Oxidized mtDNA flips into Z

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Acetaminophen overdose triggers mitochondrial DNA oxidation, which drives a B to Z conformational switch. This left-handed Z-DNA is sensed by ZBP1, unleashing a MAVS-caspase-8 apoptotic cascade that causes lethal liver failure, a pathway that can be reversed by OGG1 activation.

Acetaminophen (APAP) hepatotoxicity remains a leading cause of acute liver failure (ALF) worldwide. Beyond the eight-hour window after overdose, the standard antidote N-acetylcysteine (NAC) loses much of its efficacy[1]. In a paper recently published in *Vita*, Yang and colleagues uncover a surprising mechanism that drives this refractory injury[2] (Fig. 1). Oxidative damage to mitochondrial DNA (mtDNA) forces it into an unusual left-handed Z-conformation. This abnormal DNA is then detected by the innate immune sensor ZBP1, which triggers hepatocyte apoptosis independently of canonical inflammasome or necroptotic pathways. Most excitingly, they show that promoting enzymatic deoxidation via the DNA repair enzyme OGG1[3] not only reverses the Z-form back to canonical B-DNA but also rescues mice from lethal APAP poisoning. This benefit remains even when treatment is delayed, and it shows striking synergy when combined with NAC.

The central observation is that leaked cytosolic mtDNA after APAP does not engage the well-studied cGAS-STING axis[3,4], which is poorly expressed in hepatocytes. Instead, ZBP1, a Z-nucleic acid sensor constitutively present in the liver, becomes essential. Genetic deletion of *Zbp1* drastically reduces liver necrosis, caspase-3 cleavage, and mortality. Importantly, ZBP1 triggers apoptosis via the mitochondrial adaptor MAVS and caspase-8[5], not through the RIPK1-FADD axis or necroptosis (RIPK3 is absent in hepatocytes)[4,6,7]. Co-immunoprecipitation, proximity ligation, and genetic epistasis firmly place MAVS downstream of ZBP1 in this context. Deleting *Mavs* phenocopies *Zbp1* loss. This ZBP1-MAVS-caspase-8 pathway is an unexpected departure from prior work focused on ZBP1-RIPK3-MLKL necroptosis[4,6,7]. It highlights how cell type and redox environment dictate signaling outcomes.

The most conceptually provocative finding is that oxidation itself flips DNA from B to Z. Using synthetic GC repeat duplexes with increasing numbers of 8-oxoguanine (8-oxoG) substitutions[8], the authors demonstrate that even at physiological salt concentrations, 8-oxoG drives a progressive loss of the A260/295 ratio characteristic of Z-DNA. This oxidized Z-DNA directly binds the Zα domain of ZBP1, whereas unmodified B-DNA does not. In cells, transfected oxidized DNA forms Z-DNA independently of ZBP1 or ADAR1, proving that oxidation alone is sufficient to drive the conformational change. Moreover, the OGG1 small molecule agonist TH10785[9] removes 8-oxoG, reverses Z-DNA back to B-DNA, and abrogates cell death. The structural implication is profound. A single oxidized base can help flip an entire double helix into a conformation that is immunologically active, adding a new layer to the "oxidative modification as a mechanism of signaling" paradigm.

From a therapeutic perspective, the delayed treatment model is what makes this work stand out. Ten hours after a lethal APAP dose, a time when NAC offers less than 50% survival, TH10785 alone achieves 90% survival. The combination of TH10785 plus NAC reaches 100% survival. TH10785 acts by removing oxidized guanines from both mitochondrial and nuclear DNA, thereby blocking both ZBP1-dependent and ZBP1-independent cytotoxic pathways (for example, PARP1 hyperactivation). Its on-target specificity is rigorously validated. Protection is lost in *Ogg1*-knockout mice and in *Ogg1*-knockdown cells. TH10785 does not affect APAP metabolism, glutathione levels, ROS production, or ZBP1 expression. This is a rare example of a DNA repair agonist being repurposed for acute pharmacotoxic shock. It raises the possibility that OGG1 activators could find use in emergency medicine.

Several important questions remain. First, how precisely does 8-oxoG promote the B to Z transition? Does the oxidized base alter hydration, stacking, or backbone torsion in a way that favors the left-handed form? Second, how does APAP stress redirect ZBP1 toward MAVS instead of RIPK1 or RIPK3? The authors show that the same Z-DNA ligand can trigger canonical ZBP1-RIPK3 death in fibroblasts, so the deciding factor is likely something in the hepatocyte's unique redox or adduct environment, possibly NAPQI modification of signaling proteins or altered MAVS oligomerization. Third, what fraction of mtDNA must be oxidized to trigger the switch, and is the effect local or cooperative along the specific regions in mtDNA? Finally, will OGG1 activation be safe in humans, given that it enhances removal of oxidative lesions from nuclear DNA? The liver's remarkable regenerative capacity may tolerate transient repair activation, but chronic effects need exploration.

In a broader context, this work joins a recent study showing that amyloid β also drives mtDNA B to Z transitions in microglia to fuel neuroinflammation in Alzheimer's disease[10]. Together, these papers suggest that oxidation-driven Z-DNA may be a common pathogenic node in diverse diseases from drug-induced liver failure to neurodegeneration. Z-DNA itself, rather than just oxidative stress, could be a therapeutic target. The OGG1 agonist approach has the additional advantage of reversing the modification rather than merely inhibiting a downstream sensor, potentially preserving the beneficial roles of ZBP1 in antiviral defense.

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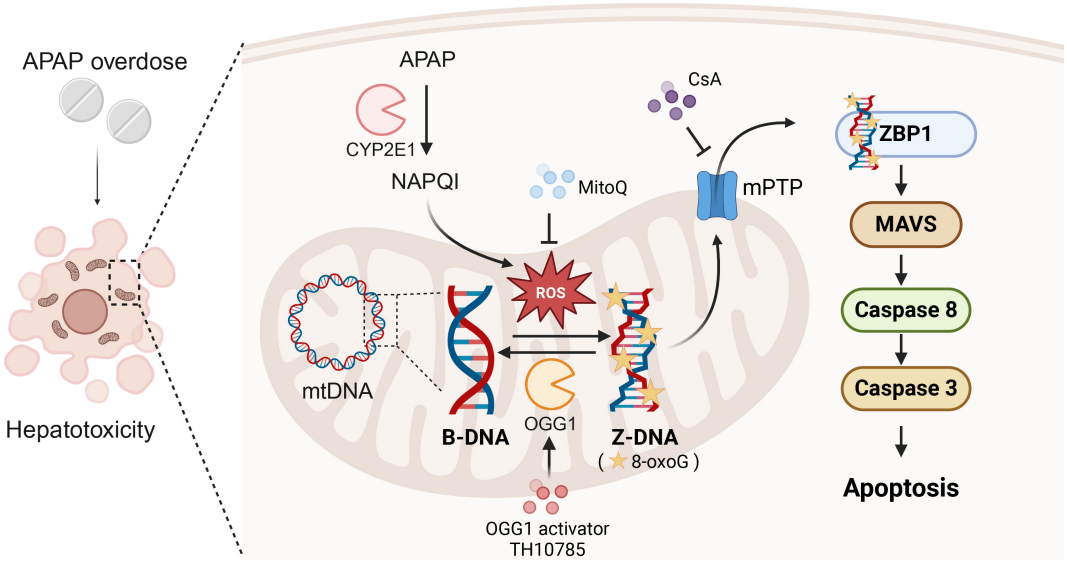

Fig. 1 Schematic of the oxidation-driven B-to-Z mtDNA switch in APAP hepatotoxicity. APAP converts to NAPQI, which induces mtROS and 8-oxoG lesions in mtDNA. Oxidized mtDNA adopts a left-handed Z conformation (even at low salt) that is recognized by the Zα domain of ZBP1. ZBP1 then engages MAVS (not RIPK1 or RIPK3) to activate caspase 8 and downstream caspase 3, driving hepatocyte apoptosis. The OGG1 agonist TH10785 removes 8-oxoG, reverts Z-DNA to B-DNA, and blocks cell death.

For the clinician, the message is clear. After APAP overdose, it is not just mitochondrial dysfunction but the shape shifting of oxidized mtDNA into an immunogenic Z form that propagates late-stage lethality. Intervening with an OGG1 activator to flip Z-DNA back to B-DNA, especially together with NAC, could transform the management of APAP-induced ALF, a condition that today still sends hundreds of patients each year to liver transplantation.

COMPETING INTERESTS

The authors declare no competing interests.

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ADDITIONAL INFORMATION

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