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Fluoxetine as an Anti-Inflammatory Therapy in SARS-CoV-2 Infection - Protocol v1.1

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1 Works for me dx.doi.org/10.17504/protocols.io.bscjnaun

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SUBMIT TO PLOS ONE

ABSTRACT

Hyperinflammatory response caused by infections such as Severe Acute Respiratory SyndromeCoronavirus 2 (SARS-CoV-2) increase organ failure, intensive care unit admission, and mortality. Cytokine storm inpatients with Coronavirus Disease 2019(COVID-19) drives this pattern of poor clinical outcomes and is dependent upon the activity of the transcription factor complex nuclear factor kappa-light-chain-enhancer of activated B cells(NF-κB) and its downstream target gene interleukin 6 (IL6). In this study, we compare transcriptomic signatures from a variety of drug-treated or genetically suppressed (i.e.knockdown) cell lines in order to identify a mechanism by which antidepressants such as fluoxetine demonstrate non-serotonergic anti-inflammatory effects. Our results demonstrate a critical role for the IL6 signal transduction protein(IL6ST or gp130) in fluoxetine's ability to act as a potential therapy for hyperinflammatory states such as asthma and sepsis.

THIS PROTOCOL ACCOMPANIES THE FOLLOWING PUBLICATION

Creeden, Justin and Imami, Ali Sajid and Eby, Hunter M. and Gillman, Cassidy and Becker, Kathryn N. and Reigle, Jim and Andari, Elissar and Pan, Zhixing K. and O'Donovan, Sinead M. and McCullumsmith, Robert E. and McCullumsmith, Cheryl B., Fluoxetine as an Anti-Inflammatory Therapy in SARS-CoV-2 Infection. Available at SSRN: https://ssrn.com/abstract=3736012 or http://dx.doi.org/10.2139/ssrn.3736012

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PROTOCOL CITATION

Justin Fortune Creeden, Ali Sajid Imami, Hunter M. Eby, Cassidy Gillman, Kathryn N. Becker, Jim Reigle, Elissar Andari, Zhixing K Pan, Sinead M O'Donovan, Robert E McCullumsmith, Cheryl B McCullumsmith 2021. Fluoxetine as an Anti-Inflammatory Therapy in SARS-CoV-2 Infection - Protocol v1.1. **protocols.io** https://dx.doi.org/10.17504/protocols.io.bscjnaun

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KEYWORDS

iLINCS, LINCS, Drug Repurposing, Bioinformatics

IMAGE ATTRIBUTION

Thumbnail Designed by Justin Fortune Creeden

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GUIDELINES

Please ensure that you have the appropriate amount of time, computational resources and access before executing this workflow.

MATERIALS TEXT

R programming language 3.3.3 of later
source by The R Foundation

R Studio Desktop 1.1.463
by The R Studio, Inc.

ssri_il6 1.1
source by Ali Sajid Imami, Justin Fortune Creeden

iLINCS

SAFETY WARNINGS

Citation: Justin Fortune Creeden, Ali Sajid Imami, Hunter M. Eby, Cassidy Gillman, Kathryn N. Becker, Jim Reigle, Elissar Andari, Zhixing K Pan, Sinead M OÃ¢ÂÂDonovan, Robert E McCullumsmith, Cheryl B McCullumsmith (02/11/2021). Fluoxetine as an Anti-Inflammatory Therapy in SARS-CoV-2 Infection - Protocol v1.1. https://dx.doi.org/10.17504/protocols.io.bscjnaun

No Applicable Warnings.

BEFORE STARTING

Please ensure that you have the following tools installed:

1. R v 3.6 or later
2. RStudio v 1.2 or later
3. Rtools appropriate to the version of R if using Windows
4. Command Line Tools with XCode if working on macos

Follow the instructions on the README for running.

Workflow

1 Identify Drug Signatures

We searched iLINCS for the L1000 drug signatures for Fluoxetine, Paroxetine, Bupropion and Dexamethasone.

Fluoxetine Signature List

Paroxetine Signature List

Dexamethasone Signature List

Bupropion Signature List

curate_signature.R v1.1

source by Ali Sajid Imami, Justin Fortune Creeden

2 Download Drug Signatures

We downloaded all the 436 identified signatures for further processing.

Citation: Justin Fortune Creeden, Ali Sajid Imami, Hunter M. Eby, Cassidy Gillman, Kathryn N. Becker, Jim Reigle, Elissar Andari, Zhixing K Pan, Sinead M OÃ¢ÂÂDonovan, Robert E McCullumsmith, Cheryl B McCullumsmith (02/11/2021). Fluoxetine as an Anti-Inflammatory Therapy in SARS-CoV-2 Infection - Protocol v1.1. https://dx.doi.org/10.17504/protocols.io.bscjnaun

Signature To Drug Mapping

process_signatures.R v1.1
source by Ali Sajid Imami, Justin Fortune Creeden

Downloaded L1000 Signatures

3 Generating High Confidence Signatures

We filtered all signatures to keep only the genes that had a Log_2 Fold Change value greater than 0.85 or less than -0.85 to generate a high confidence signature

process_signatures.R v1.1
source by Ali Sajid Imami, Justin Fortune Creeden

Filtered L1000 Signatures

4 Identifying Concordant Signatures

The generated high confidence signatures were uploaded to iLINCS and searched against the Consensus Gene Knockdown Signature database for concordance against 27 inflammation related genes.

process_signatures.R v1.1
source by Ali Sajid Imami, Justin Fortune Creeden

Concordant Gene Knockdown Signature List

Citation: Justin Fortune Creeden, Ali Sajid Imami, Hunter M. Eby, Cassidy Gillman, Kathryn N. Becker, Jim Reigle, Elissar Andari, Zhixing K Pan, Sinead M OÃ¢ÂÂDonovan, Robert E McCullumsmith, Cheryl B McCullumsmith (02/11/2021). Fluoxetine as an Anti-Inflammatory Therapy in SARS-CoV-2 Infection - Protocol v1.1. https://dx.doi.org/10.17504/protocols.io.bscjnaun

5 Cell Line Matching

The resulting list of concordant signatures was matched with the list of input signatures and only those signatures were kept that had the input and concordant signature in the same cell line. This resulted in 779 total signatures.

analyse_data.R v1.1
source by Ali Sajid Imami, Justin Fortune Creeden

Cell Line Matched Concordance Scores

6 Maximising Absolute Concordance

The list of 779 total signatures was further simplified by only keeping the match with the maximum absolute concordance score in a given combination of drug, gene and cell line. This reduced the list of signatures to 395.

analyse_data.R v1.1
source by Ali Sajid Imami, Justin Fortune Creeden

Cell Line Matched Maximum Absolute Concordance Scores

7 Summarising Concordance

The concordance scores were then further summarised by calculating an arithmetic mean of the concordance scores across multiple cell lines for the same drug-gene combination.

analyse_data.R v1.1
source by Ali Sajid Imami, Justin Fortune Creeden

Averaged Concordance Scores

Citation: Justin Fortune Creeden, Ali Sajid Imami, Hunter M. Eby, Cassidy Gillman, Kathryn N. Becker, Jim Reigle, Elissar Andari, Zhixing K Pan, Sinead M OÃ¢ÂÂDonovan, Robert E McCullumsmith, Cheryl B McCullumsmith (02/11/2021). Fluoxetine as an Anti-Inflammatory Therapy in SARS-CoV-2 Infection - Protocol v1.1. https://dx.doi.org/10.17504/protocols.io.bscjnaun

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