16.1

Mats-Pro: An Integrated Proteomics Data Management System for Neuroscience Research

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Proteomics is a rapidly advancing field and represents data accumulated from many types of experiments, including: 2D gels, HPLC, mass spectrometry and protein arrays. The analysis of protein profiles in biological processes represents a major challenge of the post-genome era. More recently, higher throughput methods such as SELDI-TOF, which can be used to examine un-fractionated and un-purified samples, have also been used to elucidate the proteome of various disease processes. In addition, the technological advances in LC/MS and LC/MS/MS were applied to protein identifications characterizations. The production of such vast amounts of proteomic data requires advance computational and database technologies for storage, integration, management, analysis and visualization of data.

We have developed a MATS-Pro (the Management, Analysis and Tracking System for Proteomics) module as part of our integrated bioinformatics research support and management system that allows scientists to manage, access and analyze data through the life cycle of the research projects and clinical protocols. It is a robust web-based database application using Oracle (10g) as the back-end for management and tracking of proteomics projects including data mining and analysis capabilities to support our intramural neuroscience research through one single user interface. The module is designed to allow our researchers to manage, visualize and analyze SELDI-TOF, LC/MS and LC/MS/MS experiments and data in native data or XML formats. In addition, the proteomics data were integrated with our bioinformatics data management module that contains microarray, SNP, protein and antibody assays and linked to the clinical informatics system that contains protocol and patient information, diagnoses, physiological and lab tests as well as brain imaging data. Moreover, the MATS-Pro module is linked to external resources such as Expasy, Mascot, Uniport and NCBI Entrez. This comprehensive and integrated system including the MATS-Pro module is currently utilized to support complicated clinical trials such as biomarker studies of neurological diseases.

16.2

The Mitochondria and Cancer Detection

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Mitochondrial dysfunction and mutations in mitochondrial DNA (mtDNA) have been frequently reported in cancer, neurodegenerative diseases, diabetes, and aging syndromes. The mitochondrion genome (16.5 Kb) codes only for a small fraction (estimated to be 1%) of the proteins housed within this organelle. Thus, a proteomic approach is needed to fully understand the nature and extent of mutated and modified proteins resident in the mitochondria of cancer cells. Identification of mitochondrial proteins that are aberrantly expressed in cancer cells and other diseases is now possible through recent developments in proteomic and bioinformatics technologies. These developments set the stage for a comprehensive organelle-based proteomic approach for the identification of new markers, for early detection, risk assessment and diagnosis of cancer and other diseases, as well as for the identification of new targets for therapeutic prevention and intervention.

16.3

Profiling Four Homocysteine-Related Enzymes in the NCI60 Human Cancer Cell Lines

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Multiple aberrations in methionine metabolism are a hallmark of cancers. Thus, a majority of cancer cells exhibit a methionine-dependent phenotype whereby they are unable to grow in medium in which methionine is replaced by its precursor, homocysteine. Additionally, CpG island hypermethylation of promoters of tumor suppressor genes is observed in a background of global hypomethylation. Methionine metabolism provides two key cellular reagents: S-adenosylmethionine and glutathione, derived from the common intermediate, homocysteine, through competing transmethylation and transsulfuration pathways. In this study, we have profiled the expression levels of four homocysteine-related enzymes, methionine synthase, methionine synthase reductase cystathionine beta-synthase and cytochrome P450 reductase in the NCI60 cancer cell lines. The doubling time of non-small lung cancer lines which exhibit the lowest levels of methionine synthase within NCI60, was significantly correlated with expression of methionine synthase. The ratio of methionine synthase to methionine synthase reductase varied over a 5-fold range in the different cell type and may modulate methionine synthesis. Interestingly, markedly reduced cystathionine beta-synthase expression was seen in the methionine-dependent phenotype of the prostate cancer cell line, PC-3, but not in the methionine-independent cell line, DU-145. However, provision of the transsulfuration pathway product, cysteine, did not rescue the growth impairment indicating that reduced cystathionine beta-synthase was not responsible for the methionine-dependent phenotype in this cell line. Our studies are consistent with occurrence of complex and multifactorial aberrations in methionine metabolism associated with cancer.