Title: Metabolic Stress and Somatic Mutation: Exploring Links to Sleep Disorders

Authors: Viktor Stolc*[1], Friedemann Freund[2], Maurice M. Ohayon[3]

Author Affiliations: 1. NASA Ames Research Center, 2. SETI Institute, 3. Stanford University School of Medicine

Abstract

The relationship between metabolic stress, genomic instability, and sleep health is an important area of research with potential clinical benefits. This paper focuses on the harmful effects of oxidative stress-induced RNA damage and dysfunction (RDDs). RDDs are not simply differences between RNA and DNA sequences; they represent a broader range of RNA damage and malfunctions. This damage disrupts the fidelity of the *transcriptome*—the complete set of RNA molecules (mRNA, rRNA, tRNA, and non-coding RNA) which represents the functional output of the genome. RDDs occur when antioxidant enzymes cannot control excess *reactive oxygen species (ROS)* generated by metabolic stress, leading to damage of RNA and DNA molecules. This process is different from *RNA editing*, a normal and essential process where RNA sequences are intentionally modified to fine-tune gene expression. While both RDDs and RNA editing affect gene expression, their causes and consequences are very different.

Glossary

Antioxidants	Substances and enzymes that protect cells from damage caused by reactive oxygen species (ROS).
Circadian rhythm	The body's internal 24-hour clock that regulates sleep-wake cycles and other physiological processes.
ER stress	Stress on the endoplasmic reticulum, a cellular organelle involved in protein synthesis and folding.
Metabolic dysfunction	Impaired metabolic processes, increasing the risk of obesity, diabetes, and other health problems.
Metabolic stress	A state of physiological imbalance that can trigger cellular dysfunction, including disruption of sleep-wake cycles.
Mitochondrial dysfunction	Impaired function of mitochondria, the cell's energy producers, leading to increased ROS production.
Mutated proteins	Proteins with altered amino acid sequences due to RDDs, potentially leading to cellular dysfunction.
NAD+ metabolism	A metabolic pathway involved in energy production and cellular repair.
Oxidative damage	Damage to cellular components caused by excessive ROS.
Reactive Oxygen Species (ROS)	Byproducts of metabolic processes that, in excess, can cause cellular damage.
Redox switching	The regulation of cellular processes by changes in the balance between oxidants and antioxidants.
RNA editing	A normal, regulated process for modifying RNA sequences to fine-tune gene expression.
RNA-DNA Differences (RDDs)	A broad term encompassing various types of RNA damage and dysfunction, often caused by oxidative stress.
Transcriptome	The complete set of RNA molecules in a cell, representing the functional output of the genome.

Introduction

The intricate relationship between metabolic stress, genomic instability, and sleep health represents a largely uncharted area of research, ripe with potential for realizing actionable clinical benefits. This paper focuses on the detrimental consequences of oxidative stress-induced RNA-DNA differences (RDDs), a term initially used to describe discrepancies between RNA and DNA sequences but used here to encompass a broader range of RNA damage and dysfunction. This dysregulated process disrupts the fidelity of the transcriptome—the complete set of RNA molecules (mRNA, rRNA, tRNA, and non-coding RNA) representing the functional readout of the genome (RNA Structure and Function, 2023). These RDDs arise when antioxidant enzymes fail to limit excess reactive oxygen species (ROS) generated by metabolic stress, that can lead to damage of RNA (and DNA) molecules. In addition to metabolic processes, ROS can also be generated by abiotic processes within the body, notably those linked to geological activity. For example, Freund & Stolc (2013) describe that the buildup of mechanical stresses in the Earth's crust lead to the activation of highly mobile electronic charge carriers in rocks. At the Earth's surface these charge carriers can ionize the air, thereby creating positive airborne ions, or oxidize water, thereby producing hydrogen peroxide. These processes interfere with RNA editing, a tightly regulated and essential biochemical mechanism for modifying RNA sequences that plays a crucial role in the fine-tuning of gene expression. While both RDDs and RNA editing can influence gene expression, their underlying mechanisms and implications differ significantly.

Core Hypothesis

Based on the evidence presented in this paper, the following core hypothesis is proposed:

Oxidative stress-induced* RNA damage and dysfunction *(RDD) is a key driver of circadian rhythm disruptions, leading to sleep disorders.

This hypothesis is supported by observations from mice flown on the International Space Station (ISS), which exhibited metabolic dysfunction and RDDs (somatic mutations) induced by the unique stressors of the spaceflight environment (Stolc, et al., 2024). This hypothesis offers a unifying framework for understanding how oxidative damage, genomic instability, and sleep health may be interconnected. By positing that oxidative stress-induced RNA damage directly impacts the molecular clock mechanisms regulating circadian rhythms, it highlights an essential, yet underexplored, link between cellular redox states and systemic physiological balance. This perspective inspires new research directions aimed at uncovering how environmental and metabolic stressors may synergistically disrupt sleep-wake cycles. Furthermore, the hypothesis underscores the translational potential of targeting oxidative stress in therapeutic strategies to alleviate circadian rhythm-related sleep disorders. Such interventions could have far-reaching implications for improving quality of life, particularly for individuals exposed to chronic stress or adverse environmental conditions. The mice flown on the ISS also displayed a range of physiological and behavioral changes, including pronounced stress behavior, changes in blood chemistry such as lipidosis resulting from direct oxidative damage of lipids, and muscle atrophy.

Bridging the Gap: Spaceflight Stress in Mice and Human Sleep Disorders

To further elaborate on the relevance of the mouse model to human sleep health, it's crucial to consider the shared underlying mechanisms between spaceflight-induced stress as studied in mice and sleep disorders in humans. Both involve a complex interplay of physiological responses, including:

- **HPA Axis Dysregulation:** The hypothalamic-pituitary-adrenal (HPA) axis plays a central role in regulating the stress response and circadian rhythms. Spaceflight has been shown to disrupt the HPA axis in mice, leading to altered hormone levels and sleep-wake cycles. Similarly, dysregulation of the HPA axis is implicated in various human sleep disorders, particularly those related to stress and anxiety (Choi, et al., 2020; Buckley & Schatzberg, 2005; McEwen, 2006).
- **Oxidative Stress and Neuronal Function:** Oxidative stress, a key feature of both spaceflight and metabolic dysfunction, can impair neuronal function and disrupt sleep-wake circuits. Excessive ROS can damage neurons involved in regulating sleep and wakefulness, leading to imbalances in neurotransmitter systems and contributing to sleep disturbances (Behrens, et al., 2007; Choi, et al., 2020; Bélanger, et al., 2011).
- **Genetic and Epigenetic Factors:** Genetic and epigenetic factors likely contribute to individual susceptibility to stress as induced by spaceflight and to sleep disorders. Identifying common genetic or epigenetic markers could therefore help predict vulnerability and develop personalized interventions (Garrett-Bakelman, et al., 2019; Hu, et al., 2019; Archer, et al., 2008).

By understanding these shared mechanisms, the findings from the mouse model can provide valuable insights into the development of potential biomarkers, therapeutic targets, and countermeasures to mitigate the impact of stress on human sleep health. This convergence emphasizes the importance of considering environmental factors, including those encountered during spaceflight and as part of human sleep disorders (Malicki et al., 2023).

To investigate this hypothesis in humans, forthcoming studies could focus on individuals with metabolic syndrome, cardiovascular disease, type 2 diabetes (T2D) and sleep disorders like insomnia or excessive sleepiness (hypersomnia). These studies could measure RDDs in RNA from blood samples and measure biomarkers of oxidative damage to RNA (8-oxo-guanine) and DNA (8-oxo-2'-deoxyguanosine) in urine (Loft, et al., 2012; Roszkowski & Olinski, 2012). Established quantitative methods like RNA-seq with variant analysis could be employed to simultaneously study gene expression and identify genetic variants in the transcriptome such as SNPs and insertions/deletions (Stolc, et al., 2024), thereby providing insights into the complex interplay between metabolic stress, RDDs, and sleep disturbances.

Studies could also investigate drugs that affect the metabolic ROS production and/or the RDD formation. For example, phenelzine, an antidepressant, may work by reducing excess metabolic ROS. Monoamine oxidase, an enzyme targeted by phenelzine, produces hydrogen peroxide (H_2O_2) that can contribute to oxidative stress in the brain (Shih, 2018). By inhibiting monoamine oxidase, phenelzine will reduce ROS production, thereby potentially lessening the damage to nucleic acids, proteins, and lipids.

Furthermore, the ability of phenelzine to prolong the reductive phase of metabolic cycles, as observed in yeast, suggests it could limit ROS-induced disruptions in the cellular redox homeostasis (Li & Klevecz, 2006). This dual mechanism of action — reducing enzymatic ROS production and modulating metabolic oscillations — provides a novel perspective on phenelzine and its antidepressant effects, linking metabolic stress mitigation with improved neural function.

In addition, for patients with severe depression who have undergone deep brain stimulation (DBS) surgery, RDDs could also be directly quantified in the brain using single-neuron RNA-seq by means of implanted electrodes. This approach could provide valuable insights into the potential role of RDDs in treating depression and other mood disorders that are often associated with sleep disturbances.

This paper focuses on why and how RNA damage and dysfunction (RDDs) can lead to the production of mutated proteins within cells, including neurons. The mutated proteins that are involved in these processes can disrupt essential neural functions and the body's internal clock, known as the circadian rhythm, which regulates our sleep-wake cycles. This paper explores the consequences of these disruptions, particularly their impact on sleep health. Disruptions to these processes can trigger a cascade of adverse effects, including impaired cognitive function (e.g., difficulty concentrating and poor judgment), emotional and behavioral changes (e.g., irritability, anxiety; Walker et al., 2020), and detrimental physical health consequences (e.g., increased risk of obesity and weakened immune system; Fishbein, et al., 2021; Tracey et al., 2020).

Metabolic Stress and Oxidative Damage

Central to this detrimental cascade is a vicious cycle created by metabolic stress and oxidative damage. Metabolic stress is often induced by factors like chronic inflammation, obesity, or environmental insults, like air pollution (e.g. pollen dust), toxic metals, tobacco smoke and low plasma antioxidant levels. These metabolic stress factors increase the production of reactive oxygen species (ROS). Certain geological events can also trigger abiotic ROS production. For instance, Freund & Stolc (2013) have pointed to the release of carbon monoxide (CO) from the ground due to geophysical processes such as in the lead-up to the 2001 Gujurat earthquake represented a major stressor. Indeed, any increase in the CO concentration in the local environment will disrupt cellular respiration and increase ROS generation, contributing to RNA oxidation and RDD generation.

While moderate levels of ROS are a natural byproduct of mitochondrial respiration, excessive production of ROS will inflict oxidative damage on cellular components, notably RNA and DNA. This oxidative damage is particularly concerning for mitochondrial RNA–processing enzymes such as RNase MRP and RNase P, which contain catalytic RNA subunits particularly vulnerable to oxidation, specifically 8-oxo-guanine (8-oxoG). This damage leads to RDDs that can impair these enzymes' functions that are essential for mitochondrial DNA replication and ribosomal RNA processing (Altman & Stolc, 1997; Stolc et al., 1998). This impairment directly affects ATP production, which is inevitably coupled with ROS generation, perpetuating a cycle of oxidative damage. This vulnerability is additionally exemplified by the ribosomal RNA gene *Rn45s*, where RDDs induced by metabolic stress during spaceflight have been mapped (Stolc et al., 2024). Critically, this RNA oxidation can further impair mitochondrial function, leading to

increased ROS production, thus perpetuating the cycle of damage and dysfunction. This is further corroborated by the studies of the mice flown on the International Space Station (ISS). During and after the flight these mice exhibited a range of physiological and behavioral changes, including increased stress behavior (Choi, et al., 2020), changes in blood chemistry such as lipidosis resulting from direct oxidative damage of lipids (Ross & Zolfaghari, 2004), and muscle atrophy (Lee et al., 2020). Some of these changes may be directly attributed to the RDDs created by the unique spaceflight environment.

Moreover, the mice on the ISS displayed hyperactive behavior and a lack of normal diurnal activity patterns, including sleeplessness (Smith et al., 2018). This is likely due to the arousal of certain neurons triggered by the elevated CO_2 levels on the ISS. Those neurons caused the mice to maintain vigilance in response to the altered atmospheric conditions. Interestingly, in humans, the retention of CO_2 in the blood is linked with sleep disorders that affect breathing, especially sleep apnea, the central hypoventilation syndrome and obesity hypoventilation syndrome (Masa et al., 2019). The findings of this work highlight the potential impact of RDDs and of oxidative stress on sleep regulation. They suggest that similar mechanisms may contribute to sleep disturbances in astronauts during long-duration space missions.

RDDs and Cellular Dysfunction

Beyond their role in disrupting protein synthesis, RDDs in RNA components of various ribonucleoprotein (RNP) complexes can have widespread and detrimental effects on cellular processes. For instance, RDDs in the signal recognition particle (SRP) RNA can impair protein targeting to the endoplasmic reticulum (ER), leading to ER stress and additional ROS production (Jiang et al., 2020). In addition to metabolic stress, abiotic factors, such as those produced by geological activity, can also contribute to RDDs. Shitov (2010) documented a significant increase in hospital admissions for neurological conditions starting about 10 days *before* the 2003 magnitude 7.3 Chuya earthquake in the Altai Republic, Russia, in the border region of Mongolia, China, and Kazakhstan. Hypertension, vegetative vascular dystonia, and epilepsy were reported to be major causes for the hospital admissions. These geophysical conditions may reflect acute changes in neural excitability, potentially linked to induced oxidative stress. Furthermore, RDDs in spliceosome RNA components can interfere with micro-RNA (mRNA) splicing, resulting in the production of aberrant proteins (Cech, 2018). Gene expression can also be dysregulated by RDDs in mRNA, which alter mRNA binding sites and contribute to disease (Vaghf et al., 2022). RDDs can have unintended consequences beyond their primary targets. Imagine RNA as a cellular message with specific instructions for its destination and function. RDDs can distort these messages, disrupting their ability to reach the correct location within the cell and perform their intended tasks (Cui et al., 2022). This disruption can ultimately impair essential cellular processes.

Furthermore, these distorted RNA molecules can trigger the cell's internal alarm system. Cells possess sensors that detect irregularities in RNA structure, interpreting these alterations as signs of foreign invaders. This triggers innate immune responses, leading to inflammation as the body attempts to defend itself (Yuan et al., 2023).

This process can also affect Y-RNAs, a type of RNA vital for cellular stress response, immune regulation, and maintaining the integrity of the genome (Boccitto & Wolin, 2019). Damage to Y-RNAs further compromises the cell's ability to function correctly and maintain stability.
In essence, RDDs not only disrupt the intended RNA targets but also trigger broader cellular dysfunction and inflammation. This understanding has significant implications for physicians, highlighting the importance of careful monitoring for potential side effects and informing the development of more targeted therapies with reduced unintended consequences.

RDDs and Disrupted Circadian Rhythms

The widespread disruptions caused by RDDs as mentioned here can ultimately affect the delicate balance of cellular processes, including the intricate mechanisms that govern our sleep-wake cycles. Properly functioning circadian rhythms, orchestrated by molecular clock genes, are crucial for synchronizing metabolic activities with environmental cues, ensuring optimal physiological timing (Malicki et al., 2023; Potter et al., 2016; Masri & Sassone-Corsi, 2018; Shimizu et al., 2016; Czeisler & Gooley, 2007; Roenneberg & Merrow, 2016). Crucially, it is not only the light and dark cycles that are influenced by these clock genes but also the rhythmic oscillations of the ROS themselves within our cells. This "redox switching" drives the diurnal clock, causing it to respond to changes in cellular metabolism and the occupancy of energy levels involved, enabling the clock to achieve optimal synchronization of physiological processes. Disruptions to these rhythmic balances, often caused by lifestyle factors like shift work or out-of-phase ROS oscillations, can impair cognitive function and exacerbate metabolic dysfunction (Sack et al., 2007; Ohayon, et al., 2010). The present paper explores the intricate connections between RDD formation, disrupted circadian rhythms, and their joined impact on sleep health. It places a particular focus on how oxidative stress can disrupt the redox-sensitive timekeeping mechanisms of the cellular clock.

The Consequences of Chronic Sleep Disruption

Having established the detrimental impact of RDDs on cellular processes, we now turn our attention to the broader consequences of chronic sleep loss itself. While sleep deprivation or, more generally, sleep restriction consistently leads to cognitive decline, individuals vary in their vulnerability due to genetic and physiological factors. This section explores these individual differences and their implications for how to understand sleep disorders and how to treat them. Epidemiological studies highlight the high prevalence of sleep disorders, such as insomnia and hypersomnia, underscoring the importance of understanding their underlying mechanisms and health consequences (Ohayon, 2002).

Chronic sleep disruptions, including insomnia and hypersomnia, are associated with significant physical and mental health risks. Studies indicate that deviations from normative sleep patterns due to conditions such as insomnia can lead to cumulative health deficits (Ohayon, 2004, Ohayon & Pakpour, 2022). Despite being highly prevalent, insomnia often remains underdiagnosed and undertreated, resulting in significant health concerns. Recognizing the broader health risks of insomnia is critical for developing effective interventions (Ohayon, 2005).

Restricting sleep to 6 hours or less per night results in cumulative cognitive deficits comparable to total sleep deprivation (Van Dongen et al., 2003). Affected individuals may be unaware of the extent of their impairment, highlighting the insidious nature of sleep deprivation. Beyond cognition, chronic sleep loss disrupts metabolic processes, increasing the risk of obesity, diabetes, and even cancer (McHill & Wright, 2017; Masri & Sassone-Corsi, 2018). Sleep deprivation and circadian misalignment dysregulate the overall energy balance, hormone secretion, and glucose homeostasis, thereby promoting weight gain, insulin resistance, and other metabolic abnormalities (Roenneberg & Merrow, 2016). Obstructive sleep apnea (OSA) can further exacerbate these metabolic detriments through circadian clock disruption (Malicki et al., 2023).

Individual Differences in Sleep Vulnerability

Individual susceptibility to the adverse effects of sleep loss and sleep deprivation varies considerably. This variability is influenced by genetic factors regulating circadian rhythms and associated metabolic stress responses. A genome-wide association study (GWAS) with 89,283 individuals identified 15 loci associated with morningness, many situated near circadian genes such as *PER2*, *PER3*, *FBXL3*, and *VIP* (Hu Y, et al., 2016). *This particular GWAS study linked morningness to a less insomnia and depression, correlating it with body mass index (BMI), suggesting potential health benefits*. Pathway analysis further confirmed that the circadian clock pathways diversify, highlighting the intricate connection between circadian rhythms and metabolic processes.

Another multivariate GWAS revealed shared and distinct genetic influences on various sleep traits, including circadian rhythms as expressed in sleep duration and quality. This suggests a complex genetic architecture underlying sleep health, paving the way for personalized sleep medicine tailored to individual genetic profiles.

At a physiological level, clock proteins like CLOCK and BMAL1 integrate metabolic and circadian signals. Disruptions to these proteins, often worsened by metabolic stress, can cause cognitive deficits and increase the risk of sleep disorders like insomnia and hypersomnia (Shimizu et al., 2016). Chronic sleep deprivation has been found to increase oxidative stress, thereby amplifying genomic instability and disrupting neural circuits crucial for cognition and sleep regulation. The immune system also plays a role in these processes, with inflammation triggered by metabolic dysfunction further impairing sleep quality (Zeng et al., 2024).

Natural Short Sleep: Insights from Genetics

Research at the University of California School of Medicine has identified gene mutations linked to "natural short sleep," where individuals thrive on fewer sleep hours without experiencing typical negative consequences (Shi G, et al., 2019). This discovery offers potential therapeutic avenues for addressing sleep disorders. Mutations in genes like *DEC2*, *ADRB1*, and *NPSR1* have been implicated in natural short sleep, each affecting different aspects of sleep regulation (He et al., 2009; Shi et al., 2019). Understanding how these genes interact with metabolic pathways and respond to oxidative stress could offer valuable insights into targeted therapies for sleep disorders and enhancing cognitive resilience.

RNA Damage and Dysfunction (RDDs)

RDDs, arising from oxidative damage and enzymatic editing processes, can significantly impact sleep regulation. While some RDDs are adaptive, stress-induced errors can alter gene expression and protein function, contributing to sleep disorders (Bahn et al., 2012; Xu et al., 2020; Hwang et al., 2016). For instance, RDDs in genes related to GABAergic neurotransmission can contribute to insomnia (de Leon AS & Tadi P, 2025).

Clinical Implications and Future Directions

Given the intricate links between metabolic stress, RDDs, and sleep regulation, targeted therapies offer promising avenues for intervention. Antioxidants, such as N-acetylcysteine (NAC) or a combination of the amino acids glycine and NAC (GlyNAC), could mitigate ROS damage, reducing somatic mutations and preserving neural signaling pathways crucial for sleep regulation (Kumar & Atkinson, 2023), NAD+ metabolism support, and chronotherapy (timing interventions based on circadian rhythms) may help mitigate the adverse effects of sleep deprivation and improve sleep quality (Reinke & Asher, 2019; Masri & Sassone-Corsi, 2018). Further research into RNA editing modulators, such as ADAR inhibitors or activators, holds promise for preventing RDDs or correcting the effects, by which they contribute to sleep disorders.

Ethical Considerations

Any research involving human subjects must prioritize ethical considerations and participant well-being. Studies investigating the link between geological activity, ROS production, and sleep disorders should adhere to strict ethical guidelines, including:

- **Informed Consent:** Participants must be fully informed about the study's purpose, procedures, potential risks and benefits, and their right to withdraw at any time.
- **Privacy and Confidentiality:** Participant data must be kept confidential and anonymized to protect their privacy.
- **Minimizing Risks:** Researchers should carefully assess and minimize any potential risks to participants.
- **Scientific Rigor:** Studies must be scientifically rigorous to ensure the validity and reliability of the findings.
- **Oversight:** All research involving human subjects should be reviewed and approved by an Institutional Review Board (IRB) or ethics committee to ensure compliance with ethical standards.

By carefully considering and addressing ethical implications, researchers will be able to conduct human studies responsibly and contribute to the advancement of knowledge in this field while safeguarding participant well-being.

Conclusion

Metabolic stress and RDD-induced genomic instability provide a critical link between oxidative stress and sleep disorders. By disrupting circadian regulation and neural signaling, metabolic dysfunction exacerbates conditions like insomnia and hypersomnia. This underscores the importance of addressing metabolic health as a key component for improving sleep quality and overall well-being. Future research should focus on:

- The role of RDDs in sleep-related genes
- Targeted therapies addressing oxidative stress and NAD+ metabolism
- Chronotherapy to optimize treatment efficacy
- Personalized medicine approaches considering individual genetic susceptibility and environmental factors

These efforts offer hope for mitigating the impact of metabolic stress on sleep health and improving overall well-being. Further investigation into the complex interplay between metabolic regulators and the circadian clock may lead to novel therapeutic interventions, particularly in populations with high exposure to environmental stressors such as shift workers and astronauts. These effects, as highlighted by Ohayon (2010), emphasize the role of environmental and lifestyle factors in sleep health. Indeed, this work has revealed a novel convergence of endogenous (metabolic) and exogenous (geological) processes on similar ROS-mediated pathways that can disrupt circadian rhythms and induce sleep disorders. This understanding underscores the interconnectedness of planetary health and human health, demonstrating how environmental factors can affect cellular-level changes that ultimately impact sleep and overall well-being.

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