1. Divergent Energy Dependencies of Brain and Skeletal Muscle

The brain consumes roughly 20% of total body energy despite constituting only 2% of body weight [32], and depends almost exclusively on mitochondrial oxidative phosphorylation (OXPHOS). Skeletal muscle, by contrast, possesses robust glycolytic capacity: fast-twitch fibers can generate ATP rapidly through anaerobic glycolysis independent of mitochondrial function. This asymmetry means that partial OXPHOS impairment preferentially affects the brain while leaving gross motor function relatively intact (Table 5). Notably, the perception of exceptional strength in autistic individuals may in some cases reflect catecholamine-driven fight-or-flight responses during emotional dysregulation—transient sympathetic activation rather than evidence of sustained muscle power.

Table 5. Energy Metabolic Profiles: Brain vs. Skeletal Muscle.

Parameter	Brain (Neurons)	Skeletal Muscle
Primary ATP source	OXPHOS (~95%)	OXPHOS + glycolysis (variable)
Glycolytic capacity	Very limited	High (type II fibers)
Glycogen reserves	Minimal	Substantial
Tolerance to OXPHOS impairment	Very low	Moderate to high

Note: OXPHOS = oxidative phosphorylation. Brain energy consumption during infancy is even higher (~40% of total body energy) [32], coinciding with peak vulnerability to mitochondrial dysfunction.

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4.3.2. Hypotonia and Hyperlactatemia: Evidence That Muscle Is Not Entirely Spared

Despite preserved gross motor strength, skeletal muscle does show signs of mitochondrial compromise. Hypotonia is one of the most frequently reported motor findings in autistic children, with prevalence estimates of 30–51% [33]—comparable to rates seen in primary mitochondrial diseases such as MELAS and Leigh syndrome. Additionally, Rossignol and Frye [34] found that approximately 30% of autistic children exhibit elevated blood lactate, indicating compensatory upregulation of anaerobic glycolysis in response to impaired OXPHOS. This metabolic signature is precisely what the energy-deficit hypothesis predicts. The pattern mirrors established mitochondrial disorders, where neurological symptoms typically precede and dominate over myopathic features due to the brain's extreme OXPHOS dependence.

5. Consequences of Cerebral Energy Deficit

The present model posits that chronic TNF-α elevation, regardless of its source, leads to persistent mitochondrial dysfunction and cerebral energy deficiency. As established in Section 4.3, the brain's near-exclusive dependence on oxidative phosphorylation renders it uniquely vulnerable to this energy deficit, which manifests in four critical domains that explain core autism symptoms and associated features.

5.1. Impaired Synaptic Pruning

The Energy Cost of Synaptic Pruning: The developing brain undergoes massive synaptic pruning, eliminating approximately 50% of synapses from infancy to adolescence. This process is extraordinarily energy-intensive because:

- Microglia actively phagocytose synapses, requiring substantial ATP
- The infant brain consumes **40% of total body energy** [32]—far exceeding adult proportions
- Complement cascade activation and autophagy pathways require ATP

Evidence of Pruning Deficits in Autism: Postmortem studies reveal striking differences in synaptic density between autistic and neurotypical brains:

Table 6. Synaptic Pruning in Neurotypical vs Autistic Brains.

Parameter	Neurotypical	Autism
Synaptic density reduction (childhood→adolescence)	~50%	**~16%**
Dendritic spine density	Normal	**Elevated**
mTOR pathway activity	Normal	**Hyperactive**
Autophagy function	Normal	**Impaired**

Source: Tang et al. [35], Neuron (Columbia University study).

Consequences of Excess Synapses: The failure to prune synapses results in:

- **Local over-connectivity:** Excess short-range connections creating "neural noise"
- **Long-distance under-connectivity:** Insufficient resources for developing major "highway" connections between brain regions
- **Reduced signal-to-noise ratio:** Difficulty filtering relevant from irrelevant information
- **Sensory overload:** Heightened sensitivity due to failure to attenuate sensory inputs

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5.2. Impaired Social Cognition and Gaze Avoidance

The Energy Demands of Social Processing: Social cognition—including face recognition, gaze processing, and emotion interpretation—is among the most computationally and energetically demanding brain functions. It requires simultaneous activation of:

- Fusiform Face Area (FFA): Face identity processing
- Superior Temporal Sulcus (STS): Gaze direction and biological motion
- Amygdala: Emotional salience and threat detection
- Prefrontal Cortex: Social context integration and decision-making

Eye Contact as Energy Conservation: This framework suggests that gaze avoidance in autism may represent an adaptive energy conservation strategy. Several lines of evidence are consistent with this interpretation:

Table 7. Self-Reported Experiences of Eye Contact in Autism.

Experience Category	Representative Quote
Energy Exertion	*"Eye contact feels like I'm using up a lot of energy. Maximum 2-6 seconds."*
Audiovisual Integration Failure	*"I cannot listen to someone while making eye contact at the same time."*
Cognitive Trade-off	*"When I focus on eye contact, I can't process what's being said."*
Recovery Requirement	*"The longer I maintain eye contact, the more recovery time I need afterward."*

Source: Trevisan et al. [36], PLOS ONE - Qualitative analysis of first-hand accounts.

Neural Evidence: Functional neuroimaging studies demonstrate that in autism, eye contact triggers amygdala hyperactivation, suggesting heightened metabolic demand [37]. Gaze avoidance may thus function to reduce this hyperarousal and conserve limited neural energy for other cognitive tasks.

5.3. Epilepsy Comorbidity as Supporting Evidence

The high comorbidity between autism and epilepsy provides additional support for the TNF-α-mediated energy deficit hypothesis. Approximately 20-30% of autistic individuals experience epileptic seizures, compared to 1-2% in the general population. In autism with intellectual disability, prevalence rises to approximately 40% [38].

TNF-α and Seizure Susceptibility: TNF-α directly increases neuronal excitability through multiple mechanisms:

- TNF-α has been reported to increase AMPA receptor surface expression, enhancing excitatory transmission
- TNF-α may promote GABA receptor internalization, reducing inhibitory tone
- The resulting excitation/inhibition imbalance may lower seizure threshold

Energy Deficit and Seizure Vulnerability: Mitochondrial dysfunction further predisposes to seizures through:

- Impaired Na+/K+-ATPase function due to ATP deficit, destabilizing membrane potential
- Compromised GABAergic inhibition, which is highly energy-dependent
- Notably, primary mitochondrial diseases (e.g., MELAS, Leigh syndrome) frequently present with epilepsy

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The autism-epilepsy comorbidity thus reflects converging consequences of TNF-α-mediated neuroinflammation and mitochondrial energy deficit: neuroinflammation increases excitability while energy deficit impairs the inhibitory circuits required to prevent seizures.

5.4. Impaired Protein Synthesis: The Critical Energy Bottleneck

Protein synthesis is the most energy-intensive cellular process, consuming approximately 25-30% of total cellular ATP [39]. Each amino acid incorporation requires ~4 ATP equivalents, making the synthesis of large synaptic proteins extraordinarily energy-demanding. During neurodevelopment, when neurons must produce vast quantities of synaptic proteins, any ATP deficit creates a critical bottleneck.

5.4.1. Mitochondrial Protein Synthesis as Rate-Limiting Step

The electron transport chain requires both nuclear- and mitochondrial-genome-encoded subunits. Critically, mitochondrial protein synthesis by the 55S ribosome is the rate-limiting step in ETC synthesis [40]. Of the 230 genes in the Mitochondrial Central Dogma, 59 are associated with neurodevelopmental delay, representing a 2-fold enrichment ($p < 8.95E-9$) [40]. This age of onset coincides with the brain's peak glutamatergic synapse density, emphasizing the developmental linkage between energy consumption and brain maturation.

Table 8. Critical Synaptic Proteins Vulnerable to Energy Deficit.

Protein	Function	ASD Association	Energy Cost
SHANK3	Synaptic scaffold	0.5-2% of ASD cases	Large (1,731 aa)
NRXN/NLGN	Synaptic adhesion	Multiple variants	Transmembrane
PSD-95	Postsynaptic density	Altered in ASD	Scaffold assembly
BDNF	Neuron survival	Reduced in ASD	Activity-dependent
FMRP	mRNA regulation	Fragile X syndrome	Translation control

Note: aa = amino acids. All listed proteins are critical for synaptic formation and function.

5.4.2. The SHANK3-Mitochondria Connection

Phelan-McDermid syndrome, caused by SHANK3 deletion, may illustrate the intimate connection between synaptic proteins and mitochondrial function. The 22q13.3 region containing SHANK3 also harbors several mitochondrial genes, including SCO2 (cytochrome c oxidase assembly), NDUFA6 (Complex I), TYMP, TRMU (mtDNA maintenance), CPT1B (fatty acid metabolism), and ACO2 (TCA cycle). Deletions affecting SHANK3 may therefore simultaneously disrupt mitochondrial function, potentially creating a dual vulnerability.

6. Integrated Pathophysiological Model

Figure 1 presents the unified model linking parental immune dysregulation—via both external (maternal systemic inflammation) and internal (mitonuclear immune conflict) pathways—to offspring autism through decidual immune circuit disruption, placental amplification, fetal brain mitochondrial dysfunction, cerebral energy crisis, and two convergent neurodevelopmental pathways leading to ASD phenotypes.

Figure 2 provides a detailed view of the decidual-placental transmission pathway proposed in Section 3.5, illustrating how subclinical decidual immune dysregulation may relay inflammatory signals to the developing fetal brain during a vulnerable gestational window.

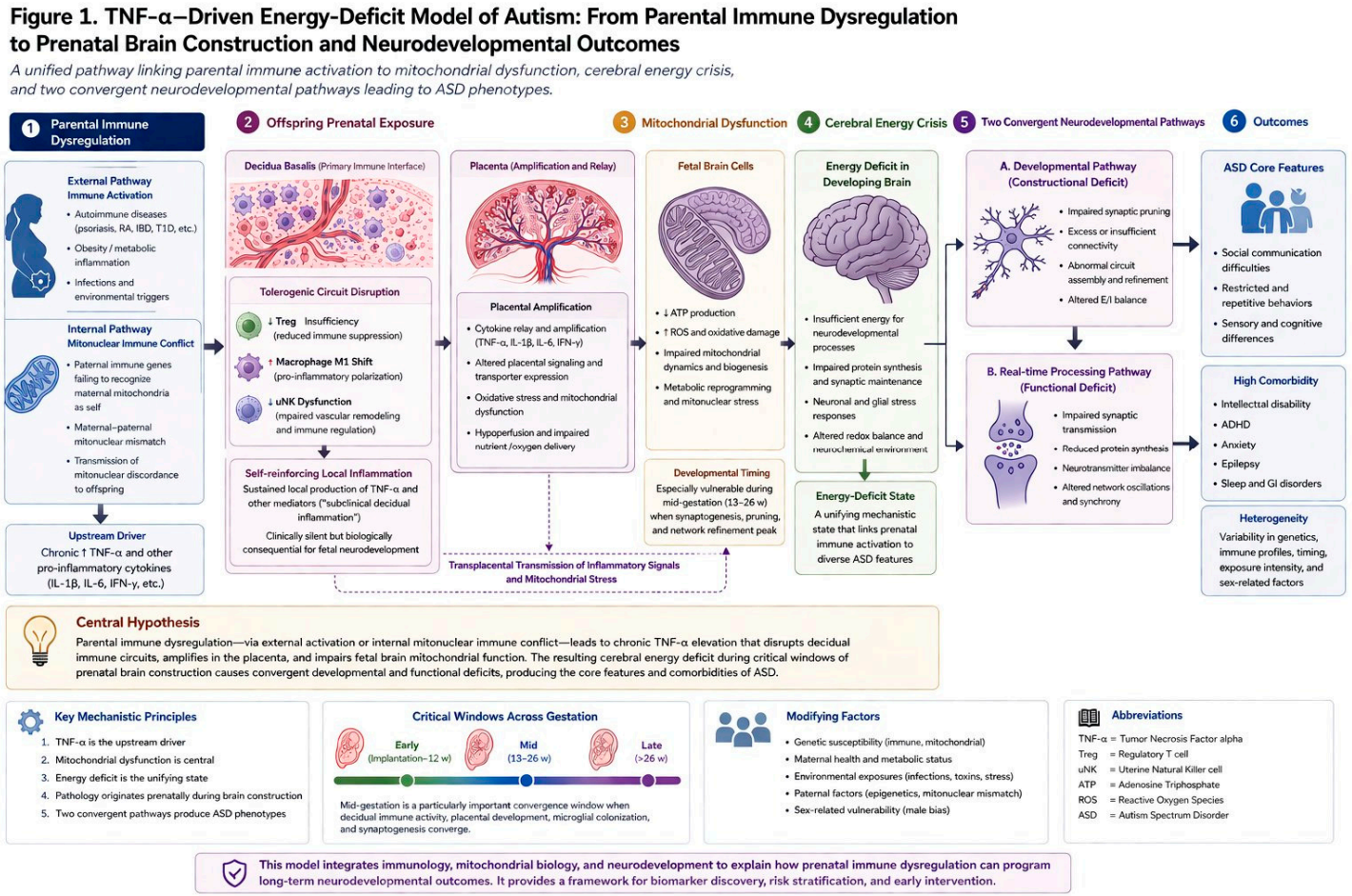

Figure 1. TNF-*α*–Driven Mitochondrial Dysfunction and Cerebral Energy Crisis Pathway Leading to ASD. Integration of external and internal pathways from parental immune dysregulation to core neurodevelopmental and cognitive phenotypes. The model illustrates five stages: (1) parental origin via external (maternal systemic inflammation) and internal (mitonuclear immune conflict) pathways, (2) prenatal transmission through decidual immune dysregulation and placental amplification, (3) fetal exposure and bioenergetic impact including mitochondrial dysfunction and cerebral energy crisis, (4) two convergent neurodevelopmental consequences—impaired developmental pathway (construction deficit) and impaired real-time processing pathway (performance deficit), and (5) resulting ASD phenotypes and frequent comorbidities.

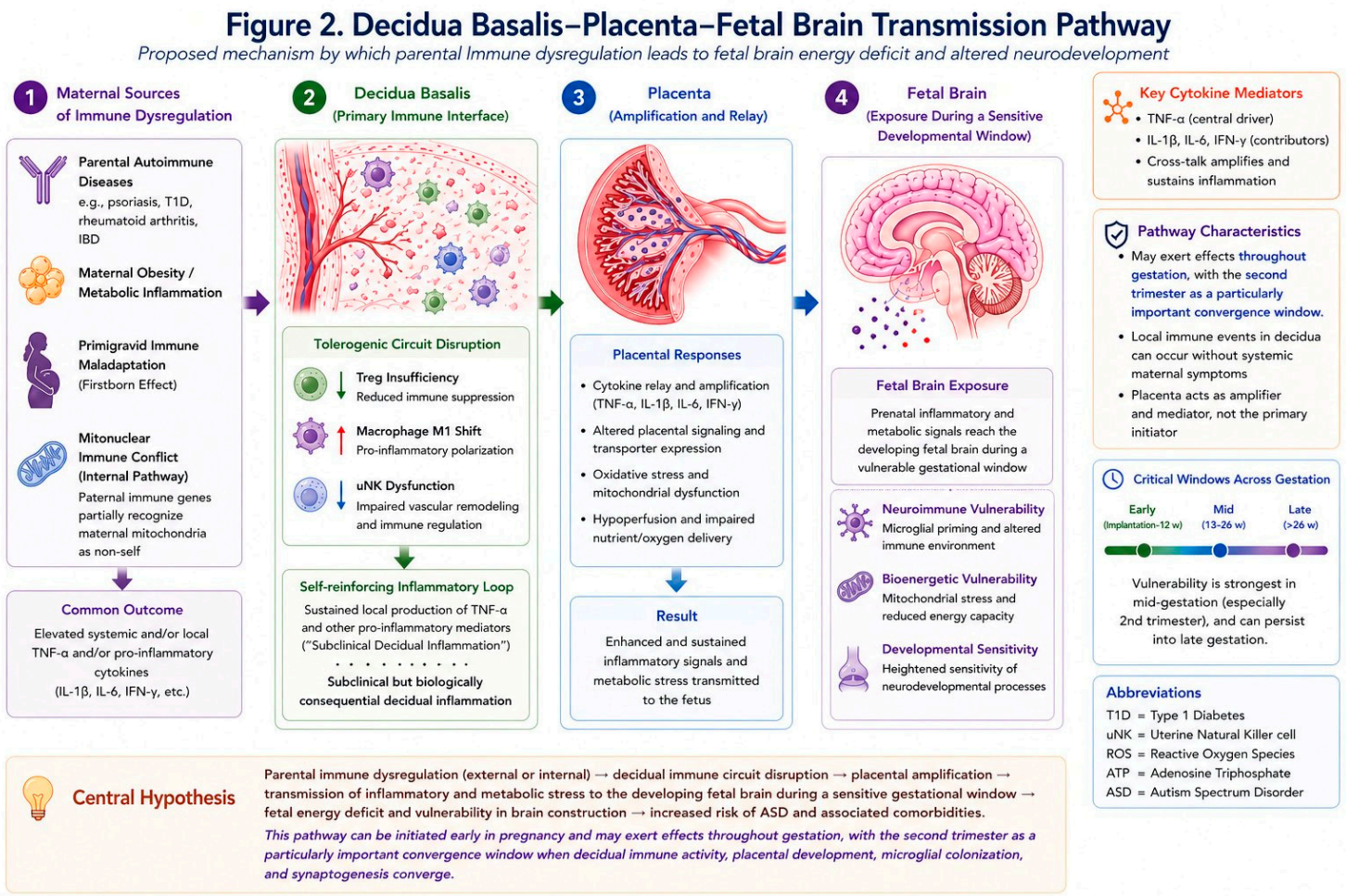

Figure 2. Decidua Basalis–Placenta–Fetal Brain Transmission Pathway. Proposed mechanism by which parental immune dysregulation leads to fetal brain exposure during a sensitive developmental window. The pathway illustrates four stages: (1) maternal sources of immune dysregulation via external and internal pathways, (2) tolerogenic circuit disruption at the decidua basalis generating subclinical but biologically consequential local inflammation, (3) placental amplification and relay of inflammatory signals, and (4) fetal brain exposure including neuroimmune vulnerability, bioenergetic vulnerability, and developmental sensitivity. Effects may occur throughout gestation, with the second trimester as a particularly important convergence window.

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7. Exploratory Prediction: Normal-Tension Glaucoma and Autism

Normal-tension glaucoma (NTG) offers a potentially useful test case for the present hypothesis. Emerging evidence implicates TNF-α in NTG pathogenesis, yet NTG has never been examined in the context of offspring neurodevelopment—the present framework predicts that parental NTG should be associated with elevated autism risk if the TNF-α pathway is indeed central. NTG affects retinal ganglion cells (RGCs) and shares overlapping inflammatory and neurodegenerative features with the autoimmune conditions linked to autism risk.

7.1. NTG as a TNF-α-Mediated Condition

Evidence supporting TNF-α involvement in NTG:

- Elevated TNF-α levels have been reported in aqueous humor and serum of NTG patients [8]
- TNF-α directly induces RGC apoptosis via TNF-R1 signaling [8]
- Anti-TNF interventions have shown protective effects in some animal models [8]
- Disease progression occurs despite normal intraocular pressure, suggesting the involvement of IOP-independent neurodegenerative mechanisms

7.2. The Untested Association

If the TNF-α energy deficit hypothesis is correct, children of parents with NTG may show elevated autism prevalence compared to the general population.

To my knowledge, no published study has examined the association between parental NTG and offspring autism. This remains an untested question that may be worth investigating.

Table 9. TNF-α-Mediated Conditions and Autism Association Studies.

Parental Condition	TNF-α Role	Autism Association Studied?
Psoriasis	Substantial	Yes (OR 1.59)
Type 1 Diabetes	Central	Yes (OR 1.49-2.36)
Rheumatoid Arthritis	Central	Yes (OR 1.51)
Normal-Tension Glaucoma	Central	*No studies identified*

Note: The absence of studies on parental NTG and offspring autism represents a critical research gap and a testable prediction of the present hypothesis.

8. Therapeutic Implications

The energy-deficit hypothesis suggests several therapeutic approaches:

8.1. Anti-TNF-α Interventions

Existing anti-TNF biologics (etanercept, infliximab, golimumab, adalimumab) have proven efficacy in TNF-α-mediated diseases. In type 1 diabetes, golimumab preserved β-cell function in a phase 2 trial [7]. These observations raise the possibility that TNF-α-targeted strategies could eventually be evaluated for risk modification in carefully defined high-risk pregnancies, although substantial safety, ethical, and regulatory issues would first need to be resolved.

Preclinical evidence is consistent with this therapeutic rationale. Liu et al. (2023) demonstrated in a preeclampsia mouse model that maternal TNF-α elevation drives ASD-like phenotypes in offspring through fetal NFκB signaling, and that TNF-α neutralization during pregnancy ameliorated these ASD-like behaviors and restored NFκB activation to normal levels [41]. This study provides

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preclinical support for a causal contribution of maternal TNF-α signaling to offspring ASD-like phenotypes and suggests that this pathway may be pharmacologically modifiable. Although Liu et al. examined a preeclampsia model specifically, their findings are consistent with the possibility that diverse prenatal inflammatory exposures converge on a shared TNF-α-dependent pathway that perturbs fetal neurodevelopment.

In humans, existing pregnancy-exposure studies of anti-TNF biologics are reassuring with respect to developmental safety. The PIANO registry and other cohort studies have not shown increased long-term neurodevelopmental risk among children exposed to anti-TNF therapy in utero [42]. However, these studies were designed to assess safety rather than ASD-specific outcomes, and none has demonstrated a reduction in autism risk. An especially informative future test of the present hypothesis would be a well-powered, disease-severity-adjusted registry analysis comparing ASD rates in offspring of biologic-treated versus untreated pregnancies in women with TNF-α-mediated disorders.

8.2. Early Identification

If validated, parental TNF-α-mediated disorders (psoriasis, T1D, RA, NTG) could serve as clinically accessible markers of pregnancies at elevated autism risk, potentially enabling earlier surveillance and stratified intervention.

9. Limitations and Future Directions

Limitations: This paper synthesizes existing evidence into a theoretical framework and does not present new experimental data. Several specific limitations should be acknowledged. First, the epidemiological associations between parental autoimmune diseases and offspring autism risk are based on observational studies and may be subject to confounding by shared genetic factors; sibling comparison designs that could better control for familial confounding have not been applied to most of the specific associations cited here. Second, while TNF-α elevation is consistently observed in autistic individuals, the causal direction of this association remains unestablished. Third, the effect sizes for parental autoimmune disease–autism associations (OR 1.28–2.36) are moderate and are compatible with a TNF-α-mediated mechanism but do not exclude the contribution of parallel or partially overlapping pathways. Fourth, the mitonuclear immune conflict hypothesis (Section 3.4) remains speculative, and while preliminary evidence from Zhang et al. [20] is consistent with this mechanism, larger studies with parental autoimmune stratification are needed. Fifth, although anti-TNF exposure during pregnancy would represent a natural human quasi-intervention relevant to the TNF-α hypothesis, current clinical data primarily address safety outcomes and composite neurodevelopmental endpoints rather than ASD-specific risk reduction; thus, the present hypothesis is not yet supported by direct human interventional evidence. Sixth, the present hypothesis prioritizes TNF-α as the principal integrative upstream driver; however, cytokine networks are bidirectional and highly interactive. For example, IL-6/JAK-STAT signaling may amplify TNF-α production in some contexts, whereas TNF-α can reciprocally induce IL-6. The contribution of parallel cytokine pathways, including IL-6—which has been shown to disrupt protein translation and radial glia development in human brain organoid models of maternal immune activation [43]—therefore warrants further investigation. Seventh, the decidual-placental transmission pathway proposed in Section 3.5 remains a hypothesis built on indirect evidence; direct human studies linking decidual immune parameters specifically to offspring ASD outcomes are extremely limited, and the distinction between decidual-level and systemic-level immune contributions to fetal neurodevelopmental risk has not yet been empirically resolved.

Future Directions: Key studies needed include: (1) Epidemiological investigation of parental NTG and offspring autism risk; (2) Longitudinal studies of mitochondrial function in infants at high autism risk; (3) Clinical trials of mitochondrial support interventions; (4) Mechanistic studies of TNF-α effects on synaptic pruning in animal models; (5) Disease-severity-adjusted registry analyses comparing ASD rates in offspring of anti-TNF-treated versus untreated pregnancies in women with

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TNF-α-mediated disorders, which would provide an informative test of the proposed causal pathway; (6) Targeted investigation of decidual immune parameters—including macrophage polarization state, Treg density, and local cytokine concentrations—in pregnancies followed prospectively for offspring neurodevelopmental outcomes. Accordingly, the present model should be interpreted as a convergent, hypothesis-generating framework rather than a definitive causal account of ASD.

10. Conclusion

I propose that autism spectrum disorder may be understood as an immune-metabolic disorder characterized by TNF-α-mediated mitochondrial dysfunction leading to cerebral energy deficiency. This energy deficit may impair synaptic pruning during development and compromise real-time social cognitive processing, potentially explaining core autism symptoms from a unified mechanistic perspective.

The hypothesis generates a novel, testable prediction: that parents with normal-tension glaucoma—a neurodegenerative condition in which TNF-α-related signaling has been implicated, not previously linked to offspring autism—will show elevated prevalence of autistic children. Confirmation of this prediction would be consistent with the broader hypothesis.

This hypothesis therefore locates the origin of pathology not primarily in postnatal dysfunction, but in disrupted prenatal brain construction. In the subgroup of cases addressed here, aberrant immune signaling during pregnancy may impair the formation of neural circuits before birth, such that vulnerability is built into early brain development itself.

If validated, this framework carries a fundamental implication: autism, in the subgroup of cases addressed here, is a condition of prenatal origin. The neural circuit abnormalities that underlie autistic traits—excess synaptic density, altered connectivity, and compromised real-time social processing—are not acquired postnatally but are established during fetal brain development through in utero inflammatory and metabolic insult. This reframing suggests that the most effective window for risk modification is not after diagnosis in early childhood, but during pregnancy itself—through identification of high-risk pregnancies based on parental immune profiles and, if future research supports it, through targeted anti-inflammatory or mitochondrial support interventions during the prenatal period.

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