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Application of Omics Technologies to Neural Stem Cell Studies

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Editorial

Neural stem cells (NSCs) are multipotent stem cells that are capable of self-renewal and differentiation into the three major cell types of the central nervous system (CNS): neurons, astrocytes and oligodendrocytes. Since Reynolds et al. [1,2] successfully isolated and propagated neural progenitor cells in vitro in 1992, NSCs have offered perspectives into the mechanisms regulating CNS development in vivo, aided the development of new strategies including transplantation to treat devastating neurological diseases (e.g. Parkinson's disease), and have been used in numerous drug discovery and neurotoxicity studies. These applications require the NSCs to be extensively profiled at the transcriptional, translational, and cellular levels.

Search for Differentially Expressed Genes during NSC Differentiation

It has been demonstrated that the transformation of NSC proliferation to differentiation involves cell autonomous factors [**3**]. Moreover, in vitro studies have demonstrated that NSCs can transform from the proliferating to the differentiating state at any time when the culture environment is altered [**4**], indicating that the process is significantly influenced by microenvironment and that complex interactions between intracellular and intercellular factors play critical roles in determining the fate of NSCs.

The term "omics" generally refers to studies such as genomics, proteomics and metabolomics. DNA microarray technology can simultaneously detect perturbations in tens of thousands of genes in one single experiment. Differences in gene expression profiles between proliferating NSCs and differentiating neural cells have previously been observed [**5**,**6**]. For instance, Gurok et al. [**6**] assessed gene expression changes during neural progenitor cell differentiation and summarized that several categories of genes had significantly changed during differentiation. Notably, genes expressed by neural progenitor cells [e.g. growth factor encoding genes: Hbegf (heparin-binding EGF-like growth factor), Ptn (pleiotrophin), and Nell2 (neural epidermal growth factor-like-like 2)] were down-regulated during differentiation. Similarly, all genes related to DNA synthesis and cell cycle progression were down-regulated, indicating cessation of NSC proliferation after differentiation. Meanwhile, differentiated neurons also lost their proliferation potential and contributed to the down-regulation of genes relevant to DNA synthesis. Other genes that were significantly different after differentiation were related to extracellular matrix components, the tubulin cytoskeleton, ion channels, transporters, and lipoproteins. Although findings from different research groups seem to share few or limited similarities due to various cell culture conditions, differences in cell origins, or even the passage number of cells, each study has revealed genes that are now commonly associated with NSC maintenance, migration or differentiation. Changes in gene expression during the early transition of NSCs from proliferation to differentiation have also been observed [**5**], indicating the unique roles these genes play during proliferation and/or differentiation.

In general, detection of changes in gene expression profiling of NSCs before and after differentiation at the mRNA level using microarray analysis can provide opportunities/platforms toward identifying differentially expressed genes and pathways that regulate/control NSC proliferation and differentiation.

Characterization of Functional Molecules in NSCs Using Proteomics

Although DNA microarray is an efficient tool, mRNA levels do not always parallel protein levels and protein function, since proteins can be chemically modified in various ways/conditions after synthesis. Many dynamically regulated processes within cells also contribute to the inconsistency. Since proteins are the final functional molecules for regulating cell phenotype and fate, proteomics, the study of a cell or an organism's complete complement of proteins, has been actively applied to NSC studies. Proteomic profiling, aiming to identify the main proteins found in a particular sample and proteins differentially expressed in related samples, has been broadly used for comparison of protein expression in NSCs at proliferation and differentiation states. Two-dimensional gel electrophoresis (2-DE) and mass spectrometry (MS) are two technologies that are frequently applied to proteomic profiling, revealing proteins that mediate the intricate process of NSC proliferation and differentiation. In addition, proteomics can help to elucidate many important issues, such as protein stability, subcellular localization, post-translational modifications and protein-protein interactions [**7**]. In searching for critical protein molecules that regulate NSC proliferation and differentiation, a shotgun proteomics study by Abraham et al. [**8**] demonstrated high expression of the High Mobility Group B (HMGB) family in mouse NSCs. This finding was further verified by real-time PCR and immunoblot analyses. The researchers concluded that HMGB chromatin structural proteins were differentially expressed in proliferating and differentiating NSCs, and HMGB may play a regulatory role in NSC processes [**8**]. Melo-Braga and colleagues [**9**] performed a quantitative analysis of the membrane proteome of human embryonic stem cells and NSCs. This most comprehensive study identified several potential cell surface markers for NSCs, which can help distinguish NSCs from embryonic stem cells and improve our understanding on the differentiation process [**9**]. Although various studies indicate differing perspectives, these findings have largely improved our understanding of NSC features.

Identification of Specific Metabolites as NSC Markers

In contrast to DNA microarray and proteomic analyses that directly reveal cellular functions, metabolites are the products of biochemical reactions. The level of each metabolite is a consequence of gene function and specific physiological, developmental, and pathological state of a cell or tissue [**10**]. To understand the complex metabolome data, various analytical strategies have been developed. Metabolomic fingerprinting is used to profile intracellular metabolites of a tissue; while metabolomic footprinting is used to analyze extracellular metabolites in a given sample [**10**]. Application of metabolomics in NSC studies can provide insight into the biochemical transition of NSCs from proliferation to differentiation and identify specific markers. Chung et al. [**11**] profiled the metabolite changes during human NSC differentiation using 1H-magnetic resonance spectroscopy (MRS) and found several metabolites, such as phosphocholine (PC), glycerophosphocholine (GPC) and myo-inositol (mI) to have markedly changed during differentiation; they were higher in NSCs and dramatically decreased upon differentiation. Their data highlighted the possible role of PC, GPC and mI as markers of the NSC state, although it was acknowledged that metabolite profiles can vary at different developmental stages [**11**]. Moreover, metabolites are not only final products of metabolic reactions, but they can also drive stem cell differentiation [**12**]. Previous work has shown that metabolites of embryonic stem cells can promote neurogenesis and cardiogenesis [**12**].

Current Endeavors: Beyond Omics

Better understanding of NSC developmental processes will undoubtedly improve NSC applications related to cell therapy, drug discovery, and safety assessment of drugs. In addition to these omics studies, researchers have been working on developing new models and methods to deepen our understanding of NSCs. Recent emerging cellular microarrays have shown the ability to track NSC developmental processes, quantify NSC marker expression, and explore signals coming from the NSC microenvironment in a high-throughput manner [**13**,**14**]. A three-dimensional (3-D) cellular microarray platform [**14**] has been developed to analyze human NSC growth and differentiation. Using this 3-D platform, human NSCs are grown on a miniaturized cell culture chip for expansion and differentiation. The platform is versatile and can complement the cell culture chip technology with a chamber system for screening differences in toxicities of small molecules [**14**]. This cellular 3-D microarray platform seems to have a promising future in NSC research because it can properly predict in vivo results, maintain the capability for proliferation and differentiation and allow the safety assessment of compounds in a high-throughput manner [**14**].

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References

1. Reynolds BA, W Tetzlaff, S Weiss (1992) A multipotent EGF-responsive striatal embryonic progenitor cell produces neurons and astrocytes. J Neurosci 12: 4565-4574.
2. Reynolds BA, S Weiss (1992) Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 255: 1707-1710.
3. Gilley JA, CP Yang, SG Kernie (2011) Developmental profiling of postnatal dentate gyrus progenitors provides evidence for dynamic cell-autonomous regulation. Hippocampus 21: 33-47.
4. Fritsche E, Kathrin G, Schreiber Timm (2011) Neurospheres as a model for developmental neurotoxicity testing. In Vitro Neurotoxicology.
5. Zhou FC, Duguid JR, Edenberg HJ, McClintick J, Young P, et al. (2001) DNA microarray analysis of differential gene expression of 6-year-old rat neural striatal progenitor cells during early differentiation. Restor Neurol Neurosci 18: 95-104.
6. Gurok U, Steinhoff C, Lipkowitz B, Ropers HH, Scharff C, et al. (2004) Gene expression changes in the course of neural progenitor cell differentiation. J Neurosci 24: 5982-6002.
7. Hoffrogge R, Beyer S, Völker U, Uhrmacher AM, Rolfs A (2006) 2-DE proteomic profiling of neuronal stem cells. Neurodegener Dis 3: 112-121.
8. Abraham AB, Bronstein R, Chen EI, Koller A, Ronfani L (2013) Members of the high mobility group B protein family are dynamically expressed in embryonic neural stem cells. Proteome Sci 11: 18.
9. Melo-Braga MN, Schulz M, Liu Q, Swistowski A, Palmisano G, et al. (2014) Comprehensive quantitative comparison of the membrane proteome, phosphoproteome, and sialiome of human embryonic and neural stem cells. Mol Cell Proteomics 13: 311-328.
10. Maletić-Savatić M, Vingara LK, Manganas LN, Li Y, Zhang S, et al. (2008) Metabolomics of neural progenitor cells: a novel approach to biomarker discovery. Cold Spring Harb Symp Quant Biol 73: 389-401.
11. Chung YL, El Akabawy G, So PW, Solanky BS, Leach MO, et al. (2013) Profiling metabolite changes in the neuronal differentiation of human striatal neural stem cells using 1H-magnetic resonance spectroscopy. Neuroreport 24: 1035-1040.
12. Yanes O, Clark J, Wong DM, Patti GJ, Sánchez-Ruiz A, et al. (2010) Metabolic oxidation regulates embryonic stem cell differentiation. Nat Chem Biol 6: 411-417.
13. Fernandes TG, Diogo MM, Clark DS, Dordick JS, Cabral JM (2009) High-throughput cellular microarray platforms: applications in drug discovery, toxicology and stem cell research. Trends Biotechnol 27: 342-349.
14. Meli L, Barbosa HS, Hickey AM, Gasimli L, Nierode G, et al. (2014) Three dimensional cellular microarray platform for human neural stem cell differentiation and toxicology. Stem Cell Res 13: 36-47.