MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Tissue Protective And Regenerative Therapies Counteracting Nerve Agent Damage

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Toxic effects of nerve agents pose threats to warfighters and civilians. Symptoms of nerve agents can develop immediately following exposure, and even sub-lethal concentrations can cause delayed and long-term neurological damage. Treatments against nerve agents are limited and prophylactic protection do not exist. Upon a nerve agent exposure, cholinergic overstimulation is caused by accumulation of the neurotransmitter acetylcholine (ACh) at nerve endings and uncontrolled ion flux leading to cell death. We hypothesize that to recover normal cellular function after cholinergic crisis, we need to identify and target common fundamental regulatory mechanisms. The purpose of this work is to mitigate toxic exposure effects by allowing for rapid identification of repurposed or broadly acting medical countermeasures (MCMs) to serve as prophylactic treatment.

We initiated an investigative study seeking to uncover survival and regenerative response mechanisms in mature human motor neurons (hMNs) triggered by ion flux imbalance upon exposure to acute doses of Ach and organophosphate agent paraoxon ethyl (a VX surrogate). We performed unbiased global transcriptome profiling of hMNs, skeletal muscle fibers, and complex tissue structures forming functional neuromuscular junctions (NMJs) exposed to both ACH and nerve toxin. Our analytical approach uncovered novel inflammatory and metabolic disorders in hMNs that can be ameliorated by repurposing of Food and Drug Administration (FDA)-approved compounds. The tested potential prophylactic compounds included natural metabolites, synthetic anticonvulsant drugs, and anti-inflammatory glucocorticoids with known bioavailability and pharmacokinetics. Our electrophysiological assays coupled with transcriptomic studies have indicated that post OP exposure treatment of NMJ organoids with the small molecule compounds improved neuronal performance compared to untreated controls. Additionally, we have applied SmartTensors Artificial Intelligence (AI) platform, and unsupervised AI method, to fuse our global transcriptome data with transcriptomics datasets generated by other research labs to investigate the effects of various classes of neurotoxic agents on MN function. By integrating our existing data with additional sources, we leverage information from multiple modalities, leading to more comprehensive and insightful potential discoveries SmartTensors AI utilizes advanced tensor decomposition methods to model the complex multi-faceted details of our multi-modular data, and to extract latent (hidden) patterns that reveal useful insights.

Here, by investigating the patterns discovered by the SmartTensors AI framework, we have identified novel molecular targets for development of broad-spectrum prophylactics or tissue regenerative antidotes to nerve agent induced injuries. We uncovered survival and regenerative response mechanisms triggered in mammalian cells by ion flux imbalance upon exposure to the neurotransmitter acetylcholine and OP agent. This effort holds great potential in the discovery of cellular wiring patterns triggered by various chemical stimulants of cholinergic crisis, extraction of essential features underlying neuronal cell recovery, and prediction of broadly acting MCMs against chemical threats. This research can be used to further develop novel prophylactic treatment against nerve agents by repurposing FDA approved drugs.

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