Hypothesis

The Energy-Deficit Hypothesis of Autism: Linking Parental Autoimmune Diseases to Offspring Autism Risk via TNF-α-Mediated Mitochondrial Dysfunction, Impaired Protein Synthesis, and Maternal Immune Maladaptation

Byul Kang *

Posted Date: 7 January 2026

doi: 10.20944/preprints202512.2808.v2

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

 doi:10.20944/preprints202512.2808.v2

Hypothesis

The Energy-Deficit Hypothesis of Autism: Linking Parental Autoimmune Diseases to Offspring Autism Risk via TNF-α-Mediated Mitochondrial Dysfunction, Impaired Protein Synthesis, and Maternal Immune Maladaptation

Byul Kang

Independent Researcher, Republic of Korea; halococoa@gmail.com

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 is fundamentally an immune-metabolic disorder characterized by TNF-α-mediated mitochondrial dysfunction leading to cerebral energy deficiency. This energy deficit impairs 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 primary mechanism involves TNF-α pathway dysregulation—through genetic inheritance from parents with autoimmune diseases such as psoriasis, type 1 diabetes, and rheumatoid arthritis, and/or through 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, I propose a speculative secondary mechanism: mitonuclear immune conflict, where paternal immune genes may partially recognize maternal mitochondria as non-self, generating endogenous TNF-α. Implications: This hypothesis unifies disparate observations about autism pathophysiology and suggests that anti-inflammatory interventions targeting the TNF-α pathway may have therapeutic potential, particularly when administered early in neurodevelopment.

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

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.

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.

 doi:10.20944/preprints202512.2808.v2

In this hypothesis paper, I propose that autism is fundamentally an immune-metabolic disorder characterized by TNF-α-mediated mitochondrial dysfunction. I argue that the resulting cerebral energy deficiency impairs two critical processes: synaptic pruning during neurodevelopment and real-time social cognitive processing. This framework explains core autism symptoms from a unified energetic perspective and generates testable predictions.

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
Type 1 Diabetes (T1D)	1.49-2.36	1.21-4.12	JAMA 2018, IJE 2023
Rheumatoid Arthritis	1.51	1.14-2.00	Keil et al. 2010
Hypothyroidism	1.64	1.16-2.32	Atladóttir et al. 2009
Any Autoimmune Disease	**1.28-1.50**	1.11-1.75	Wu et al. 2015 Meta

Note: All listed conditions are TNF-α-mediated autoimmune/inflammatory disorders. CI = Confidence Interval.

2.2. The TNF-α Common Denominator

A critical observation is that all parental diseases strongly associated with offspring autism risk share a common pathogenic mechanism: dysregulation of TNF-α signaling. TNF-α is a master pro-inflammatory cytokine that plays central roles in:

- **Psoriasis:** TNF-α drives keratinocyte proliferation and inflammatory cascade; anti-TNF biologics are first-line therapy
- **Type 1 Diabetes:** TNF-α directly induces β-cell apoptosis and promotes autoimmune destruction of pancreatic islets
- **Rheumatoid Arthritis:** TNF-α orchestrates synovial inflammation and joint destruction; anti-TNF therapy revolutionized treatment
- **Normal-Tension Glaucoma:** TNF-α mediates retinal ganglion cell death independent of intraocular pressure elevation

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.

 doi:10.20944/preprints202512.2808.v2

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 36-67% increased risk of offspring autism (OR 1.36-1.67). Importantly, the risk increases in a dose-dependent manner with maternal BMI, suggesting a biological gradient rather than confounding.

3.2.2. Obesity as a Chronic Inflammatory State

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

- Adipose tissue is a major source of TNF-α production
- Circulating TNF-α levels are 2-3 fold higher in obese individuals
- Other inflammatory markers (IL-6, CRP, leptin) are also elevated
- Inflammation correlates with degree of adiposity

3.2.3. Mechanism of Fetal Exposure

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

- **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—remain the same. This convergence explains why maternal obesity and parental autoimmune conditions show similar effect sizes for autism risk and may have additive effects when co-occurring.

3.3. The Birth Order Effect: Maternal Immune Maladaptation

 doi:10.20944/preprints202512.2808.v2

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 5. Birth Order and Autism Risk: Evidence Summary.

Finding	Effect Size	Reference
Firstborn autism risk (Utah)	OR 1.8	Bilder et al. 2009
Firstborn autism risk (Sweden, n=1.5M)	~20% higher	Meta-analysis
Short interpregnancy interval (<12 mo)	OR 3.39	Cheslack-Postava 2011
Preeclampsia in nulliparous women	**Significantly higher**	Robillard et al.
Partner change resets preeclampsia risk	**Returns to primigravid**	Dekker et al.

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

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. 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.

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. Prior abortion with the same partner reduces preeclampsia risk by half (OR 0.54), but abortion with a different partner confers no protection. These findings demonstrate that paternal antigen-specific tolerance develops during first pregnancy and provides lasting protection—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

 doi:10.20944/preprints202512.2808.v2

disease? I propose that mitonuclear immune conflict may represent an endogenous source of TNF-α that activates the same pathogenic pathway.

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.
- **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.

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 7. 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

 doi:10.20944/preprints202512.2808.v2

	Pathway 1: External	Pathway 2: Internal
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 explains why:

- 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

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

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

4.1. Direct Effects of TNF-α on Mitochondrial Function

TNF-α exerts profound inhibitory effects on mitochondrial function through multiple mechanisms. Table 2 summarizes the key pathways by which TNF-α impairs cellular energy production.

Table 2. 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

 doi:10.20944/preprints202512.2808.v2

PDH Suppression	Inhibits pyruvate dehydrogenase, blocking glucose entry into TCA cycle
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:

- 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

5. Consequences of Cerebral Energy Deficit

I propose that chronic TNF-α elevation, regardless of its source, leads to persistent mitochondrial dysfunction and cerebral energy deficiency. This energy deficit 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—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 3. 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

 doi:10.20944/preprints202512.2808.v2

Autophagy function	Normal	Impaired

Source: Tang et al. 2014, 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

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: I propose that gaze avoidance in autism represents an ***adaptive energy conservation strategy***. Direct evidence supports this interpretation:

Table 4. 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. 2017, 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. Gaze avoidance thus serves 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 40%.

 doi:10.20944/preprints202512.2808.v2

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

- Increases AMPA receptor surface expression, enhancing excitatory transmission
- Promotes GABA receptor internalization, reducing inhibitory tone
- Creates excitation/inhibition imbalance that lowers 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

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. 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. Of the 230 genes in the Mitochondrial Central Dogma, 59 are associated with neurodevelopmental delay, representing a 2-fold enrichment ($p < 8.95E-9$). This age of onset coincides with the brain's peak glutamatergic synapse density, emphasizing the developmental linkage between energy consumption and brain maturation.

Table 6. 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

 doi:10.20944/preprints202512.2808.v2

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

6. Integrated Pathophysiological Model

Figure 1 presents the unified model linking parental TNF-α-mediated diseases to offspring autism through mitochondrial dysfunction and energy deficiency.

PARENTAL GENETIC PREDISPOSITION

TNF-α Pathway Dysregulation Genes

↓

PARENTAL DISEASE MANIFESTATIONS

Psoriasis | Type 1 Diabetes | Rheumatoid Arthritis | Normal-Tension Glaucoma

↓

OFFSPRING EXPOSURE

Genetic inheritance of TNF-α susceptibility

+

In utero exposure to maternal TNF-α elevation

↓

MITOCHONDRIAL DYSFUNCTION

ETC Inhibition → ATP Production ↓↓ → ROS Production ↑↑

↓

CEREBRAL ENERGY CRISIS

↓ ↓

 doi:10.20944/preprints202512.2808.v2

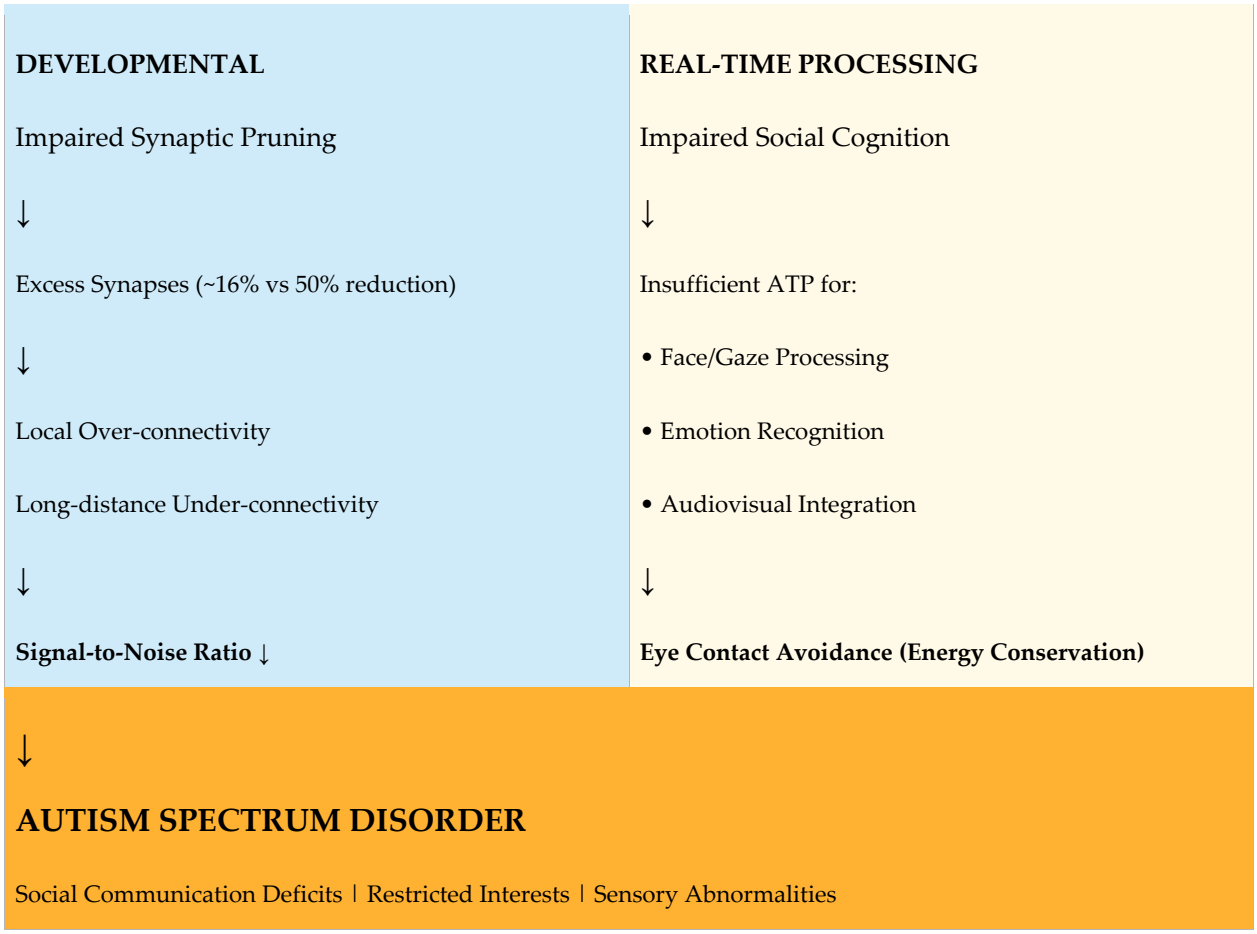

Figure 1. Integrated Pathophysiological Model of Autism as an Immune-Metabolic Disorder.

Figure 1 Legend: *The model illustrates how parental TNF-α pathway dysregulation leads to offspring autism through two converging pathways: developmental (impaired synaptic pruning) and real-time (impaired social cognition). Both pathways result from ATP deficiency secondary to mitochondrial dysfunction. ETC = Electron Transport Chain; ROS = Reactive Oxygen Species.*

7. Novel Prediction: Normal-Tension Glaucoma and Autism

A critical test of this hypothesis involves normal-tension glaucoma (NTG). NTG is a neurodegenerative condition affecting retinal ganglion cells (RGCs) that shares key pathophysiological features with both the TNF-α-mediated autoimmune diseases associated with autism and with autism itself.

7.1. NTG as a TNF-α-Mediated Condition

Evidence supporting TNF-α involvement in NTG:

- Elevated TNF-α levels in aqueous humor and serum of NTG patients
- TNF-α directly induces RGC apoptosis via TNF-R1 signaling
- Anti-TNF therapy shows protective effects in animal models
- NTG frequently co-occurs with systemic inflammatory conditions (e.g., psoriasis)
- Disease progression occurs despite normal intraocular pressure, implicating IOP-independent 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.

 doi:10.20944/preprints202512.2808.v2

To my knowledge, *no published study has examined the association between parental NTG and offspring autism*. This represents a critical gap in the literature that warrants investigation.

Table 7. TNF-α-Mediated Conditions and Autism Association Studies.

Parental Condition	TNF-α Role	Autism Association Studied?
Psoriasis	Central	**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 EXIST**

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 (NEJM 2020). Similar approaches might be considered for autism prevention in high-risk pregnancies, though significant safety and ethical considerations would need to be addressed.

8.2. Mitochondrial Support

Interventions supporting mitochondrial function may provide benefit:

- **Coenzyme Q10:** Essential electron carrier in ETC
- **L-Carnitine:** Facilitates fatty acid transport into mitochondria
- **NAD+ Precursors (NR, NMN):** Support ETC function and cellular energy production
- **B Vitamins:** Cofactors for mitochondrial enzymes

8.3. Early Identification

Screening for parental TNF-α-mediated diseases (psoriasis, T1D, RA, NTG) could identify pregnancies at elevated autism risk, enabling earlier monitoring and potentially earlier intervention.

9. Limitations and Future Directions

Limitations: This hypothesis paper synthesizes existing evidence but does not present new experimental data. The proposed mechanisms, while supported by converging lines of evidence, require direct experimental validation.

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.

 doi:10.20944/preprints202512.2808.v2

10. Conclusion

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

The hypothesis generates a novel, testable prediction: that parents with normal-tension glaucoma—a TNF-α-mediated neurodegenerative condition not previously linked to offspring autism—will show elevated prevalence of autistic children. Confirmation of this prediction would provide strong support for the broader hypothesis.

If validated, this framework has important implications for autism prevention and treatment, suggesting that anti-inflammatory and mitochondrial support interventions may have therapeutic potential, particularly when administered early in neurodevelopment.

References

1. Wu S, Ding Y, Wu F, et al. Family history of autoimmune diseases is associated with an increased risk of autism in children: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2015;55:322-332.
2. Xiang AH, Wang X, Martinez MP, et al. Maternal Type 1 Diabetes and Risk of Autism in Offspring. JAMA. 2018;320(1):89-91.
3. Persson M, et al. Maternal type 1 diabetes, pre-term birth and risk of autism spectrum disorder. Int J Epidemiol. 2023;52(2):377-386.
4. Keil A, Daniels JL, Forssen U, et al. Parental autoimmune diseases associated with autism spectrum disorders in offspring. Epidemiology. 2010;21(6):805-808.
5. Atladóttir HO, Pedersen MG, Thorsen P, et al. Association of family history of autoimmune diseases and autism spectrum disorders. Pediatrics. 2009;124(2):687-694.
6. Tang G, Gudsnuk K, Kuo SH, et al. Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits. Neuron. 2014;83(5):1131-1143.
7. Trevisan DA, Roberts N, Lin C, Birmingham E. How do adults and teens with self-declared Autism Spectrum Disorder experience eye contact? PLOS ONE. 2017;12(11):e0188446.
8. Dalton KM, Nacewicz BM, Johnstone T, et al. Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci. 2005;8(4):519-526.
9. Morris G, Berk M. The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. BMC Med. 2015;13:68.
10. Quattrin T, Haller MJ, Steck AK, et al. Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes. N Engl J Med. 2020;383(21):2007-2017.
11. Chen Y, et al. The role of the immune system in autism spectrum disorder. Neuropsychopharmacology. 2017;42(1):284-298.
12. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012;17(3):290-314.
13. Nakazawa T, et al. Tumor necrosis factor-alpha mediates oligodendrocyte death and delayed retinal ganglion cell loss in a mouse model of glaucoma. J Neurosci. 2006;26(49):12633-12641.
14. Deng W, et al. Rapid mitochondrial dysfunction mediates TNF-alpha-induced neurotoxicity. J Neurochem. 2015;132(4):443-451.
15. Ashwood P, et al. Immunological cytokine profiling identifies TNF-α as a key molecule dysregulated in autistic children. Mol Psychiatry. 2017;22(6):809-816.