Amyloid Beta and the Immune System: Repurposing Neurodegenerative Pathways for Cancer Immunotherapy

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ABSTRACT

Amyloid beta (Aβ), which was previously recognized predominantly for its neurotoxic properties in Alzheimer's disease, is now being acknowledged for its unforeseen potential to inhibit oncogenic proliferation. Recent research indicates that Aβ can enhance tumor antigen presentation and invigorate the activity of innate immune cells. This observation aligns with the established inverse relationship between neurodegeneration and cancer, which modifies the tumor microenvironment in an anti-cancer manner. Antitumor immunity is amplified through Aβ-induced microglial activation and cytokine production, which emulates the modulation of immunological checkpoints. These findings contribute to the development of innovative immunotherapeutic strategies that modulate neuroinflammatory signals and peptides derived from Aβ. Researchers are integrating the fields of oncology and neurology to precisely target cancer treatment by harnessing Aβ's immune-enhancing attributes while ensuring neuroprotection. This presents novel avenues for repurposing neurodegenerative pathways in the pursuit of precision cancer therapy.

Keywords: Amyloid beta, Neuroinflammation, Antitumor immunity, Tumor microenvironment, Immunotherapy, Neuroprotection, Microglial Activation, cytokine production, Precision oncology, Peptide modulation.

INTRODUCTION

The Mystery of Alzheimer's Disease and Cancer.

Numerous epidemiological studies have indicated a negative correlation between the incidence of cancer and neurological illnesses, particularly Alzheimer's disease (AD). Recent studies have shown that adults with AD aged >59 years have a 21-fold lower risk of developing cancer. In contrast to the controls of the same age. This study outlines the translational potential of amyloid beta biology and cancer immunotherapy in aging and disease by examining their cellular, molecular, and clinical interactions. [1]

Amyloid Beta and Its Role Beyond Neurodegeneration:

Central Nervous System (CNS) Regulation of Immune Responses in Cancer

The central nervous system (CNS) organizes immune activity critical to tumor modulation through sophisticated neuro-immune interactions. Neuronal signaling pathways, encompassing the catecholaminergic and cholinergic systems, profoundly influence the activation and migration of cytotoxic T cells and macrophages within

neoplasms and lymphoid organs. For example, catecholamines released by neurons in the ventrolateral medulla carefully control CD8+ T cell activation, thereby impacting tumor progression and exemplifying the direct regulation of antitumor immunity by the nervous system [2]. Furthermore, tumors can mimic CNS-derived immune evasion mechanisms by expressing nervous system-specific enzymes, such as N-acetyltransferase 8-like (NAT8L), and metabolites, such as N-acetyl aspartate, which diminish immune cell cytotoxicity and disrupt immunological synapses, thereby facilitating immune escape [3].

Structure and Pathological Functions in the CNS

Amyloid beta (Aβ) is formed by sequential β- and γ-secretase cleavage of the amyloid precursor protein (APP). In Alzheimer's disease, excessive Aβ accumulates extracellularly, forming toxic oligomers and plaques that disrupt synaptic communication and promote oxidative stress. APP processing and Aβ accumulation impairs mitochondrial homeostasis and mitophagy. Aβ blocks the PINK1/Parkin pathway and lysosomal degradation, inhibiting damaged mitochondria elimination. Persistent defective mitochondria generate excess reactive oxygen species (ROS). ROS damage neuronal components, intensifying cellular toxicity and dysfunction. Aβ also alters mitochondrial membrane permeability and calcium levels. This drives energy deficits, synaptic failure, and apoptotic cascades, ultimately leading to neurodegeneration and cognitive decline in AD [4].

Inverse Association with Cancer

Contrary to its neurotoxic role in the CNS, amyloid beta (Aβ) has protective functions in peripheral tissues. Recent evidence has shown that Aβ can act as an immunostimulatory peptide, activating innate immune responses. It enhances macrophages and dendritic cell activities, improving antigen presentation and cytokine release. Aβ also modulates the tumor microenvironment, promoting an antitumor inflammatory state [1]. Studies have shown that Aβ-derived fragments may mimic immune checkpoint modulation mechanisms. These effects contribute to tumor clearance through enhanced T-cell activation and cytotoxicity. Amyloid precursor protein (APP) expression in immune cells further supports coordinated immune responses [2]. This highlights the remarkable duality of Aβ as both a neurotoxin and an immune regulator. Ongoing research is exploring how neuroinflammatory cues can strengthen cancer immunity, and Aβ and APP are emerging as potential mediators and targets in antitumor immunotherapy [1].

Shared Mechanisms Between Neurodegeneration and Cancer

There exists a mechanistic convergence centered on immune dysregulation and inflammation. Both neurodegenerative diseases and tumors feature chronic activation of innate immune pathways, such as NF-κB signaling and NLRP3 inflammasome activation. In neurodegeneration, persistent microglial activation leads to neurotoxicity, whereas in tumors, similar pathways promote tumor survival, angiogenesis, and immunosuppression. The polarization of macrophages and microglia toward immunosuppressive or pro-inflammatory phenotypes further exemplifies this shared biology. Therapeutically, targeting inflammasomes, NF-κB, and immune checkpoint pathways can potentially tackle both neurodegeneration and cancer by modulating immune cell function and inflammation [5].

Neurotransmitter Modulation as an Immunotherapeutic Approach

Neurotransmitters and neuropeptides play a crucial role in modulating immune cells within the tumor microenvironment (TME). For example, adrenergic signaling through β-adrenergic receptors affects the retention and exit of T cells from lymph nodes, thereby influencing systemic antitumor immunity. Meanwhile, cholinergic signaling regulates the function of immunosuppressive T cells and macrophages [2]. Medications originally designed to target neurological pathways, such as adrenergic receptor blockers, are now being explored for their potential to boost the effectiveness of immune checkpoint therapy and change the immunosuppressive nature of the TME [6].

Molecular and Metabolic Crosstalk

Neurodegenerative pathways play a pivotal role in reshaping immune metabolism, which is essential for efficient cancer immunosurveillance. Proteins involved in neurodegeneration, such as amyloid precursor protein (APP)

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and amyloid beta aggregates, have emerged as regulators of T cell mitochondrial function and metabolism. Unlike their harmful role in neurons, these proteins in immune cells can inhibit mitophagy and preserve mitochondrial fitness, thereby vitalizing T cells for sustained antitumor activity [7]. This unexpected reprogramming has led to novel strategies, including mitochondrial transplantation and metabolic supplementation, which in turn bring back immune cells against cancer [6].

Therapeutic Implications and Integration

Therapeutic strategies exploiting neuro-immune crosstalk include

- The combination of neurotransmitter modulators with immune checkpoint inhibitors can improve tumor-infiltrating lymphocyte function while reducing adverse effects [1].
- Targeting neuro-immune pathways sensitizes tumors, such as glioblastoma and pancreatic cancer, to chemotherapy and radiotherapy, enhancing treatment responses [1].
- Nanotechnology facilitates the targeted delivery of neuro-regulatory agents across physiological barriers, optimizing therapeutic outcomes and minimizing systemic toxicity [1].

These neuroimmune interactions regulate immune cell activity within the tumor microenvironment through complicated signaling involving neurotransmitters, neuropeptides, and immune checkpoints. For example, modulation of adrenergic signaling can overcome immunosuppression by promoting CD8+ T cell activity. Chronotherapy approaches, which involve timing treatments with circadian rhythms, further enhance immunotherapy efficiency. This integrated strategy demonstrates the next generation of immunotherapies inspired by neurodegenerative biology, offering promising approaches for precision cancer therapy and improved patient outcomes.

Such multi-target approaches symbolize next-generation immunotherapies derived from neurodegenerative biology research [8].

Mechanistic Insights: The Mitochondrial Connection

Mitochondrial Dysfunction in AD and Cancer

Mitochondrial health is a pivotal regulator of cellular fate in both the nervous system and cancer biology. In neurodegenerative disorders, impaired mitochondrial quality control compromises the energy homeostasis. A key example is amyloid-beta (Aβ), which disrupts mitophagy in the neurons. This blockade results in the accumulation of damaged mitochondria and progressive energy failure. Energetic crises accelerate synaptic loss and cognitive decline [4]. Prominently, mitophagy inhibition does not always yield negative outcomes; in certain immune contexts, particularly within tumor-infiltrating T-cells, reduced mitophagy can be advantageous. By limiting mitochondrial yield, these cells retain a high mitochondrial mass. This supports sustained glycolysis and oxidative phosphorylation during stress. Ultimately, such metabolic potency enhances antitumor activity [7].

APP, TOMM Complex, and Ceramide Synthase

Recent research has indicated that amyloid precursor protein (APP) binds to the translocase of the outer mitochondrial membrane (TOMM) complex, a key gateway for protein import into the mitochondria. This interaction blocks the mitochondrial trafficking of ceramide synthase (CerS6), an enzyme involved in ceramide production that promotes mitophagy [9]. Consequently, the suppression of ceramide-mediated mitophagy prevents excessive mitochondrial yield, allowing T-cells to maintain mitochondrial integrity and metabolic function during aging [10].

Fumarate: Metabolic Control Point

A decline in intracellular fumarate levels occurs when mitophagy becomes excessive in T cells. This reduction interferes with key metabolic pathways that are dependent on the tricarboxylic acid (TCA) cycle. As fumarate

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levels decrease, ATP generation and anabolic processes are impaired. Energy stress leads to diminished T cell proliferation and effector function [11]. Likewise, amyloid beta (Aβ) metabolically modulates this process. By stabilizing intracellular fumarate levels, Aβ helps sustain the TCA cycle flux. This prevents excessive mitochondrial degradation through overactive mitophagy. Consequently, Aβ indirectly supports mitochondrial retention and T cell metabolic fitness [7].

Immunological Rewiring: Amyloid Beta in T-Cell Rejuvenation

Recent findings from 2024 to 2025 revealed that amyloid beta (Aβ) can metabolically reprogram aged T-cells by enhancing their mitochondrial mass and functional capacity. When mitochondria are isolated from Alzheimer's disease (AD) patients, T-cells are transplanted into senescent T-cells from healthy donors, and these recipient cells regain efficient energy metabolism and renewed tumor-killing potential. This rejuvenation effect is amplified by the supply of fumarate, which stabilizes mitochondrial metabolism and supports sustained bioenergetic recovery [12].

Table 1: Summary of Key Molecular Effects

Pathway/Mechanism	CNS Result (AD)	Immune Result (Cancer)
Aβ inhibits mitophagy	Neuronal damage	T-cell rejuvenation
APP,TOMM,CerS6 axis	Ceramide-driven damage	Mitochondria preserved
Fumarate supplementation	—	T Maintains T-cell activity

Translational Strategies: From Bench to Clinic

Mitochondrial Transplantation

Mitochondrial transfer is emerging as a potent method to boost T-cell and CAR-T therapy by introducing healthy mitochondria into aged or dysfunctional T-cells to restore respiration, ATP production, and balanced energy metabolism, resulting in improved survival, tumor infiltration, and sustained cytotoxicity, as well as delayed exhaustion, extending therapeutic effectiveness, which is being explored to strengthen CAR-T performance, especially against solid tumors [13].

Fumarate Supplementation

In both in vitro studies and mouse models, fumarate supplementation revitalizes aging immune cells by restoring mitochondrial metabolism and the energy balance [14]. This metabolic boost sustains their antitumor activity over time and lays the ground for combining fumarate with other metabolic interventions to enhance immunotherapy outcomes [11].

Clinical Implications and Trials

Repurposing Oncology Drugs for AD

A significant trend in recent research is the two-way repurposing of cancer and Alzheimer's disease (AD) therapies for treating cancer [6].

Several oncology drugs, including Nilotinib, letrozole, and irinotecan, have shown potential neuroprotective effects and are being evaluated for AD treatment, targeting pathways such as autophagy regulation, amyloid processing, and neuroinflammation, and their success in oncology offers a strong pharmacological foundation for rapid clinical translation; conversely, some AD-related metabolic modulators are being tested to suppress tumor growth, and more than 60 repurposed drugs are under active investigation across multiple stages of AD clinical trials[15].

Amyloid-Based Immunotherapy in Oncology

Targeting the amyloid precursor protein (APP) E1 domain, conveniently located on the cell surface, is an innovative approach for direct cancer immunotherapy. This extracellular domain has a dominant role in promoting tumor growth by suppressing immune cell infiltration, particularly by limiting CD8+ T cell and natural killer (NK) cell-mediated anti-tumor responses [16]. It accomplishes this by attenuating type I interferon (IFN) signaling within the tumor microenvironment, thereby diminishing chemokines, that attract effector immune cells to the tumor [3]. Because the E1 domain is accessible on the cell surface, it is an ideal target for antibody- or vaccine-based therapies aimed at enhancing immune infiltration and activation [2]. Experimental vaccines targeting the mutant E1 domain have shown promise in preventing tumor growth by eliciting vigorous immune responses. Combining APP-targeted therapies with existing antibody and cellular immunotherapies could synergistically overcome immune suppression and enhance the efficacy of cancer treatment outcomes [3]. This strategy not only enhances T cell infiltration but may also improves their cytotoxic function, making APP E1 a compelling target for oncologic immunotherapy development. Ongoing research is focused on understanding its vast immunosuppressive roles and optimizing combination therapies [16].

Table 2: Representative Clinical Trials

Innovative Therapeutic Combinations: Mitochondrial Transplantation Combined with Chemotherapy

Disease Target	Intervention	Mechanism	Trial Phase
Alzheimer's	Nilotinib	A Tyrosine kinase inhibition	II/III
Alzheimer's	Irinotecan	Topoisomerase inhibitor	II
Cancer (immunotherapy)	Fumarate	Metabolic modulation	Preclinical
Cancer (T-cell transfer)	Mitochondrial Tx	Bioenergetics reprogramming	Preclinical

Mitochondrial transplantation is a novel approach that enhances chemotherapy effectiveness by reprogramming cellular metabolism and boosting antitumor immunity. In lung cancer models, combination of functional mitochondria with cisplatin significantly improved immune cell infiltration, reversing chemotherapy-induced immune suppression. This dual therapy shifts tumor metabolism away from the Warburg effect (aerobic glycolysis) and back toward mitochondrial oxidative phosphorylation, thereby reducing tumor proliferation and malignancy signals. This treatment also elevates reactive oxygen species (ROS) levels within tumor cells, triggering mitochondria-mediated apoptosis and enhancing cancer cell death. Importantly, mitochondrial transplantation alleviates chemotherapy side effects, such as immune cell damage, and preserves immune function, which is critical for tumor control [13].

Cell Death Reprogramming through Triple Therapy

Triple therapy aims to induce immunogenic cell death, a form of tumor cell death that promotes immune activation against cancer. By combining agents that provoke specific cell death pathways, this approach stimulates the release of tumor antigens and danger signals, thereby priming and sustaining effective immune responses. This self-limiting, immune-mediated tumor control reduces the reliance on continuous drug dosing and improves the body's defenses to contain or eradicate tumors. The integration of mitochondrial transplantation within such regimens can further enhance the metabolic health of immune cells and tumors, potentiating therapeutic outcomes [1].

Challenges and Limitations

Translational Barriers

The translation of mitochondrial therapies and metabolic modulators into clinical practice faces several significant obstacles. First, rigorous safety profiling is essential, especially in elderly and vulnerable populations,

as mitochondria-targeting treatments can have complex effects on cellular metabolism and the production of reactive oxygen species. Second, mechanistic understanding remains incomplete for some repurposed drugs that impact immune responses and mitochondrial functions, posing challenges in predicting their efficacy and side effects. Finally, clinical translation requires the validation of promising preclinical findings through randomized human trials to determine optimal dosing, safety, and long-term outcomes. Overall, overcoming these hurdles is critical for the safe and effective implementation of mitochondrial and metabolic therapies in patients [1].

Future Perspectives:

The Intersection of Neurodegeneration and Cancer in Immunotherapy

Emerging research highlights a deep biological link between neurodegenerative diseases, such as Alzheimer's disease, and cancer, revealing shared and opposing molecular pathways that modify cellular function and fate. This intersection fuels a new immunotherapy paradigm focuses used on cellular energy dynamics, immune resilience, and metabolic adaptability [1]. Enhancing mitochondrial health is vital, as mitochondria regulate both neuronal viability and immune cell function, impacting both neurodegeneration and anti-tumor immunity.

Amyloid beta (Aβ), a hallmark of Alzheimer's pathology, modulates immune metabolism, influencing T-cell mitochondrial function and metabolic programming [10]. By controlling mitophagy and cellular bioenergetics, Aβ shapes the balance between immune activation and exhaustion, suggesting that modulating Aβ signaling may improve cancer immunosurveillance while protecting neural cells [2].

This dual role unveils opportunities to harness metabolic reprogramming strategies originally designed for cancer to support aging immune systems, potentially enhancing systemic immunity in the elderly. Furthermore, optimizing mitochondrial function and Aβ pathways may improve surgical outcomes by reducing immune dysfunction and promoting tissue repair in the brain. By integrating insights from aging biology, neurodegeneration, and oncology, this approach elevates immunotherapy beyond tumor targeting to restore immune system robustness and resilience, with broad implications for age-related diseases and regenerative medicine [1].

CONCLUSION

Recent research highlights how repurposing amyloid beta and mitochondrial pathways at the intersection of neurodegeneration and cancer is composed to revolutionize immunotherapy. Amyloid beta, known for its neurodegenerative role, also enhances T cell metabolism and antitumor immunity by preserving mitochondrial function and regulating mitophagy. Mitochondrial transplantation and fumarate supplementation have shown promise in restoring aged immune cells, enabling them to better resist cancer. These findings suggest new metabolic and immune-targeted therapies that could complement and enhance existing cancer treatments.

As clinical trials advance and the underlying mechanisms become clearer, these strategies are expected to augment conventional oncology approaches while transforming perioperative care, geriatric immune support, and immuno-oncology. By bridging these fields, this paradigm shift offers innovative therapies that not only target tumors but also restore immune resilience, with broad applications in aging and regenerative medicine.

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