Early-life disruption of epigenetic marks may contribute to the origins of mental illness

Epigenetic marks, including DNA methylation (DNAm), histone modifications and small inhibitory RNAs, are heritable and provide critical layers of gene regulatory control; however, they also are dynamic and can be influenced by environmental exposures [1–3]. Studies primarily focused on cancer and late-onset diseases have revealed that a growing number of human diseases are linked to epigenetic disruptions. For example, DNAm became a hallmark of human cancer, a link that was first recognized in 1983, when tumor cells were found to be aberrantly methylated compared with their normal cell counterparts due to a loss of methylation from repetitive regions of the genome [4]. Together with the finding that healthy monozygotic twins show indistinguishable childhood DNAm [5], epigenetic mechanisms have long been thought to be highly coordinated throughout early development and more susceptible to drift in adulthood. In this article, we will discuss the impact that recent findings, of dramatic DNAm changes throughout childhood, will have on future epigenetic studies conducted in children and adults.

“Knowing the complete repertoire of effects that early-life adversity has on epigenetic marks will improve an individual’s prognosis, diagnosis and treatment...”

DNAm is the best understood epigenetic modification and it primarily occurs at cytosines located 5’ to guanines in CpG dinucleotides of differentiated eukaryotic cells [6]. This modification is less common in CpG-rich areas, known as CpG islands, which are often located in the promoter regions of many genes and function to repress transcription. In addition, DNAm plays a key role in chromatin structure, chromosome stability, genomic imprinting and the maintenance of the inactive X chromosome in females. DNAm has long been considered a stable epigenetic mark; however, molecular evidence indicates that it can vary during embryogenesis, the establishment of X inactivation and in stem cell lineage formation. To study ‘normal’ DNAm variation early in life, we examined nearly half a million CpG dinucleotides throughout the genomes of almost 400 boys aged 3–17 years and found significant changes in DNAm at nearly 10% of loci throughout the genome [7]. A preference for specific nucleotides immediately surrounding the interrogated CpG dinucleotide suggested that these changes are not stochastic, which was also evident by their primary association with developmental and immune ontological functions. Indeed, these are biologically relevant activities for this developmental period. Finally, these studies revealed a significant overlap between the pediatric age-associated loci and previously identified adult loci; however, the pediatric loci were changing at a much faster rate (three- to five-times), indicating a more robust age-associated DNAm variation in children than adults. These data challenge the dogma regarding the susceptibility of DNAm to drift throughout life, suggesting it is even more susceptible during early-life development, which may contribute to disease in children as well as adults.

Changes in DNAm during early childhood could partially explain the discordance of psychiatric disease in monozygotic twins. Despite their identical genomes, the development of mental illness varies between twin pairs, resulting in the following concordance rates: 37% for depression; 40% for bipolar disorder; 50% for schizophrenia; and up to 80% for attention deficit hyperactivity disorder [8–11]. Moreover, numerous groups have shown that early diagnosis and treatment of children with attention deficit hyperactivity disorder and autism has...
profound effects on improving their outcome and quality of life. Thus, it is of great interest to
determine the epigenetic marks associated with
these diseases, and the environmental factors
that cause them to vary, which could dramati-
cally advance our diagnostic ability and poten-
tially lead to the development of therapies aimed
to prevent these modifications.

Studies in animal models often provide clues
to improve our understanding of the effects of
early-life adversity. One such study revealed
that maternal grooming in rodents was inversely cor-
related with the DNAm level at the promoter
of the glucocorticoid receptor gene, \textit{NR3CI},
resulting in altered \textit{NR3CI} expression levels
[12]. A consistent finding was shown in humans
when suicide victims with a history of abuse or
neglect have a similar relationship between life
experiences, DNAm and \textit{NR3CI} expression lev-
els [13]. These data shed light on the potential
role of DNA methylation in the development of
pediatric disorders such as depression, suggesting
that changes in DNAm are established presym-
ptomatically due to early-life adversity. Knowing
the complete repertoire of effects that early-life
adversity has on epigenetic marks will improve
an individual’s prognosis, diagnosis and treat-
ment, all of which are in need of advancement
in the field of psychiatry.

“schizophrenia is a neurodevelopmental
disorder and ... epigenetic marks established
early in life could provide a blueprint towards
its pathogenesis.”

Schizophrenia, which also presents later in
life, may have a similar etiology that is initi-
ated by perinatal insults, resulting in deficits
in cortical maturation during childhood and adolescence [14]. Consistent with this notion,
the \textit{RELN} gene, which encodes a protein
involved in long-term memory formation, has
increased DNAm and reduced expression in
schizophrenic patients [15]. In addition, while
increased DNAm of the \textit{GAD1} promoter results
in decreased expression of \textit{GAD1} in cortical tis-
sues, reduced DNAm at the catechol-\textit{O}-methyl-
transferase promoter contributes to alterations
of the GABAergic circuitry [16]. Together, these
findings are cultivating a perception that schizo-
phrenia is a neurodevelopmental disorder and
that epigenetic marks established early in life
could provide a blueprint towards its patho-
genesis. Consistent with this perception, a recent
study found that the promoter region of \textit{\alpha-N}-
acetylgalactosaminide \textit{\alpha-2,6-sialytransferase 1}
was significantly differentially methylated in the
peripheral blood of monozygotic twins discord-
ant for schizophrenia and bipolar disorder [17].
Future studies that determine the developmental
timing of these changes (i.e., presymptomati-
cally and/or during childhood) will direct the
diagnosis and treatment of these patients in the
coming years.

“...the likelihood of finding markers for early
detection and diagnosis of molecularly less
well-defined diseases seems within
our reach.”

Finding roles for epigenetics in neuro-
psychiatric disease may reveal novel pathways for
therapeutic drug development, primarily taking
advantage of the fact that epigenetic modifica-
tions are reversible. For example DNA methyl-
transferase inhibitors such as 5-azacytidine
reverse the hypermethylated marks at the \textit{RELN}
promoter \textit{in vitro}, producing a 60-fold increase
in \textit{RELN} mRNA levels [18]. Valproic acid, which
is commonly used to treat bipolar disorder, has
histone deacetylase inhibitor properties and has
been shown to increase the expression of \textit{RELN}
and \textit{GADI} in animal models [19]. Clearly these
data suggest that molecular management of epi-
genetics marks associated with neuropsychiatric
disorders has extreme therapeutic potential.

Epigenetics marks are used as biomarkers
to molecularly diagnose diseases associated
with disruption in genomic imprinting (e.g.,
Beckwith–Wiedemann syndrome), an approach
that also could be adapted for psychiatric dis-
orders. Since current psychiatric diagnoses are
based on subjective criteria from the diagnos-
tic and statistical manual [20], development of
a less subjective tool is of great interest. Several
groups have begun to explore these options and
have had limited success in finding biological
correlates for diseases such as depression, schizo-
phrenia and bipolar disorder [21]. By contrast,
a promising study recently found blood based
biomarkers associated with Alzheimer’s disease
and standardized tests for these marks are cur-
rently under development [22]. As our under-
standing of epigenetic associations with disease
improves, the likelihood of finding markers for
early detection and diagnosis of molecularly less
well-defined diseases seems within our reach.

Armed with the knowledge that epigenetic
marks are susceptible to change early in life and
throughout childhood, research can now focus
on earlier molecular origins of mental illness.
These studies may begin to discover marks that
Early-life disruption of epigenetic marks may contribute to the origins of mental illness

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

