What is the significance of sustained microglial activation and NAD+ depletion from wildfire smoke?

Sustained microglial activation and **NAD+ depletion** from wildfire smoke may prime long-term neurodegeneration and accelerate brain aging.

Wildfire smoke exposure drives persistent microglial activation in the hippocampus that fails to resolve even 28 days post-exposure, while simultaneously depleting hippocampal NAD+ and reducing the NAD+/NADH ratio (Scieszka et al., 2023). These two phenomena are mechanistically linked: activated microglia consume NAD+ through enzymes such as CD38, poly(ADP-ribose) polymerases, and sirtuins, creating a metabolic deficit that impairs the brain's capacity to resolve inflammation (Scieszka et al., 2023; Roboon et al., 2021). The convergence of chronic neuroinflammation with loss of neuroprotective metabolites has been implicated in priming **inflammaging** and aging-related neurodegenerative phenotypes (Scieszka et al., 2021; Scieszka et al., 2023).

Evidence for Persistent Neuroinflammation and Metabolic Decline

Evidence Strength	Claim
Strong	Activated microglia (CD11b+/CD45low) remained significantly elevated in wood smoke-exposed mice at **day 28** post-exposure, indicating failure of inflammatory resolution (Scieszka et al., 2023).
Moderate	Hippocampal **NAD+ abundance decreased** at day 28, corroborated across multiple wildfire and wood smoke exposure studies (Scieszka et al., 2023; Scieszka et al., 2021).
Moderate	Wildfire smoke extract triggered **delayed but sustained** inflammatory cytokine release (TNF-α, IL-33) persisting at 96 hours in aged human microglia, with greater vulnerability in older donors (Cuní-López et al., 2024).

FIGURE 1 Evidence strength for persistent microglial activation and NAD+ loss findings

Mechanistic Link Between Microglial Activation and NAD+ Consumption

Activated microglia release **quinolinic acid**, a potentially excitotoxic NAD+ pathway metabolite whose hippocampal concentration increased progressively to statistical significance by day 28 (Scieszka et al., 2023). Persistent quinolinic acid production raises the prospect of neurological damage if the activated microglial state is sustained (Scieszka et al., 2023). Separately, NAD+ depletion reflects increased demand from NAD+-consuming enzymes within the brain parenchyma, including sirtuins and poly(ADP-ribose) polymerases, and this loss removes a critical buffer against inflammatory persistence (Scieszka et al., 2023). In a related model, CD38-mediated NAD+ consumption directly drove neuroinflammation and glial activation, while CD38 deletion or NAD+ precursor supplementation suppressed these responses (Roboon et al., 2021).

Implications for Aging and Neurodegeneration

- Wildfire-derived PM exposure increased **pathological amyloid-beta accumulation**, a hallmark of neurodegeneration, alongside decreased NAD+ and taurine (Scieszka et al., 2021).
- NAD+ supplementation via nicotinamide riboside reduced microglial activation, proinflammatory cytokines, and cellular senescence in an Alzheimer's disease mouse model through a cGAS-STING-dependent pathway (Hou et al., 2021).
- NMN supplementation boosted brain NAD+ by 2.04-fold and reduced activated microglia by 27–86% across brain regions after PM exposure, confirming that restoring NAD+ can counteract PM-induced neuroinflammation (Jiang et al., 2024).
- In aged mice, wood smoke caused a **sustained serotonin reduction** in the prefrontal cortex persisting 10 weeks post-exposure, accompanied by behavioral changes and neuroinflammatory markers (Scieszka et al., 2025).

Therapeutic Targeting of the NAD+–Microglia Axis

The combination of resveratrol and nicotinamide mononucleotide (RNMN) conferred the greatest mitigating effect against wood smoke-induced neurometabolomic and behavioral alterations in aged mice, with resveratrol activating NAD+-consuming sirtuins for longevity effects and NMN serving as an NAD+ precursor (Scieszka et al., 2025). Blocking mitochondrial complex I in pro-inflammatory microglia protects against neurotoxic damage, identifying the metabolic machinery sustaining microglial activation as a therapeutic target for chronic neuroinflammatory conditions (Peruzzotti-Jametti et al., 2024). These findings collectively suggest that wildfire smoke exposure creates a self-reinforcing cycle in which sustained microglial activation drains NAD+ reserves, and the resulting metabolic deficit in turn impairs the brain's ability to resolve inflammation—potentially accelerating neurodegenerative trajectories, particularly in aging populations (Scieszka et al., 2023; Cuní-López et al., 2024).

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