Out of Synch:

Targeted Therapies Based on Desynchronization of the Prefrontal Cortex as an Epigenetic Model for Cognitive Deficits in Schizophrenia

By Julian Szieff
Presentation Overview

- Schizophrenia Overview
- Role of the Prefrontal Cortex in Cognitive Functions
- Epigenetic Overview
- Epigenetic Dysregulation in Schizophrenia
  - Role of GAD1 and RELN in Deficits of GABA inhibition
- Enzyme Targets for Epigenetic Restoration
  - Enzyme Inhibitors as Treatments for Cognitive Deficits
- Future Research Directions
- Real-World Context
Symptoms of Schizophrenia

Positive Symptoms:
Hallucinations, Delusions
Symptoms of Schizophrenia

**Positive Symptoms:**
- Hallucinations,
- Delusions

**Negative Symptoms:**
- Depression,
- Lack of Energy and/or Motivation
Symptoms of Schizophrenia

Positive Symptoms: Hallucinations, Delusions

Negative Symptoms: Depression, Lack of Energy and/or Motivation

Cognitive Symptoms: Deficits in Attention, Concentration, Memory
Symptoms of Schizophrenia

- Positive Symptoms
- Negative Symptoms
- Cognitive Symptoms
Symptoms of Schizophrenia
Cognitive Functioning

Cognitive Deficits → Social Outcomes
Cognitive Functioning

Schizophrenia Drugs

Cognitive Deficits

Social Outcomes
Prefrontal Cortex Role in Cognitive Function

Made up of...

- Pyramidal cells (in green)
- Basket Cells (in red)

https://www.janelia.org/lab/spruston-lab/research
Prefrontal Cortex Role in Cognitive Function

- Basket Cells synapse with a localized group of pyramidal neurons.
- They release GABA, a neurotransmitter which inhibits the pyramidal neurons.

https://www.janelia.org/lab/spruston-lab/research
Prefrontal Cortex Role in Cognitive Function

- Basket Cells act as “starting gun” to synchronize the firing of pyramidal neurons

https://pxhere.com/en/photo/869535
DNA as a Blueprint

[Diagram of a blueprint house plan]

Building

Expression

DNA

Protein


https://www.advancedhouseplans.com/collections/1-story-house-plans
DNA as a Blueprint

Building Committee

Epigenetics

DNA  Protein

https://www.advancedhouseplans.com/collections/1-story-house-plans
Epigenetic Dysregulation in Schizophrenia

methylation and acetylation


Epigenetic Dysregulation in Schizophrenia

Techniques:

1. Bisulfite sequencing
2. Chromatin immunoprecipitation

https://en.wikipedia.org/wiki/Prefrontal_cortex#/media/File:Prefrontal_cortex_(left)_-_lateral_view.png
Epigenetic Dysregulation in Schizophrenia

https://en.wikipedia.org/wiki/Police_lineup
Epigenetic Dysregulation in Schizophrenia

GABA

GAD1

RELN

https://en.wikipedia.org/wiki/Police_lineup
Epigenetic Dysregulation in Schizophrenia

**GAD1**: Encodes Glutamate Decarboxylase, a protein which catalyzes the conversion of Glutamate to GABA
Epigenetic Dysregulation in Schizophrenia

**RELN**: Encodes an extracellular protein which guides GABA neurons to connect properly during gestation.
Epigenetic Modifications of *RELN*

(Grayson et al., 2005)
Modifications of \textit{GAD1}

(Modified from Tang et al., 2011)
Epigenetic Modifications of **GAD1**

GAD1 Protein Level

(Modified from Curley and Lewis, 2012)
Effect of Epigenetic Dysregulation

GABA -> Desynchronization -> Cognitive Deficits

GAD1, RELN
Effect of Epigenetic Dysregulation

How do we increase GABA production to decrease cognitive deficits?

GABA → Desynchronization → Cognitive Deficits
Mechanisms for Treatments

2 Mechanisms

Decrease Methylation of Gene Promoters

Increase Acetylation of Gene Promoters

Goal

GABA production
Targets for Treatment

<table>
<thead>
<tr>
<th>Enzyme Name</th>
<th>DNA Methyltransferase (DNMT)</th>
<th>Histone Deacetylase (HDAC)</th>
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<tbody>
<tr>
<td>Enzyme Function</td>
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GABA production
Inhibiting Enzyme Targets

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<td><img src="false" alt="Inhibition Arrow" /></td>
<td><img src="false" alt="Inhibition Arrow" /></td>
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<tr>
<td>Lack of Enzyme Function</td>
<td>Methylation</td>
<td>Acetylation</td>
</tr>
<tr>
<td><img src="false" alt="Up Arrow" /></td>
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DNMT1 Binds to GAD1 and RELN In Schizophrenia

DNMT is more frequently bound to GAD1 and RELN promoter in Schizophrenia

(Modified from Dong et al., 2015)
MBD2 is also frequently bound to GAD1 and RELN promoter in Schizophrenia.

(Modified from Dong et al., 2015)
Multiple Enzymes Make a Repressor Complex

DNMT forms part of a repressor complex.

(Dong et al., 2015)
DNMT1 Inhibitor Decreases RELN and GAD1 Methylation

DNMT inhibitors decrease the methylation % of the gene promoter

(Modified from Kundakovic et al., 2009)
Combining a HDAC1 inhibitor and the anti-psychotic, clozapine decreases the methylation % of the gene promoter

White: Control
Black: HDAC inhibitor
Grey: Anti-psychotic
Striped: HDAC inhibitor and anti-psychotic

(Dong et al., 2008)
Both the DNMT inhibitor and the HDAC inhibitor are hypothesized to inhibit the repressor complex.

(Dong et al., 2015)
Future Research Directions

What is the effect of *GAD1* methylation?

- Conflicting research
Future Research Directions

What is the effect of \textit{GAD1} methylation?

- Conflicting research

Do HDAC or DNMT inhibitors work better together or alone?
Future Research Directions

What is the effect of $GAD1$ methylation?
- Conflicting research

Do **HDAC** or **DNMT** inhibitors work better together or alone?

Side effects?
- Short term or Long term
- Carcinogenic Effects
Larger Context

1. HDAC inhibitors
   +
   DNMT inhibitors
   +
   Antipsychotics

- Currently in clinical trials and partial implementation

Better Schizophrenia Treatment
Reintegration of schizophrenia patients into their communities

http://www.clipartpanda.com/categories/community-clip-art-free
Thank You:
Fernan, Raka, The Biology Department, My Parents, My Friends, All my science teachers over the years, and everyone who came today

Questions?