MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Organophosphate Nerve Agent-induced Transcriptome Changes In Human Cells To Identify Drug Targets

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The toxic effects of chemical warfare agents (CWA) present persistent threats to both warfighters and civilians. Symptoms develop immediately following exposure, and readily available blood tests for identifying specific chemical poisoning agents are lacking. Furthermore, treatment options are scarce, and when available, they are administered at high doses, approaching toxic levels. Understanding the toxicity of agents to biological systems requires consideration of the molecular and cellular processes involved, as well as the relationships between exposure concentration, toxic effects, and time. The goal of this study is to identify the aforementioned effects through changes in differential gene expression across cell types as a function of time and toxicant concentration (organophosphate nerve agent simulant, diisopropyl fluorophosphates - DFP).

In this work, we have developed a complementary approach to extrapolate signatures of toxicant exposures using microphysiological systems. By creating an integrated platform, we can leverage complex human cell cultures, conduct exposure studies, and analyze transcriptomic sequencing to identify common elements underlying cellular responses to exposure, triggering cellular stress and inducing toxicity.

Rapid and pronounced changes were observed in both lung and motor neurons upon DFP exposure, with neurons displaying higher sensitivity, evidenced by visible necrosis at earlier time points and lower concentrations, within 1 minute of exposure. It was also observed through the time-series RNA-seq data that the temporal dynamics is a more critical factor than concentration in influencing the cellular responses to toxicant exposure. Multiple time and concentration-specific molecular and cellular processes were identified in both cell types, as well as several potential drug targets. In neurons, some of the top upregulated processes observed were metabolism of nucleic acids, rRNA processing pathways, cell division processes, and DNA damage responses, highlighting upregulated cellular stress responses. In comparison, the significant downregulated processes were cellular metabolic and other mitochondrial functions as well as lipid catabolic and localization processes. Similarly, in lung exposures, the concentration-specific effects demonstrated a trend where medium agent concentration exposure was less disruptive compared to low and high concentrations. In lung, the main upregulated processes included chromatin organization and stress response, while downregulated processes involved glycoprotein metabolism and programmed cell death.
Lastly, through further in silico modeling the study also identified several potential drug targets for which the representative genes were significantly upregulated post-exposure, such as Topoisomerase 1 (cancer target), Calcium voltage-gated channel subunit α1A (a drug target for neurological disorders), and Bromodomain-containing protein 4 (a drug target for malignant tumors, as well as coronary heart disease, neurological disorder, and obesity).

The outcome of this work has the potential to be used in identifying strategies for mitigating toxic exposure effects by enabling the rapid identification of medical countermeasures (MCM).
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