FKBP5 GENETICS & THE STRESS RESPONSE

AUTHORS: Tahkliq Amir, Owen Luo
ARTIST: Cathy Lu

Pathoprofile

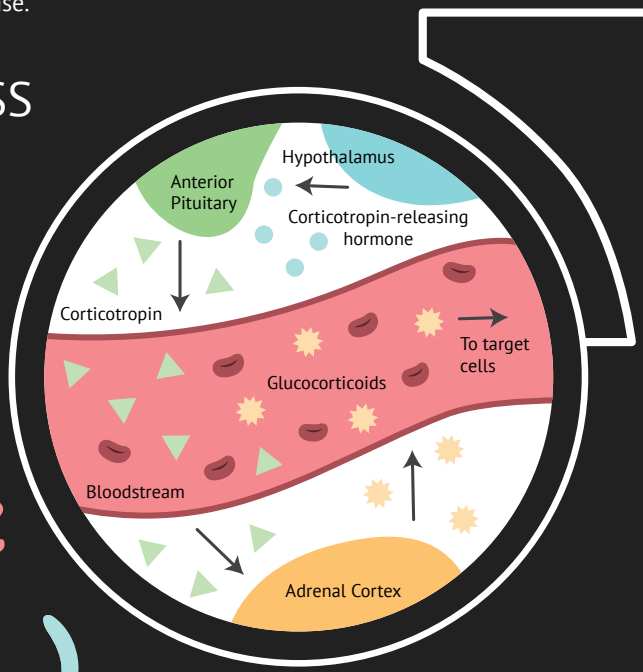
INTRODUCTION

Stress, generally defined as mental or emotional strain, primarily involves the hypothalamic-pituitary-adrenal (HPA) axis.[1,2] In this process, hypothalamic neurons release corticotropin-releasing hormone, which indirectly leads to the secretion of glucocorticoids, such as cortisol, into the bloodstream.[3-5] Circulating glucocorticoids act on receptors throughout the body, including the intracellular glucocorticoid receptor (GR).[v] The GR participates in a negative feedback loop with FK506 binding protein 51, or FKBP5, a co-chaperone protein that inhibits GR signalling in response to stress.[3,5,6] This has significant implications for health and disease.

FKBP5-MEDIATED PATHWAY OF STRESS

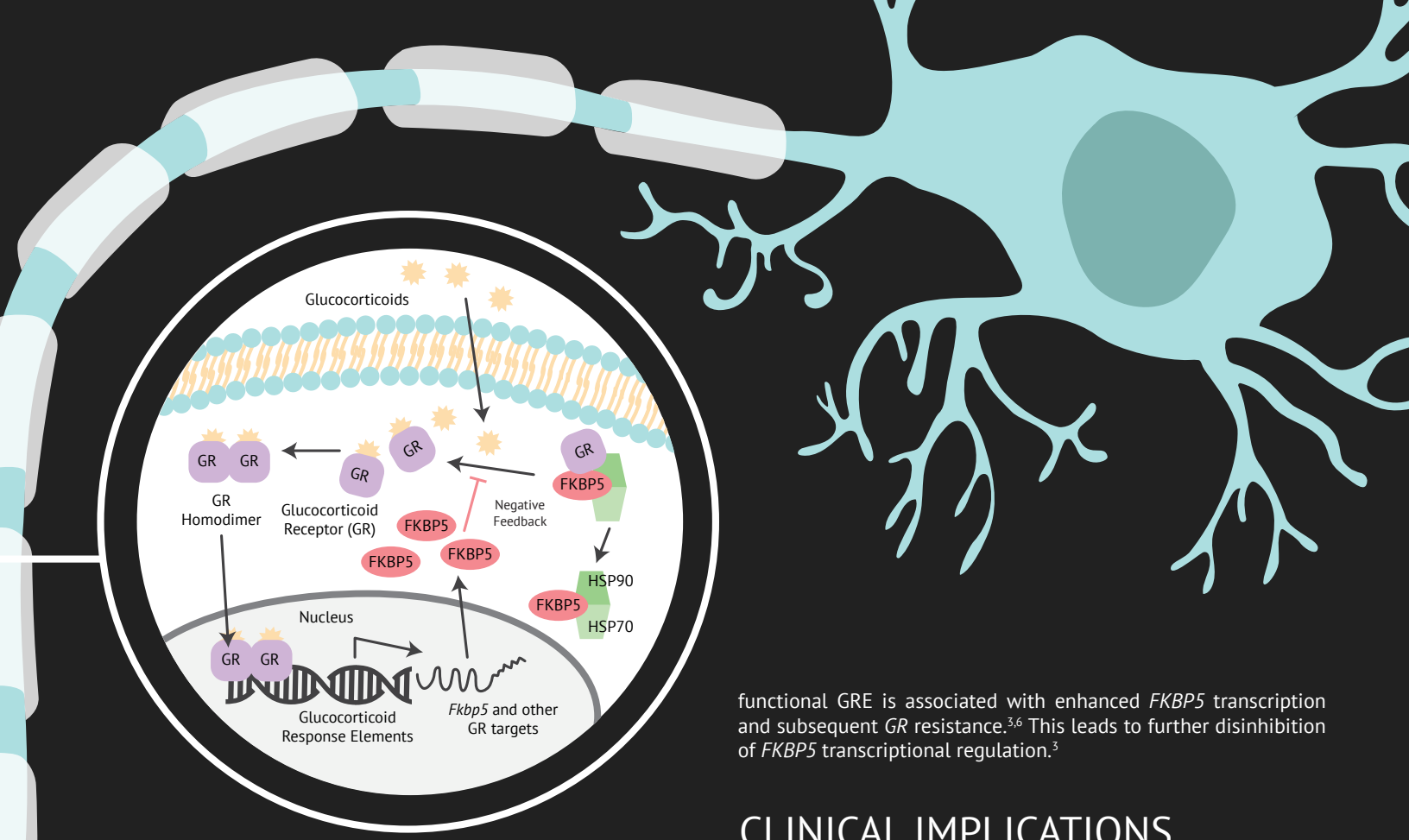
FKBP5 regulates GR sensitivity by binding to co-chaperone proteins of the receptor, lowering GR glucocorticoid-binding affinity and attenuating GR transcriptional activity.[3,6] Upon glucocorticoid binding, FKBP5 is replaced by FK506-binding protein 52 (FKBP52/FKBP4), a co-chaperone protein with opposing functions.[3]

The GR controls *FKBP5* gene transcription by 1) forming a homodimer that binds to glucocorticoid response element (GRE) sequences in introns of the *FKBP5* gene, and 2) interacting as a monomer with other transcription factors.[4] Thus, glucocorticoid release promotes FKBP5 expression, initiating the negative feedback loop and enabling cortisol self-regulation.[5]



REFERENCES

1. Richard S Lazarus and Susan Folkman. Stress, appraisal, and coping. Springer Publishing Company, 1984.
2. McEwen BS, Bowles NP, Gray JD, Hill MN, Hunter RG, Karatsoreos IN, Nasca C. Mechanisms of stress in the brain. Nature Neuroscience. 2015;18(10):1353-63. Available from: https://www-ncbi-nlm-nih-gov.libaccess.lib.mcmaster.ca/pmc/articles/PMC4933289/ [Accessed 27th February 2017].
3. Zannas AS, Wiechmann T, Gassen NC, Binder EB. Gene–stress–epigenetic regulation of FKBP5: clinical and translational implications. Neuropsychopharmacology. 2016;41(1):261-274. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4677131/ [Accessed 27th February 2017].
4. Reul JM, Collins A, Saliba RS, Mifsud KR, Carter SD, Gutierrez-Mecinas M, Qian X, Linthorst AC. Glucocorticoids, epigenetic control and stress resilience. Neurobiology of Stress. 2015;1:44-59. Available from: http://www.sciencedirect.com/science/article/pii/S2352289514000095 [Accessed 27th February 2017].
5. Menke A, Klengel T, Rubel J, Brückl T, Pfister H, Lucae S, Uhr M, Holsboer F, Binder EB. Genetic variation in FKBP5 associated with the extent of stress hormone dysregulation in major depression. Genes, Brain and Behavior. 2013;12(3):289-96. Available from: http://onlinelibrary.wiley.com.libaccess.lib.mcmaster.ca/doi/10.1111/gbb.12026/full [Accessed 27th February 2017].
6. Lee RS, Tamashiro KL, Yang X, Purcell RH, Huo Y, Rongione M, Potash JB, Wand GS. A measure of glucocorticoid load provided by DNA methylation of Fkbp5 in mice. Psychopharmacology. 2011;218(1):303-12. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3918452/ [Accessed 27th February 2017].
7. Galigniana NM, Ballmer LT, Toneatto J, Erlejman AG, Lagadari M, Galigniana MD. Regulation of the glucocorticoid response to stress-related disorders by the Hsp90-binding immunophilin FKBP51. Journal of Neurochemistry. 2012;122(1):4-18. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1471-4159.2012.07775.x/full [Accessed 27th February 2017].
8. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, Tang Y, Gillespie CF, Heim CM, Nemeroff CB, Schwartz AC. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. Jama. 2008;299(11):1291-305. Available from: 10.1001/jama.299.11.1291 [Accessed 8th March 2017].
9. Halldorsdottir T. Evidence Mounting for Gene-by-Environment Interactions at the FKBP5 Locus Predicting Psychiatric Symptoms. Biological Psychiatry. 2016;80(11):e89-91. Available from http://journals1.scholarsportal.info/pdf/00063223/v80i0011/e89_emfgiatflpps.xml [Accessed 27th February 2017].
10. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. Nature Neuroscience. 2004;7(8):847-54. Available from: 10.1038/nn1276 [Accessed 8th March 2017].
11. Turecki G, Meaney MJ. Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review. Biological Psychiatry. 2016;79(2):87-96. Available from: http://dx.doi.org.libaccess.lib.mcmaster.ca/10.1016/j.biopsych.2014.11.022 [Accessed 27th February 2017].
12. Hartmann J, Wagner KV, Liebl C, Scharf SH, Wang XD, Wolf M, Hausch F, Rein T, Schmidt U, Touma C, Cheung-Flynn J. The involvement of FK506-binding protein 51 (FKBP5) in the behavioral and neuroendocrine effects of chronic social defeat stress. Neuropharmacology. 2012;62(1):332-9. Available from: http://www.sciencedirect.com/science/article/pii/S0028390811003297 [Accessed 1st Mar 2017]
13. Gaali S, Gopalakrishnan R, Wang Y, Kozany C, Hausch F. The chemical biology of immunophilin ligands. Current Medicinal Chemistry. 2011;18(35):5355-79. Available from: http://www.ingentaconnect.com/content/ben/cmc/2011/00000018/00000035/art00004 [Accessed 1st Mar 2017]
14. Blackburn EA, Walkinshaw MD. Targeting FKBP isoforms with small-molecule ligands. Current Opinion in Pharmacology. 2011;11(4):365-71. Available from: http://www.sciencedirect.com/science/article/pii/S1471489211000592 [Accessed 2nd Mar 2017]
15. Gaali S, Kirschner A, Cuboni S, Hartmann J, Kozany C, Balsevich G, Namendorf C, Fernandez-Vizarra P, Sippel C, Zannas AS, Draenert R. Selective inhibitors of the FK506-binding protein 51 by induced fit. Nature Chemical Biology. 2015;11(1):33-7. Available from: http://www.nature.com/nchembio/journal/v11/n1/full/nchembio.1699.html [Accessed 2nd Mar 2017]



UPSTREAM FACTORS OF FKBP5

Chronic stress leads to elevated glucocorticoid levels. Gene-interaction studies have demonstrated that alleles associated with higher *FKBP5* expression induce prolonged cortisol response and increase the risk of stress-related psychiatric disorders following trauma.[3,6]

FKBP5 polymorphisms disrupt HPA axis activity and thus the glucocorticoid negative feedback loop, causing variable susceptibility to major depressive disorder (MDD), bipolar disorder, post-traumatic stress disorder (PTSD), and increased suicide risk.[5,6,7] A large cross-sectional study observed associations between four single nucleotide polymorphisms (SNPs) within the *FKBP5* gene and the severity of child abuse as a predictor of adult PTSD symptoms.[8] One of the most commonly described polymorphisms is rs1360780 in intron 2 of *FKBP5*.[5] In particular, the rs1360780 T allele upregulates *FKBP5* mRNA expression, inducing excessive GR activation. This causes GR resistance and an extended cortisol response to stressors in healthy carriers.[5,6,9] The variable effects of these polymorphisms contributes to the broad spectrum in the magnitude of HPA axis disruption in patients suffering from disorders such as MDD and PTSD.[5]

Additionally, epigenetic modifications regulate the glucocorticoid regulation pathway through the *GR* and *FKBP5* genes.[10] In particular, maternal behaviour, considered a protective influence on stressors and their appraisal, has been found in rodents to influence hippocampal GR expression in the offspring.[10] Specifically, nurturing maternal behaviour induces long-lasting epigenetic alterations, such as decreased methylation upstream of the gene encoding the *GR*, reducing stress reactivity.[10] Conversely, evidence has shown that DNA methylation of the *FKBP5* gene increases stress susceptibility.[11] In rs1360780 T allele carriers, demethylation in intron 7 of the functional GRE is associated with enhanced *FKBP5* transcription and subsequent *GR* resistance.[3,6] This leads to further disinhibition of *FKBP5* transcriptional regulation.[3]

CLINICAL IMPLICATIONS

FKBP5 disinhibition is pathologically relevant to the development of psychiatric disease in humans and thus presents a potent therapeutic target.[3] Through the use of *FKBP5* gene knockouts in animal studies, scientists have elucidated that relative to wild-type controls, *FKBP5* knockouts demonstrated increased resilience due to improved stress hormone signalling and stress-coping behaviours.[12] These findings have propelled the discovery of efficacious pharmacological agents targeting *FKBP5* activity. Previously, most *FKBP5* ligands were unselective, with significant off-target interaction with the similar binding sites of homologous *FKBP4*.[13,14] Recently, scientists have elucidated a class of potent and selective *FKBP5* inhibitors known as SAFits, which have been found to promote HPA axis regulation and stress-coping behaviors.[15] This evidence may potentially inform mechanistically new therapeutics for stress-related psychiatric diseases.

CONCLUSION

Though the etiology of psychiatric diseases remains unclear, existing literature supports the role of gene-environment interactions in causing *FKBP5* disinhibition and increased vulnerability to neurological illnesses. Excessive stress has long-term consequences for health and disease, particularly in a genetically vulnerable population, thus presenting *FKBP5* and glucocorticoid dysregulation as a pertinent therapeutic target.