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Concept of Toxicoproteomics in Identifying Biomarkers of Toxicant Action

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Humans are often exposed to a variety of environmental toxicants that contribute to an individual's risk for disease. Therefore, in toxicological research new approaches are required for effective screening of environmental risks on complex living systems. Laboratory data generated through several *in vitro*, *in vivo* and some clinical studies have supported that various environmental products produce a broad spectrum of adverse health effects including neurological disorders and cancer. However, the results of these studies are still contentious; nevertheless, their mechanism of action is clear. For identification of molecular signatures and methodical understandings of various environmental toxicants response in biological systems, toxicoproteomics is considered to be a valued approach. The cellular response to carcinogens/toxicants is complex, so to maintain genomic stability and prevent carcinogenesisthe network of events taking place in the cell needs to be determined and abundant efforts has been put in for this. There are well over 10,000 publications relating to applications of proteomics in the toxicology research. Toxicoproteomics has been enhanced by tools from proteomics, bioinformatics and other enabling high data technologies.

Today, toxicoproteomics mainly relies on high throughput technique 2-dimensional gel electrophoresis (2-DE) coupled with mass spectrometry (MS) for separation, detection and identification of proteins, which might illustrate a certain state of disease, specify toxicity or even forecast carcinogenicity.Fluorescent dyes such as Sypro ruby has been the most sensitive means of protein detection (nano- to microgram range) in recent past.Latest development of modern techniques for instance multiplex fluorescence coloring using the differential gel electrophoresis (DIGE) provides a more detailed gel-to-gel comparison and quantification of proteins separated by 2-DE. Still, there are enduring apprehensions regarding the standardization of electrophoresis protocols, the reproducibility of the data, and the subjective nature of 2-DE gel image analysis. Therefore, alternative proteomics methodologies, such as liquid chromatography (LC-MS/MS) and surface-enhanced laser desorption ionization time-of-flight mass spectrometry (SELDI-TOF-MS), are pretty more prevalent in clinical medicine and very currently in environmental toxicology. Other disparities on the LC-MS/MS method, closely linking LC separation to MS/MS instruments, have unified isotopic labelling approaches for protein quantitation and in-depth proteomic profiling of samples. Examples of such platforms are isotope coded affinity tags (ICAT), isobaric tag for relative and absolute quantitation (iTRAQ) and stable isotope labelling with amino acids in cell culture (SILAC).

Midst of numerous environmental toxicants, pesticides, used widely for controlling pest and destroying weeds are global contaminants accumulating in our environment and hence humans get unavoidably exposed to these pesticides. Organophosphates, pyrethroids and carbamates, some of the extensively used group of pesticides, have been informed to possess carcinogenic and co-carcinogenic potential in various test systems. We can use biomarkers to distinguish fundamental links and to make better quantifiable estimations of those links at relevant levels of exposure and this will enable us to expand our understanding of mechanism behind their carcinogenic potential. Studies from our laboratory, demonstrated the usefulness of toxicoproteomics technology in identification of pesticides-inducing neoplastic changes in mammalian skin system. Using this approach, we attempted to identify that SOD 1, calcyclin (S100A6) and calgranulin-B (S100A9) are associated with glyphosate (organophosphate herbicide) inducing tumor promoting potential and may be useful as biomarkers for tumor promotion. We also utilize 2-DE and MS in studying the molecular mechanism that contributes in mancozeb (carbamate fungicide)-induced carcinogenesis. The level of S100A6 and S100A9 was significantly up regulated in the mancozeb exposed mouse skin and later found to be higher in mancozeb-exposed human keratinocytes, HaCaTcells. Furthermore, using quantitative proteomics in mouse skin exposed to cypermethrin, a synthetic pyrethroid insecticide, we reported 7 proteins (carbonic anhydrase 3, Hsp-27, S100A6,galectin-7, S100A9, S100A11, SOD 1) play significant roles in many cellular functions, including oxidative stress response, proliferation, binding of calcium ions and apoptosis. Commotion of these processes plays a vital role in carcinogenesis. Hence supports that these proteins were allied with induction of cell proliferation and might be responsible for the neoplastic transformation of mouse skin preneoplastic lesions by cypermethrin.

Toxicoproteomic platform could be easily used for biomarker identification for numerous environmental stressors as most of the biological changes occur at proteome level like post translational modifications. A number of laboratories globally are now directing their attention on application of this platform and emerging data is accumulating for biomarker development, studying underlying mechanistic pathways and suitable risk assessment against many toxicants action. Though, toxicoproteomic technology's incessant progress exclusively cannot elucidate the successive steps of pesticide-induced carcinogenesis. Synergistic research efforts comprising the study of metabolic activation of chemicals, genome analysis, mRNA measurements, classical biochemical analysis, and data analysis and classification are a must. Additional modifications of MS/MS with closely integrated multi-dimensional separation schemes will continue to dominate proteomic analysis for identification and quantification and will result in following developments. MS instruments and software will become more user-friendly and accessible, such as the recently introduced orbitrap MS/MS instruments along with the

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"reduction of sample complexity" or any prepurification strategy prior to toxicoproteomics analysis will be very useful upon innovative application to appropriate biological samples and problem areas (i.e., immunodepletion of high abundance proteins like albumin or immune globulins in plasma) or research problem areas (i.e., phosphoprotein enrichment in protein signalling). Likewise, Tier II proteomics will begin to be applied totoxicoproteomics problem areas such as global and targeted protein phosphorylation and chemoproteomics using pharmaceutics or enzyme substrates like ATP as mass capture-ligands for proteins. Similarly, toxicoproteomics is readily positioned to exploit accessible biofluids (i.e., serum/plasma, urine and cerebral spinal fluid) for biomarker development and could be combined with transcriptomic analysis of blood leukocytes for a parallel approach in biomarker discovery and also the incisive use of genetically transformed animals and cell models will improve discovery of protein targets and mechanistic insights into adverse drug reactions. Lastly, continued efforts for integration of proteomics, transcriptomics and toxicology data to derive mechanistic insight and biomarkers will be a continuing goal to maximize return on the investment in Omics technologies. While there are many challenges for toxicoproteomics in preclinical valuation, the chances are also close at hand for a superior understanding of toxicant action, the association to associated dysfunction and pathology, and the growth of predictive biomarkers and signatures of toxicity.