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Hypothesis

Chromatin from Peripheral Blood Monon as Biomarkers for Epigenetic Abnormali Schizophrenia

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Abstract

Background. Studies have implicated abnormalities in epigenetic hypothesize that identifying abnormalities in chromatin structure mononuclear cells (PBMC) from schizophrenia patients could (a) h and (b) lead to targeted pharmacological interventions. *Testir* symptoms, demographics, hormonal fluctuations, substance abus illnesses, and epigenetic parameters in PBMC. In addition, exam stabilizers, as well as experimental agents both as clinically prescr effects of these agents on chromatin. *Implications*. If PBMC cou mechanisms then this could lead to a "biomarker" approac schizophrenia. This approach may provide an informed metho psychiatric disorders.

1. Background

Chromatin conformation regulates the access and attachment repressors) to gene promoters. Deacetylation of histones, cataly enzymes, dimethylation of lysine 9 of histone 3 (H3K9me2), a methyltransferase (DNMT) family of enzymes, are several exa restrictive chromatin state both site specifically and globally [1], gene regulation. Because chromatin “plasticity’’ can be modifie to the regulation of gene expression in clinical populations is possi

Increasing evidence indicates the existence of epigenetic gene r supporting this hypothesis includes studies in which mice administ endophenotypes of schizophrenia [2], as well as studies using schizophrenia candidate genes the 67 kDa isoform of glutamic ac through epigenetic mechanisms [3–5]. Several postmortem studie repressive enzymes including DNMT1 and HDAC1 in schizop abnormalities in the coordination of repressive processes [9]. Final (PBMC) from human subjects have found reduced levels of the “ schizophrenia patients compared to nonpsychiatric controls or “closed’’ chromatin mark H3K9me2 compared to controls [12] using HDAC inhibitors both as clinically administered [13] as well a

2. Presentation of the Hypothesis

2.1. Understanding Epigenetic Gene Regulatory Abnormaliti PBMC

Unlike many illnesses in which investigators and clinicians are c afflicted patient is still alive, psychiatry is limited by the inac representing the higher order cognitive dysfunctions present in s impossible. Therefore, there exists a long history of searching pathology within the brain. There are several factors which make epigenetic gene regulation in the brain.

Firstly, previous studies have demonstrated that PBMC can pro environment/life experiences on chromatin structure and DNA epigenetic parameters in lymphocytes from monozygotic twins at while 3-year-old twins are virtually indistinguishable in terms of histone 3, and acetylated histone 4, 50-year-old twins had signi older twins had greater differences in terms of epigenetic paramet to note that these differences were consistent in subjects across a epigenetic parameters in lymphocytes are a reliable method for as that chromatin from lymphocytes may provide a “molecula environment, life experience, and stochastic factors which would n

Secondly, the analysis of gene regulation in nucleated blood cells their disorder, including response to pharmacological, metabolic approach for prospective longitudinal clinical research, and appe postmortem brain studies**.** This is because PBMC share much of th such as neurohormones, neuropeptides, chemo/cytokines, metal epigenetically relevant substances present in the blood that are methionine, which both worsens psychosis in schizophrenia and a homocysteine, which has been found to be elevated in the plasma the DNA methyl donor S-adenosylmethionine [17–20], and valpr significantly alter global chromatin structure in a dose dependent n

Finally, PBMC contain the full complement of epigenetic enzymes a
neurons and peripheral nucleated cells [21, 22]. Previous studies
overall abnormalities in epigenetic mechanisms also thought to b
disease, a disorder known to be associated with dysfunctions
transcriptional repression across several chromosomes was found
shown that peripheral markers are able to discern differences in
illness [24–26], as well as show similarities in epigenetic parame
[24, 25].

Although, PBMC may be capable of reflecting overall changes in ep
for studying brain-specific processes such as synaptic plasticity a
one gene at a particular time in a PBMC may not be reflective of th
the expression of a particular gene in a pyramidal cell at a given t
or glial cell. In addition, there are some disorders in which abnor
example, cancer cells have particular abnormalities that one woul
schizophrenia is characterized by brain-specific chromatin alterati
PBMC. Also, global DNA methylation tissue patterns have been fou
28]. However, the differences between individuals or diagnostic
found to be present across tissues [23].

We now hypothesize that PBMC may be capable of reflecting th
provide a means for discerning those subsets of schizophrenia
chromatin structure or DNA methylation. It may also help unde
drugs of abuse on chromatin. Finally, it could provide a tool to bot
agents as well as identify patients most likely to benefit from these

There is now a growing literature to support the idea that PBMC
epigenetic machinery within an individual. In a previous study we
for four weeks with the only HDAC inhibitor approved for psychiatr
was shown to increase GAD67 mRNA expression in the brain [2]
serum levels of VPA there was a significant increase in GAD67 mR
at the time that chromatin in PBMC from schizophrenia subjects w
confirmed when it was noted that there was less of an increas
histones 3 and 4 in schizophrenia subjects [13]. However, unexpe
subjects had significantly lower levels of acetylated histone 3 com
associations with these measures of chromatin state and sympto
subjects with higher baseline Young Mania Rating Scale (YMRS) sc
show greater increases in acetylated histone 3 after four weeks of
baseline acetylated 3 levels showed greater improvement on the
Syndrome Scale (PANSS). In other words, those subjects who ha
alter their chromatin in response to VPA, and those subjects with
to respond favorably to VPA treatment [11].

As a consequence of these studies it was decided to attempt to p
model held several advantages relative to clinical treatment using
PBMC are protected from unforeseeable or undisclosed change
noncompliance, substance use, environmental exposures such a
differences in metabolism of HDAC inhibitors. Further, the in vivo
known chromatin altering drug approved for use in psychiatric pa
altering medications to nonpsychiatric controls would not be ethica

Similar to the previous studies in which systemic administrati
expression in human PBMC and in brains from mice, we found com

cultured with equivalent doses of VPA [11]. Also in keeping with t to have an abnormally restrictive chromatin state as indicated b levels of the "closed" chromatin mark, H3K9me2 [10, 12]. Mo demonstrating the lack of "plasticity" in schizophrenia chromat we found less change in GAD67 mRNA expression, H3K9me2 level with an HDAC inhibitor compared to nonpsychiatric controls [10, 1 of onset had higher levels of H3K9me2 [12].

3. Testing the Hypothesis

One means of testing the impact of particular environmental fac substances such as hormones, medications, or drugs of abuse and structure. These findings could then be evaluated in light of find example, recent epidemiological evidence indicates that women ma data from PBMC cultures reveal sex differences in the ability of Therefore, it is a reasonable hypothesis that female sex horm schizophrenia risk through their ability to alter chromatin. The imp be tested by culturing PBMC with estrogen, progesterone, or testos be compared to chromatin from animal and postmortem studies to tissues.

In addition, extensive studies could be conducted both in vivo and schizophrenia or characteristics of schizophrenia are associated w An examination of baseline levels of epigenetic parameters, such epigenetic enzyme expression could be conducted using samp abnormalities exist. Previous studies indicate abnormalities i schizophrenia [9–11, 13]. Chromatin altering medications could b cultured with their PBMC as molecular probes into this system. altering agent clinically approved in psychiatry, this greatly limits t of determining those schizophrenia patients with abnormalities in e from the culture could be used to select subjects most likely established using in vitro methods, clinical trials could be impleme epigenetic mechanisms could be treated with agents aimed at norm

4. Implications of the Hypothesis

If PBMC, whether exposed to chromatin altering medications as c could serve as a reliable model of overall epigenetic mechanisms, revealing pathological chromatin state in schizophrenia. This appr reaction of a subject's chromatin to medications prior to clinical method for selecting psychiatric medications for certain disorders. with symptoms and disease characteristics could lead to a better u potential for improved diagnostic validity more informed by a patie

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