NIH Public Access

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Biol Psychiatry. Author manuscript; available in PMC 2015 January 22.

Published in final edited form as:
Biol Psychiatry. 2014 June 15; 75(12): 918–919. doi:10.1016/j.biopsych.2014.03.025.

Human stem cells and surrogate tissues for basic and translational study of mental disorders

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The mechanisms underlying the complex, multifactorial nature of psychiatric disorders or conditions has eluded researchers for decades (1). While there are rare familial cases that appear to involve defined, highly penetrant genetic mutations, the majority of cases are sporadic and polygenic. To further complicate the etiological architecture, environmental interactions with genotype appear to influence the phenotype. The polygenic basis of psychiatric conditions limits the usefulness of genetic mouse models, which are often used to model known mutations. While the recently introduced Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) system may allow efficient mutation of genes at multiple sites (2), it still depends on a prior understanding of specific mutations involved. In contrast, human cells and biospecimens may offer advantages over animal models in studying the biology underlying psychiatric conditions at the molecular level, as they are likely to reflect patient-derived genetic architectures. There are several types of human biospecimens that can be used for research: (i) postmortem brains, (ii) surrogate tissues obtained from biopsy, such as blood, cerebrospinal fluid and olfactory tissues, and (iii) recently developed genetically engineered cells, which include induced pluripotent stem cells (iPS cells), induced neuronal cells (iN cells) and induced neural progenitor cells. These different types of samples can complement each other, and the advantages and limitations of each are described below (Table 1).

Human postmortem brains have been used as an important resource to study neuropsychiatric conditions, as brain biopsies are normally unattainable. Nonetheless, the limitations associated with these samples are widely understood. For example, disease-associated pathological changes, particularly those during early neurodevelopment, may not be captured or may even be masked by compensatory changes over the lifetime. In addition, there are effects of chronic medications and substance abuse, as well as postmortem changes to the tissue. Functional assays, particularly those involving stress response, cannot be addressed in the postmortem tissue. However, postmortem brains can provide us with indispensable information on brain area-specific biological and molecular signatures, especially disease-associated epigenetic modifications. Comparison of such changes among postmortem brain, surrogate tissues and genetically engineered cells (e.g., iPS cells) is also important. In this issue, Mitchell et al. (3) cover this topic, together with their efforts to

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Financial disclosures
Drs. Gamo and Sawa report no biomedical financial interests or potential conflicts of interest.

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establish protocols for capturing chromosomal conformation that reflects genomic and epigenetic predisposition to disease.

Surrogate tissues, such as blood cells, offer the advantage that they are generally easily accessible, and thus, can be obtained live across different time points of a disease, collected from a large number of patients, and are suitable for high-throughput assays. Blood lymphoblasts, in particular, are well suited to experimentation, as they are widely banked. However, peripheral cells do not necessarily express neuronal phenotypes. Olfactory cells obtained via nasal biopsy are expected to be particularly useful as surrogate tissues in this context: a recent report has indicated that olfactory cells show contrasting gene expression profiles to blood cells, but much closer profiles to those of stem cells and brain tissues (4). In this issue, Hayashi-Takagi et al. (5) discuss the advantages and limitations of using blood samples for the study of major mental illnesses.

Genetically engineered cells have recently created excitement in the field, as they offer an opportunity to investigate patient-specific neuronal mechanisms that reflect complex genetic architectures of each individual. Somatic cells can be reprogrammed, or converted by transcription factors, into iPS cells, iN cells or induced neural progenitor cells. Brennand et al. (6) discuss the use of iPS cells to study cellular mechanisms underlying neuropsychiatric conditions. Recent advances in reprogramming methods, such as episomal plasmids and Sendai virus, provide safer strategies than viral constructs that integrate into the host genome and, in turn, cause unexpected phenotypes and tumor formation when implanted. In addition, iPS cells offer the advantage of being able to differentiate into many types of cells in the central nervous system, including different subtypes of neurons (e.g., dopaminergic and GABAergic neurons), and recapitulating neurodevelopmental processes in either monolayer or organoid culture *in vitro*, or when implanted in rodent brains *in vivo*. However, generating iPS cells is laborious and expensive, and it can take many months for iPS cell-derived neurons to functionally mature. Even if they form synapses, whether they can capture the experience-dependent shaping of neuronal networks is questionable. Thus, a complementary design that combines surrogate tissues and animal models is encouraged to verify mechanisms *in vivo*.

iN cells are directly converted from skin fibroblasts, bypassing a stem cell stage to generate neuronal cells. Qiang et al. (7) further discuss the advantages of these cells compared to iPS cells, such as a simpler procedure to generate them, with the potential to avoid intra-subject variability and tumerogenicity. As synaptic formation among iN cells is difficult to establish, these cells may be used to study traits relevant to postmitotic neurons, for example, ion channels and misfolded proteins. However, iN cells cannot be expanded, which limits the number of cells that can be generated. Thus, induced neural progenitor cells may be a promising alternative to complement this limitation.

In future, these new technologies are expected to further illuminate our understanding of the biology underlying psychiatric conditions. The use of small molecule probes in highthroughput screens using iPS cell-derived cells may aid the understanding of diseaseassociated mechanisms, and Haggarty et al. (8) point towards potential therapeutic applications. These cell engineering techniques may also be expanded to other primate

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species, which would offer insights into uniquely human diseases. Hrvoj-Mihic et al. (9) introduce the study of iPS cell-derived cortical pyramidal neurons across several primate species to understand the evolution of the human brain. This topic is particularly relevant, as the prefrontal cortex, which plays a key role in psychiatric conditions, is highly evolved in primates. The utility of these cellular disease models will eventually be revealed by how well they predict patient symptoms, endophenotypes and treatment response.

Acknowledgments

Dr. Gamo was supported by 5T32MH15330-35 from NIMH. Dr. Sawa was supported by MH-084018, MH-094268 Silvo O. Conte Center, MH-069853, MH-085226, MH-088753 and MH-092443 from NIMH, as well as grants from Stanley Foundation, S&R Foundation, RUSK, NARSAD and MSCRF.

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Table 1

Comparison of the characteristics of human cells used in research.

	Key advantages	Key disadvantages
Postmortem brains	• Show brain region-specific disease signatures, including epigenetic changes	• Brain signatures may be confounded by compensatory changes, medications, substance abuse and postmortem changes • Cannot perform functional assays
Blood cells	• Easy to collect • Lymphoblasts are widely banked and are expandable	• May not show neuronal phenotypes
Olfactory cells	• Can establish neurons without reprogramming via exogenous factors • Can perform functional assays	• May not show exact brain phenotypes
iPS cells	• Recapitulate developmental trajectory while being differentiated into neurons • Can perform functional assays • Expandable	• Laborious and expensive to generate • Need to reprogram cells via exogenous factors
iN cells	• Faster and easier to generate neurons than via iPS cells • Can perform functional assays	• Need to reprogram cells via exogenous factors • Not expandable
Induced neural progenitor cells	• Faster and easier to generate neurons than via iPS cells • Can perform functional assays • Expandable	• Need to reprogram cells via exogenous factors