"Accelerating the Development of Diagnostic Biomarkers and Mitigating Drugs for Radiation Injury with Quantitative Mass Spectrometry"

Nuclear and radiological terrorism is an on-going public health concern, but very few measures exist to counter the injuries from these potential attacks or assess the extent of the injury. In response to this need, the UCLA Center for Medical Countermeasures against Radiation (CMCR) has dedicated their research efforts on radiation biodosimetry and drug development. On the diagnostic side, existing biodosimetry is only able to provide a crude estimate of radiation exposure dose. More effective diagnostic tools are needed to confirm exposure and predict tissue-specific radiation injury progression. Towards this end, we aimed to develop protein biomarkers that can assess organ-specific radiation damage. Utilizing quantitative mass spectrometry (MS)-based proteomics, we performed discovery experiments to identify proteins that have desirable biomarker characteristics. In addition, we evaluated a set of hypothesized biomarker candidates as part of antioxidant response using a targeted MS method. On the treatment side, very few medical products are available to mitigate radiation-induced injury. In fact, only three radiomitigators, through drug repurposing, have been approved by the FDA for treatment of hematopoietic acute radiation syndrome (H-ARS). The UCLA CMCR has recently identified a novel group of small molecules from high throughput screening (HTS) for inhibitors of radiation-induced apoptosis. The lead compound dramatically decreases mortality from H-ARS in mice. To elucidate the mechanism of action for the lead compound, we utilized an emerging target identification approach based on thermal stability shift upon ligand binding (i.e. thermal proteome profiling or TPP). TPP proposed hypothetical targets for the lead compound, which can later be validated by protein-ligand binding studies and other means.

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