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Does epigenetic 'memory' of early-life stress predispose to chronic pain in later life? A potential role for the stress regulator *FKBP5*.

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Main Text

Summary

Animal behaviours are not only affected by inherited genes but also by environmental experiences. For example, in both rats and humans, stressful early life events such as being reared by an inattentive mother can leave a lasting trace and affect later stress response in adult life. This is due to a chemical trace left on the chromatin attributed to so called epigenetic mechanisms. Such an epigenetic trace often has consequences, sometimes long-lasting, on the functioning of our genes, thereby allowing individuals to rapidly adapt to a new environment. One gene under such epigenetic control is *FKBP5*, the gene that encodes the protein FKPB51, a crucial regulator of the stress axis and a significant driver of chronic pain states. In this article, we will discuss the possibility that exposure to stress could drive the susceptibly to chronic pain *via* epigenetic modifications of genes within the stress axis such as *FKBP5*. The possibility that such modifications, and therefore the susceptibility to chronic pain, could be transmitted across generations in mammals and whether such mechanisms may be evolutionarily conserved across phyla will also be debated.

1. Stress experiences can leave long-lasting traces onto our chromatin *via* so-called epigenetic mechanisms

The chromatin is the association of DNA and proteins such as histones that can be found in the nucleus of our cells. The compaction of the chromatin can be modulated in a gene- and a time-dependent manner by epigenetic mechanisms, resulting in the tight regulation of gene expression. This happens through the addition and removal of chemical marks onto the chromatin, such as post-translation modification of histones and methylation of the DNA. While epigenetic marks were once believed to be subject to little alterations in mature systems, it is now well accepted that epigenetic changes are highly dynamic and allow rapid adaptation to the environment within ones' lifetime (1–5). To make a clear distinction between the epigenetic changes occurring during organismal

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development and that occurring in mature systems, in particular in non-diving adult neurones, the term neuroepigenetic has been proposed (4). We now have strong evidence that neuroepigenetic changes can lead to long-lasting modification in neural function implicated in a number of cognitive behaviour (5).

Life experiences can indeed alter the epigenome, the summation of all epigenetic marks on the chromatin, and have a lasting influence upon the way some genes are expressed. Two of the most studied epigenetic modifications are histone acetylation (6–8) and DNA methylation at CpG sites (regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide) (9–11). Both histone acetylation and decrease in DNA methylation in the promoter of a gene can lead to the localised relaxation of the chromatin and therefore are usually associated with the upregulation of gene expression (12). Alongside DNA methylation and histone modifications, non-coding RNAs are also crucial modulators of gene expression. Unlike messenger RNAs (mRNAs), non-coding RNAs or regulatory RNAs, that were first thought to possess no coding capacity, regulate gene expression by targeting mRNAs for degradation. They have also been shown to act as guides for the epigenetic machinery to target specific DNA sequence (13–15). One should note that coding properties have recently been observed from so called non-coding RNAs, suggesting that their involvement in cell function regulation is likely to be broader than currently understood (16,17).

So far, epigenetic changes induced by life experiences have been mostly studied in the context of stress exposure and genes associated with the hypothalamic-pituitary-adrenal (HPA) axis. The first pre-clinical study to elegantly demonstrate the importance of epigenetic mechanisms in the adaptation to our environment was that of Meaney and colleagues (18). They showed that highly licking and grooming rat mothers were raising pups that became themselves high licking and grooming mothers. This behaviour was associated with an increase in expression of the glucocorticoid receptor gene in the hippocampus and this increased expression was secondary to the low methylation landscape and increased acetylation of histones at the promoter of the *NR3C1* gene that encodes the glucocorticoid receptor protein. Both rodents and humans with high level of glucocorticoid receptor are more resilient to stress, and studies in human post-mortem brain tissue taken from suicide victims have demonstrated that individuals with an history of childhood trauma are likely to present with increased methylation levels in the *NR3C1* gene and therefore reduced glucocorticoid receptor expression (19–21). While most work so far has focused on the glucocorticoid receptor in the HPA axis, more recent studies have also looked at the stress regulator FK506 binding protein 51 (FKBP51).

2. FKBP51: a stress regulator under strong epigenetic regulation

FKBP51, encoded by the gene *FKBP5*, interacts with a number of molecular partners to impact upon various cellular processes. Most notably, FKBP51 binds to the heat-shock protein 90 (Hsp90) and other co-chaperones of the steroid receptor complex to regulate the stress response (22). By interacting with the steroid receptor complex, FKBP51 reduces the affinity of the glucocorticoid receptor to stress hormones, which is particularly important for stress regulation (Figure 1). Glucocorticoids are released in response to stress and activation of the glucocorticoid receptor usually feeds back to reduce this release, leading to the termination of the stress response (23). Consequently, changes in levels of FKBP51 perturb the stress response system (22). The expression of FKBP51 itself is induced by glucocorticoid receptor activation by stress hormones, producing a direct feedback that regulates GR activity. The result of this feedback is evident in humans expressing *FKBP5* variants associated with heightened induction of *FKBP5* mRNA upon stress exposure (known as a risk allele). These variants have been repeatedly associated with anxiety related disorders, including major depression and post-traumatic stress disorder (PTSD) (22,24). This is consistent with

the finding that inhibition or deletion of the protein reduces anxiety-related behaviour in mice (25,26).

Reduction in *FKBP5* DNA methylation in intronic regions, which is likely to be associated with an increase in FKBP51 expression, has often been reported following exposure to stress and glucocorticoid stimulation, both in humans and rodents (22,27–31). Importantly, the reduction in *FKBP5* DNA methylation correlates with the trauma intensity in humans (28) and with the degree of exposure to glucocorticoids in rodents (29). Interestingly, these changes are measured in peripheral blood samples in humans, and in rodents, changes in the brain correlates with those in the blood (31), suggesting that *FKBP5* DNA methylation levels in the blood could be used as a biomarker of stress exposure. A seminal study from Binder and colleagues demonstrated that long-lasting, trauma-induced, decrease in intronic regions in *FKBP5* DNA methylation measured in human peripheral blood could arise in childhood in individuals with the risk allele. Importantly, this decrease in DNA methylation increased the risk of developing stress-related psychiatric disorders in adulthood (27,32). More recently, Binder and colleagues have also identified a reduction in DNA methylation at selected enhancer-related *FKBP5* sites synergistically modulated by aging and stress (33). Individual with stress-related phenotypes show further decrease in aging-induced DNA demethylation at these specific CG bases and higher *FKBP5* mRNA expression in blood samples.

3. FKBP51: a crucial driver of chronic pain

We have recently shown that genetic deletion and pharmacological blockade of FKBP51 alleviated chronic pain states in mice. With these approaches, we were indeed able to reduce the hypersensitivity seen in a number of animal models of persistent pain across sexes: CFA-induced joint inflammation (34,35), monoiodoacetate (MIA)-induced knee inflammation (unpublished data), peripheral nerve injury (34,35) and paclitaxel-induced mechanical hypersensitivity (35). Crucially, models of acute pain, such as IL6- and PGE2- induced inflammation of the hind paw, were insensitive to FKBP51 blockade. Our study also demonstrated that spinal deletion and pharmacological blockade of FKBP51 alleviated established persistent pain as effectively as global deletion, suggesting that FKBP51 could regulate pain independently from its effect on mood, which is likely to be mediated in the brain. While the molecular mechanisms of regulation of persistent pain by FKBP51 remain to be fully elucidated, our early findings would suggest that this occur in a glucocorticoid-signalling dependent mechanism (34,35). Importantly, a significant body of work from MacLean and colleagues suggest that genetic variants of *FKBP5* alter pain sensitivity after trauma such as car crash and sexual assault (36–38), supporting the idea that FKBP51 drives persistent pain states in humans.

In our rodent preclinical studies, FKBP51 was upregulated in the dorsal horn after peripheral injury and this upregulation was accompanied at least by 2 epigenetic changes: the phosphorylation of the methyl CpG binding protein 2 (MeCP2) (39) and the decrease in DNA methylation in the promoter sequence of the *FKBP5* gene (34) (Figure 2). In these studies, the dorsal horn expression of phosphorylated-MeCP2 and FKBP51 was observed nearly exclusively in neurones (34,39). However, the changes in DNA methylation were analysed and detected from a mixture of cells and therefore, while unlikely, we cannot exclude the possibility of a change in *FKBP5* DNA methylation in cells other than neurones. All together, these observations support the idea that epigenetic mechanisms are crucial to the development of persistent pain states by promoting the relaxation of the chromatin at the gene *FKBP5*, leading to the upregulation of FKBP51. A number of rodent studies have since demonstrated that indeed, following injury, epigenetic alterations drive gene expression changes of other contributors to persistent pain states and are therefore crucial to the maintenance of persistent pain. This has been reviewed elsewhere (12,40–43) and will not be discussed further in this

manuscript, which focuses on the contribution of epigenetic mechanisms to the susceptibility to chronic pain.

Early-life trauma in humans can lead to a decrease in *FKBP5* DNA methylation, an epigenetic change that primes *FKBP5* for hyper-responsiveness and increases the susceptibility to post-traumatic stress disorder (PTSD) in adulthood (27). Could similar processes underlie the vulnerability to chronic pain?

4. Could exposure to environmental stress drive the susceptibly to chronic pain via epigenetic modifications of *FKBP5*?

To investigate the susceptibility to chronic pain, a number of hyperalgesic priming models have been developed in rodents (44,45). In these models, animals who have suffered a minor injury remain in a long-lasting latent hyper-responsiveness to an inflammatory or surgical insult. In other words, these models produce a state of sensitization closely resembling clinical situations with increased risk of developing chronic pain. Rodents that have suffered a minor injury become hyper-responsive to further mild insult that would normally not evoke persistent pain.

It is now known that pain in early life can enhance the duration of the pain response to subsequent injury in animal models, depending on both the nature and timing of the neonatal trauma (46–49). Various mechanisms have previously been suggested (50), some supporting a role for spinal microglia for the priming of the adult pain responses (44,51). Interestingly, glial cells have been shown to carry long-term epigenetic changes following peripheral injury (52) and neonatal handling (53) and therefore seem interesting potential drivers of a primed state of hypersensitivity.

While FKBP51 expression in the central nervous system has mainly been reported in neurones in rodents (35), the possibility that *FKBP5* could contribute to the susceptibility to chronic pain in adulthood following early life trauma deserves serious consideration. Indeed, not only early-life injury but also early-life stress exposure, such as sexual assault, could lead to a long-lasting decrease in *FKBP5* DNA methylation. Such a reduction in DNA methylation would prime *FKBP5* for hyper-responsiveness to injury in later life, enhancing the duration of the pain response and potentially increasing the likelihood to developing chronic pain. The extent, duration and location in the central nervous system of the trauma-induced reduction in DNA methylation remain central to the likelihood that such mechanism could contribute to the susceptibility to chronic pain. In this context, it is important to note that since pain is a stressor in itself, it is likely that, following injury, changes in FKBP51 expression and *FKBP5* DNA methylation occur not only at spinal cord level, as we have reported in mice and rats, but also in brain areas involved with stress, such as the paraventricular nucleus (PVN) of the hypothalamus (54,55). Reciprocally, whether traumatic stress experience can lead to changes at spinal cord level remains a point of discussion.

Could similar mechanisms occur in adult life? A state of latent hypersensitivity can also be induced in adulthood using priming models in rodents (45,50,56) and this latent state of hypersensitivity can last at least for 5 weeks (50).Various mechanisms have been suggested including the involvement of dopaminergic descending controls (50), GABAergic signalling at dorsal horn level (57), as well as peripheral mechanisms of nociceptor plasticity (58–60). However, in the seminal human studies from Binder and colleagues, it was reported that trauma in adult life could not lead to long-lasting changes in *FKBP5* DNA methylation, as seen in childhood (27). Mechanisms of epigenetic priming could differ across ages because epigenetic modifications might be differently engaged in the young and the mature nervous system by trauma. Indeed, the epigenome, the complete set of epigenetic modifications on the genetic material of an individual, tends to change as we age; changes in both

histones modifications and DNA methylation, specifically gene-specific and global hypermethylation and hypomethylation, have been reported with aging in various tissue, as well as in the central and peripheral nervous system (61–65). Some epigenetic actors are also expressed differently in young animals versus adults: *e.g.* the expression of DNA methyltransferase 1 (DNMT1) and 3a decreases considerably between newborn and middle-age (23-50 years old) humans (66,67). Nonetheless, using a gene specific approach, we did find in our preclinical studies that peripheral injury in adult rats induced a reduction in *FKBP5* DNA methylation, at least in the superficial dorsal horn (34). This reduction in DNA methylation lasted at least 7 days. It is therefore crucial to characterise precisely the circumstances under which (*e.g.* trauma intensity, life stages) changes in DNA methylation can occur and can be persistent. This indeed would be necessary for the long-lasting priming of the nociceptive system for hyper-responsiveness to subsequent injury.

5. Epigenetic regulation of the stress axis and the vulnerability to chronic pain: other candidate genes

While this article purposely focused on the gene *FKBP5*, other genes from the stress axis are likely to be involved in the susceptibility to chronic pain. For example, the glucocorticoid receptor itself is known to be involved in spinal mechanisms crucial to the development of persistent pain states through modulation of NMDA receptors expression (68,69). Since the glucocorticoid receptor is also under strong epigenetic regulation upon stress exposure (18,20,21), one could assume that stress-induced epigenetic regulation of this receptor could modulate the susceptibility to chronic pain. An important role for the serum and glucocorticoid-regulated kinase 1 (SGK1) in the development of persistent pain states has also been reported at spinal cord level (39,70,71). The gene that encodes this protein is also known to be sensitive to epigenetic regulation and its expression is modulated by stress in both humans and rodents (72–74). All together, these observations strongly support the hypothesis that stress exposure can leave long-lasting epigenetic marks onto genes crucial to the development and maintenance of persistent pain states. This suggests that such genes could be primed by stress for injury-induced hyper-responsiveness in later life and therefore could be key to the susceptibility to chronic pain.

6. Epigenetic transgenerational inheritance

The possibility of inheritance of acquired characteristics was first proposed by the French naturalist Jean-Baptiste Lamarck at the end of the eighteenth century. Lamarck suggested that the environment could make lasting and potentially heritable alterations in gene function. This idea has remained controversial and the possibility that acquired traits could be passed on through generation remains an intense area of investigation (75,76).

While meiotic epigenetic inheritance is strongly debated, experience-dependent transgenerational transmission has gathered significant support. Meaney et al. work was the first to clearly demonstrate in pre-clinical models that a mothering style of grooming and nursing could be passed on to the next generation through an epigenetic mechanism (18). The female rats that were resilient to stress brought up offspring that were also resilient to stress in adulthood and both mothers and progenies had lower level of DNA methylation and higher expression of the glucocorticoid receptor gene in the hippocampus than stress-vulnerable controls (18). More recent human data also support the idea that the effects of stress on the epigenome could be inherited through social interactions. In particular, the intergenerational effects of trauma have received a lot of attention and have been widely observed clinically. Parental PTSD, for example in holocaust survivors, has been linked with an increased risk for psychopathology in offspring which has been associated with epigenetic

programming of glucocorticoid functions (77–79). DNA methylation patterns of the gene *NR3C1* in particular were shown to be related to parental PTSD, with maternal and paternal PTSD having different effects (78). Similar findings have been extended to less extreme forms of stress (80). For examples, there was a positive association between the methylation status of *NR3C1* promoter in offspring of mothers stressed during pregnancy (reviewed in (80)).

It is interesting to note that changes in DNA methylation in the gene *FKBP5* were reported in both holocaust survivors and their offspring but that parents and offspring exhibited inverse methylation changes (28). These results suggested that, if the changes observed in the parents reflected exposure to extreme stress, the opposite change in the offspring could be a sign of resilience. This would suggest that epigenetic transgenerational transmission could not only sometime be the transfer of the negative consequences of stress exposure but also a mechanism to enhance environmental adaptation (80). Whether similar mechanisms could apply to the transmission of an increased vulnerability or resilience to chronic pain remains to be demonstrated.

The transgenerational transfer of potentially acquired traits through gametes remains much debated. While considerable efforts have been made in identifying the contribution of epigenetic modifications to the heritability of complex and stress related diseases, this has been extremely difficult to elucidate due to the lack of a clear mechanism. This is because, during mammalian development, the embryo goes through epigenetic reprogramming, when epigenetic marks are erased and remodeled, making it unlikely for a mark to be transferred from parents to offspring. Nonetheless, a number of genes, including imprinted genes, bypass epigenetic reprograming and can therefore carry epigenetic marks across generations (81). Occurrences of such transmission have already been reported including transmission across generation of exposure to pesticides and experiences, such as metabolic deprivation, increased fat intake and fear (82). However, evidence for this type of heritability in humans remains very limited (83).

Nevertheless, a study in mice was able to demonstrate that odor fear conditioning could be transmitted to offspring *via* changes in methylation in the germ line that were shown to affect the expression of the relevant olfactory receptor gene (84,85). Importantly, up to two generations of offspring showed increased fear of the smell that had been used to conditioned the parents and strong evidence was provided to demonstrate that the transmission occurred through the germ line and not behaviourally. In another study, traumatic stress in early life could influence the expression of small non-coding RNAs which are also known to mediate the effect of the environment on our genome (86,87). The changes in behaviour and small non-coding RNAs could be seen in the serum and hippocampus of offspring for at least 2 generations and injection of sperm RNAs from traumatized males into fertilized oocytes reproduced the same alterations in the offspring, demonstrating a non-social transmission of the traits (86). In both tudies reported here, the assimilation of environmentally induced phenotypes could act as a driver of evolutionary change and could even be seen as contributing to the rapid transformation of a learned behaviour into an instinct (88). This would undeniably be extremely beneficial to offspring to be able to react to a threat from birth. However, one could also argue that, while adapting to one's environment before birth should help with survival, these changes could have serious consequences if the environment at birth does not match the environment one was prepared for.

7. Epigenetic inheritance in other phyla

While our knowledge of epigenetic mechanisms in animals studied in medical research is rapidly expanding, it is not always the case for other species. Current understanding suggests that, while the patterns of DNA methylation are well preserved across species of vertebrates, there are large

differences in terms of the timing and nature of reprogramming and genomic imprinting. For example, fish and frogs do not undergo global DNA methylation remodeling during embryogenesis (89) while in zebrafish the maternal methylome is reconfigured to match the paternal methylome pattern (90,91). In the case of invertebrates, some genomes have no DNA methylation while others could be as methylated as vertebrates'. Importantly, DNA methylation may have different functions in invertebrates such as alternative splicing (89). More relevant to the study of pain mechanisms are observations made in one of the most studied invertebrate, Aplysia, used by Kandel and co-workers in pioneering studies in the field of learning and memory (92,93). While the DNA methyl transferase 1 (DNMT1) was only recently discovered in Aplysia, Kandel and colleagues demonstrated that DNA methylation was necessary for 5HT-dependent long term facilitation (94). These findings were supported by more recent studies indicating that DNA methylation was a crucial mechanism for both the consolidation and maintenance of long-term memory in Aplysia (95). Overall, these observations would suggest that epigenetic mechanisms are likely to contribute to the development of persistent sensitised states across phyla. However, the possibility of inheritance of some kind of vulnerable state through epigenetic mechanisms in invertebrate is still unclear and has been discussed elsewhere (89).

8. Conclusion

Epigenetic mechanisms have been highlighted as key players of the development and maintenance of persistent pain states and are expected to contribute to the susceptibility to chronic pain, at least partly through the modulation of the stress axis and in particular the gene *FKBP5*. However, it is likely that epigenetic regulation and genetic pre-dispositions are working together to drive vulnerability or resilience, as seen with the gene *FKBP5* in the context of mood disorders. While epigenetic modifications can be transmitted across generations, the transmission seems more likely to occur *via* social interactions than biological inheritance. Indeed, considering the fast dynamics of epigenetic mechanisms that allow the adaptation to the environment within a lifetime, one could question the advantage of a biological transmission of epigenetic traits (for humans at least).

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References

1. Borrelli E, Nestler EJ, Allis CD, Sassone-Corsi P. Decoding the epigenetic language of neuronal plasticity. Neuron. 2008 Dec 26;60(6):961–74.

2. Renthal W, Nestler EJ. Epigenetic mechanisms in drug addiction. Trends Mol Med. 2008 Aug;14(8):341–50.

3. Day JJ, Sweatt JD. DNA methylation and memory formation. Nature Neuroscience. 2010 Nov;13(11):1319–23.

4. Sweatt JD. The Emerging Field of Neuroepigenetics. Neuron. 2013 Oct;80(3):624–32.

5. Day JJ, Sweatt JD. Epigenetic Mechanisms in Cognition. Neuron. 2011 Jun 9;70(5):813–29.

6. Gräff J, Tsai L-H. Histone acetylation: molecular mnemonics on the chromatin. Nature Reviews Neuroscience. 2013 Jan 17;14(2):97–111.

7. Peixoto L, Abel T. The role of histone acetylation in memory formation and cognitive impairments. Neuropsychopharmacology. 2013 Jan;38(1):62–76.

8. Levenson JM, O'Riordan KJ, Brown KD, Trinh MA, Molfese DL, Sweatt JD. Regulation of histone acetylation during memory formation in the hippocampus. J Biol Chem. 2004 Sep 24;279(39):40545–59.

9. Lax E, Szyf M. The Role of DNA Methylation in Drug Addiction: Implications for Diagnostic and Therapeutics. Prog Mol Biol Transl Sci. 2018;157:93–104.

10. Szyf M. The early life social environment and DNA methylation: DNA methylation mediating the long-term impact of social environments early in life. Epigenetics. 2011 Aug;6(8):971–8.

11. Szyf M. DNA methylation, behavior and early life adversity. J Genet Genomics. 2013 Jul 20;40(7):331–8.

12. Géranton SM, Tochiki KK. Regulation of gene expression and pain states by epigenetic mechanisms. Prog Mol Biol Transl Sci. 2015;131:147–83.

13. Di Ruscio A, Ebralidze AK, Benoukraf T, Amabile G, Goff LA, Terragni J, et al. DNMT1-interacting RNAs block gene-specific DNA methylation. Nature. 2013 Nov;503(7476):371–6.

14. Ghildiyal M, Zamore PD. Small silencing RNAs: an expanding universe. Nature Reviews Genetics. 2009 Feb;10(2):94–108.

15. Dykes IM, Emanueli C. Transcriptional and Post-transcriptional Gene Regulation by Long Non-coding RNA. Genomics, Proteomics & Bioinformatics. 2017 Jun;15(3):177–86.

16. Hubé F, Francastel C. Coding and Non-coding RNAs, the Frontier Has Never Been So Blurred. Front Genet. 2018 Apr 18;9:140.

17. Pang Y, Mao C, Liu S. Encoding activities of non-coding RNAs. Theranostics. 2018;8(9):2496–507.

18. Weaver ICG, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. Nat Neurosci. 2004 Aug;7(8):847–54.

19. Suderman M, McGowan PO, Sasaki A, Huang TCT, Hallett MT, Meaney MJ, et al. Conserved epigenetic sensitivity to early life experience in the rat and human hippocampus. Proc Natl Acad Sci USA. 2012 Oct 16;109 Suppl 2:17266–72.

20. McGowan PO, Suderman M, Sasaki A, Huang TCT, Hallett M, Meaney MJ, et al. Broad epigenetic signature of maternal care in the brain of adult rats. PLoS ONE. 2011 Feb 28;6(2):e14739.

21. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009 Mar;12(3):342–8.

22. Zannas AS, Wiechmann T, Gassen NC, Binder EB. Gene–Stress–Epigenetic Regulation of FKBP5: Clinical and Translational Implications. Neuropsychopharmacology. 2016 Jan;41(1):261–74.

23. Herman JP, McKlveen JM, Solomon MB, Carvalho-Netto E, Myers B, University of Cincinnati, USA, et al. Neural regulation of the stress response: glucocorticoid feedback mechanisms. Brazilian Journal of Medical and Biological Research. 2012 Apr;45(4):292–8.

24. Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Pütz B, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat Genet. 2004 Dec;36(12):1319–25.

25. Hartmann J, Wagner KV, Liebl C, Scharf SH, Wang X-D, Wolf M, et al. The involvement of FK506-binding protein 51 (FKBP5) in the behavioral and neuroendocrine effects of chronic social defeat stress. Neuropharmacology. 2012 Jan;62(1):332–9.

26. Hartmann J, Wagner KV, Gaali S, Kirschner A, Kozany C, Rühter G, et al. Pharmacological Inhibition of the Psychiatric Risk Factor FKBP51 Has Anxiolytic Properties. J Neurosci. 2015 Jun 17;35(24):9007–16.

27. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci. 2013 Jan;16(1):33–41.

28. Yehuda R, Daskalakis NP, Bierer LM, Bader HN, Klengel T, Holsboer F, et al. Holocaust Exposure Induced Intergenerational Effects on FKBP5 Methylation. Biological Psychiatry [Internet]. 2015 Aug [cited 2016 Apr 15]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0006322315006526

29. Lee RS, Tamashiro KLK, Yang X, Purcell RH, Huo Y, Rongione M, et al. A measure of glucocorticoid load provided by DNA methylation of Fkbp5 in mice. Psychopharmacology (Berl). 2011 Nov;218(1):303–12.

30. Lee RS, Tamashiro KLK, Yang X, Purcell RH, Harvey A, Willour VL, et al. Chronic corticosterone exposure increases expression and decreases deoxyribonucleic acid methylation of Fkbp5 in mice. Endocrinology. 2010 Sep;151(9):4332–43.

31. Ewald ER, Wand GS, Seifuddin F, Yang X, Tamashiro KL, Potash JB, et al. Alterations in DNA methylation of Fkbp5 as a determinant of blood-brain correlation of glucocorticoid exposure. Psychoneuroendocrinology. 2014 Jun;44:112–22.

32. Klengel T, Binder EB. FKBP5 Allele-Specific Epigenetic Modification in Gene by Environment Interaction. Neuropsychopharmacology. 2015 Jan;40(1):244–6.

33. Zannas AS, Jia M, Hafner K, Baumert J, Wiechmann T, Pape JC, et al. Epigenetic upregulation of FKBP5 by aging and stress contributes to NF-κB–driven inflammation and cardiovascular risk. Proc Natl Acad Sci USA. 2019 Jun 4;116(23):11370–9.

34. Maiarù M, Tochiki KK, Cox MB, Annan LV, Bell CG, Feng X, et al. The stress regulator FKBP51 drives chronic pain by modulating spinal glucocorticoid signaling. Sci Transl Med. 2016 Feb 10;8(325):325ra19.

35. Maiarù M, Morgan OB, Mao T, Breitsamer M, Bamber H, Pöhlmann M, et al. The stress regulator FKBP51: a novel and promising druggable target for the treatment of persistent pain states across sexes. Pain. 2018 Jul;159(7):1224–34.

36. Auvergne L, Bortsov AV, Ulirsch JC, Peak DA, Jones JS, Swor RA, et al. Association of Epidemiologic Factors and Genetic Variants Influencing Hypothalamic-Pituitary-Adrenocortical Axis Function With Postconcussive Symptoms After Minor Motor Vehicle Collision. Psychosom Med. 2016 Jan;78(1):68–78.

37. Bortsov AV, Smith JE, Diatchenko L, Soward AC, Ulirsch JC, Rossi C, et al. Polymorphisms in the glucocorticoid receptor co-chaperone FKBP5 predict persistent musculoskeletal pain after traumatic stress exposure. Pain. 2013 Aug;154(8):1419–26.

38. Ulirsch JC, Weaver MA, Bortsov AV, Soward AC, Swor RA, Peak DA, et al. No man is an island: living in a disadvantaged neighborhood influences chronic pain development after motor vehicle collision. Pain. 2014 Oct;155(10):2116–23.

39. Géranton SM, Morenilla-Palao C, Hunt SP. A role for transcriptional repressor methyl-CpG-binding protein 2 and plasticity-related gene serum- and glucocorticoid-inducible kinase 1 in the induction of inflammatory pain states. J Neurosci. 2007 Jun 6;27(23):6163–73.

40. Denk F, McMahon SB. Chronic Pain: Emerging Evidence for the Involvement of Epigenetics. Neuron. 2012 Feb;73(3):435–44.

41. Géranton SM, Tochiki KK. Could targeting epigenetic processes relieve chronic pain states? Curr Opin Support Palliat Care. 2015 Jun;9(2):138–46.

42. Odell DW. Epigenetics of pain mediators: Current Opinion in Anaesthesiology. 2018 Aug;31(4):402–6.

43. Niederberger E, Resch E, Parnham MJ, Geisslinger G. Drugging the pain epigenome. Nat Rev Neurol. 2017 Jul;13(7):434–47.

44. Beggs S, Currie G, Salter MW, Fitzgerald M, Walker SM. Priming of adult pain responses by neonatal pain experience: maintenance by central neuroimmune activity. Brain. 2012 Feb;135(Pt 2):404–17.

45. Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. Trends Neurosci. 2009 Dec;32(12):611–8.

46. Fitzgerald M, Walker SM. Infant pain management: a developmental neurobiological approach. Nat Clin Pract Neurol. 2009 Jan;5(1):35–50.

47. Walker SM, Tochiki KK, Fitzgerald M. Hindpaw incision in early life increases the hyperalgesic response to repeat surgical injury: critical period and dependence on initial afferent activity. Pain. 2009 Dec 15;147(1–3):99–106.

48. Lidow MS, Song ZM, Ren K. Long-term effects of short-lasting early local inflammatory insult. Neuroreport. 2001 Feb 12;12(2):399–403.

49. Schwaller F, Fitzgerald M. The consequences of pain in early life: injury-induced plasticity in developing pain pathways. European Journal of Neuroscience. 2014 Feb;39(3):344–52.

50. Kim J-YV, Tillu DV, Quinn TL, Mejia GL, Shy A, Asiedu MNK, et al. Spinal dopaminergic projections control the transition to pathological pain plasticity via a D1/D5-mediated mechanism. J Neurosci. 2015 Apr 22;35(16):6307–17.

51. Moriarty O, Tu Y, Sengar AS, Salter MW, Beggs S, Walker SM. Priming of adult incision response by early life injury: neonatal microglial inhibition has persistent but sexually dimorphic effects in adult rats. J Neurosci. 2019 Feb 22;

52. Denk F, Crow M, Didangelos A, Lopes DM, McMahon SB. Persistent Alterations in Microglial Enhancers in a Model of Chronic Pain. Cell Rep. 2016 24;15(8):1771–81.

53. Schwarz JM, Hutchinson MR, Bilbo SD. Early-life experience decreases drug-induced reinstatement of morphine CPP in adulthood via microglial-specific epigenetic programming of anti-inflammatory IL-10 expression. J Neurosci. 2011 Dec 7;31(49):17835–47.

54. Herman J, Flak J, Jankord R. Chronic stress plasticity in the hypothalamic paraventricular nucleus. In: Progress in Brain Research [Internet]. Elsevier; 2008 [cited 2016 May 13]. p. 353–64. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0079612308004299

55. Gibbison B, Angelini GD, Lightman SL. Dynamic output and control of the hypothalamic-pituitary-adrenal axis in critical illness and major surgery. British Journal of Anaesthesia. 2013 Sep 1;111(3):347–60.

56. Megat S, Shiers S, Moy JK, Barragan-Iglesias P, Pradhan G, Seal RP, et al. A Critical Role for Dopamine D5 Receptors in Pain Chronicity in Male Mice. J Neurosci. 2018 10;38(2):379–97.

57. Kim J-YV, Megat S, Moy JK, Asiedu MN, Mejia GL, Vagner J, et al. Neuroligin 2 regulates spinal GABAergic plasticity in hyperalgesic priming, a model of the transition from acute to chronic pain: PAIN. 2016 Jun;157(6):1314–24.

58. Moy JK, Khoutorsky A, Asiedu MN, Dussor G, Price TJ. eIF4E Phosphorylation Influences Bdnf mRNA Translation in Mouse Dorsal Root Ganglion Neurons. Front Cell Neurosci. 2018 Feb 6;12:29.

59. Ferrari LF, Araldi D, Levine JD. Distinct Terminal and Cell Body Mechanisms in the Nociceptor Mediate Hyperalgesic Priming. J Neurosci. 2015 Apr 15;35(15):6107–16.

60. Araldi D, Khomula EV, Ferrari LF, Levine JD. Fentanyl Induces Rapid Onset Hyperalgesic Priming: Type I at Peripheral and Type II at Central Nociceptor Terminals. J Neurosci. 2018 28;38(9):2226–45.

61. D'Aquila P, Rose G, Bellizzi D, Passarino G. Epigenetics and aging. Maturitas. 2013 Feb;74(2):130–6.

62. Tammen SA, Friso S, Choi S-W. Epigenetics: The link between nature and nurture. Molecular Aspects of Medicine. 2013 Jul;34(4):753–64.

63. Rakyan VK, Down TA, Maslau S, Andrew T, Yang TP, Beyan H, et al. Human aging-associated DNA hypermethylation occurs preferentially at bivalent chromatin domains. Genome Research. 2010 Apr 1;20(4):434–9.

64. Garriga J, Laumet G, Chen S-R, Zhang Y, Madzo J, Issa J-PJ, et al. Nerve Injury-Induced Chronic Pain Is Associated with Persistent DNA Methylation Reprogramming in Dorsal Root Ganglion. J Neurosci. 2018 Jul 4;38(27):6090–101.

65. Issa J-P. Aging and epigenetic drift: a vicious cycle. J Clin Invest. 2014 Jan;124(1):24–9.

66. Oliveira AMM, Hemstedt TJ, Bading H. Rescue of aging-associated decline in Dnmt3a2 expression restores cognitive abilities. Nature Neuroscience. 2012 Aug;15(8):1111–3.

67. Zhang Z, Deng C, Lu Q, Richardson B. Age-dependent DNA methylation changes in the ITGAL (CD11a) promoter. Mech Ageing Dev. 2002 May;123(9):1257–68.

68. Wang S, Lim G, Zeng Q, Sung B, Yang L, Mao J. Central glucocorticoid receptors modulate the expression and function of spinal NMDA receptors after peripheral nerve injury. J Neurosci. 2005 Jan 12;25(2):488–95.

69. Wang S, Lim G, Zeng Q, Sung B, Ai Y, Guo G, et al. Expression of central glucocorticoid receptors after peripheral nerve injury contributes to neuropathic pain behaviors in rats. J Neurosci. 2004 Sep 29;24(39):8595–605.

70. Peng H-Y, Chen G-D, Lai C-Y, Hsieh M-C, Lin T-B. Spinal serum-inducible and glucocorticoid-inducible kinase 1 mediates neuropathic pain via kalirin and downstream PSD-95-dependent NR2B phosphorylation in rats. J Neurosci. 2013 Mar 20;33(12):5227–40.

71. Peng H-Y, Chen G-D, Hsieh M-C, Lai C-Y, Huang Y-P, Lin T-B. Spinal SGK1/GRASP-1/Rab4 is involved in complete Freund's adjuvant-induced inflammatory pain via regulating dorsal horn GluR1-containing AMPA receptor trafficking in rats. Pain. 2012 Dec;153(12):2380–92.

72. Cattaneo A, Riva MA. Stress-induced mechanisms in mental illness: A role for glucocorticoid signalling. The Journal of Steroid Biochemistry and Molecular Biology. 2016 Jun;160:169–74.

73. Iurato S, Carrillo-Roa T, Arloth J, Czamara D, Diener-Hölzl L, Lange J, et al. "DNA Methylation signatures in panic disorder." Transl Psychiatry. 2017 Dec;7(12):1287.

74. Anacker C, Cattaneo A, Musaelyan K, Zunszain PA, Horowitz M, Molteni R, et al. Role for the kinase SGK1 in stress, depression, and glucocorticoid effects on hippocampal neurogenesis. Proceedings of the National Academy of Sciences. 2013 May 21;110(21):8708–13.

75. Szyf M. Nongenetic inheritance and transgenerational epigenetics. Trends Mol Med. 2015 Feb;21(2):134–44.

76. Horsthemke B. A critical view on transgenerational epigenetic inheritance in humans. Nature Communications [Internet]. 2018 Dec [cited 2019 Apr 1];9(1). Available from: http://www.nature.com/articles/s41467-018-05445-5

77. Lehrner A, Bierer LM, Passarelli V, Pratchett LC, Flory JD, Bader HN, et al. Maternal PTSD associates with greater glucocorticoid sensitivity in offspring of Holocaust survivors. Psychoneuroendocrinology. 2014 Feb;40:213–20.

78. Yehuda R, Daskalakis NP, Lehrner A, Desarnaud F, Bader HN, Makotkine I, et al. Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. Am J Psychiatry. 2014 Aug;171(8):872–80.

79. Bader HN, Bierer LM, Lehrner A, Makotkine I, Daskalakis NP, Yehuda R. Maternal Age at Holocaust Exposure and Maternal PTSD Independently Influence Urinary Cortisol Levels in Adult Offspring. Front Endocrinol (Lausanne). 2014;5:103.

80. Bowers ME, Yehuda R. Intergenerational Transmission of Stress in Humans. Neuropsychopharmacology. 2016 Jan;41(1):232–44.

81. Iurlaro M, von Meyenn F, Reik W. DNA methylation homeostasis in human and mouse development. Curr Opin Genet Dev. 2017 Apr;43:101–9.

82. Grossniklaus U, Kelly WG, Kelly B, Ferguson-Smith AC, Pembrey M, Lindquist S. Transgenerational epigenetic inheritance: how important is it? Nat Rev Genet. 2013;14(3):228–35.

83. Skvortsova K, Iovino N, Bogdanović O. Functions and mechanisms of epigenetic inheritance in animals. Nat Rev Mol Cell Biol. 2018 Dec;19(12):774–90.

84. Szyf M. Lamarck revisited: epigenetic inheritance of ancestral odor fear conditioning. Nat Neurosci. 2014 Jan;17(1):2–4.

85. Dias BG, Ressler KJ. Parental olfactory experience influences behavior and neural structure in subsequent generations. Nat Neurosci. 2014 Jan;17(1):89–96.

86. Gapp K, Jawaid A, Sarkies P, Bohacek J, Pelczar P, Prados J, et al. Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nat Neurosci. 2014 May;17(5):667–9.

87. Gapp K, Bohacek J. Epigenetic germline inheritance in mammals: looking to the past to understand the future. Genes Brain Behav. 2018;17(3):e12407.

88. Robinson GE, Barron AB. Epigenetics and the evolution of instincts. Science. 2017 Apr 7;356(6333):26–7.

89. Head JA. Patterns of DNA Methylation in Animals: An Ecotoxicological Perspective. Integrative and Comparative Biology. 2014 Jul 1;54(1):77–86.

90. Potok ME, Nix DA, Parnell TJ, Cairns BR. Reprogramming the Maternal Zebrafish Genome after Fertilization to Match the Paternal Methylation Pattern. Cell. 2013 May;153(4):759–72.

91. Jiang L, Zhang J, Wang J-J, Wang L, Zhang L, Li G, et al. Sperm, but Not Oocyte, DNA Methylome Is Inherited by Zebrafish Early Embryos. Cell. 2013 May;153(4):773–84.

92. Bailey CH, Bartsch D, Kandel ER. Toward a molecular definition of long-term memory storage. Proc Natl Acad Sci USA. 1996 Nov 26;93(24):13445–52.

93. Hawkins RD, Kandel ER, Bailey CH. Molecular mechanisms of memory storage in Aplysia. Biol Bull. 2006 Jun;210(3):174–91.

94. Rajasethupathy P, Antonov I, Sheridan R, Frey S, Sander C, Tuschl T, et al. A role for neuronal piRNAs in the epigenetic control of memory-related synaptic plasticity. Cell. 2012 Apr 27;149(3):693–707.

95. Pearce K, Cai D, Roberts AC, Glanzman DL. Role of protein synthesis and DNA methylation in the consolidation and maintenance of long-term memory in Aplysia. Elife. 2017 09;6.

Figure captions

Figure 1: FKBP51 regulates the stress response by interacting with the steroid receptor complex. Stress exposure leads to the release of corticotropin-releasing factor (CRF) from the hypothalamus (1). CRF is transported to the anterior pituitary gland where it stimulates the production of adrenocorticotropic hormone (ACTH) (2). In turns, ACTH stimulates the adrenal glands to produce and release stress hormones (cortisol) into the blood stream (3). When cortisol levels reach a certain level, the binding of cortisol to the glucocorticoid receptor (GR) (4) usually leads to the termination of the stress response (5). FKBP51 expression is induced by GR activation by stress hormones (6) and FKBP51 interacts with the steroid receptor complex and reduces the affinity of GR to stress hormones (7), thereby prolonging the stress response.

Figure 2: After peripheral noxious stimulation, FKBP51 is upregulated in the dorsal horn following chromatin relaxation. *FKBP5* is rapidly epigenetically regulated in the dorsal horn after peripheral noxious stimulation. After Complete Freund's Adjuvant injection in the ankle joint, we observed an increase in phosphorylation of the transcriptional regulator MeCP2 (1), a decrease in DNA methylation in the promoter sequence of the gene *FKBP5* (2) and an increase in FKBP51 protein (3) (34,39). MeCP2: methyl CpG binding protein 2; HDACs: histone deacetylases; P: phosphorylation.

Competing Interests

I have no competing interests.'

Figure 1

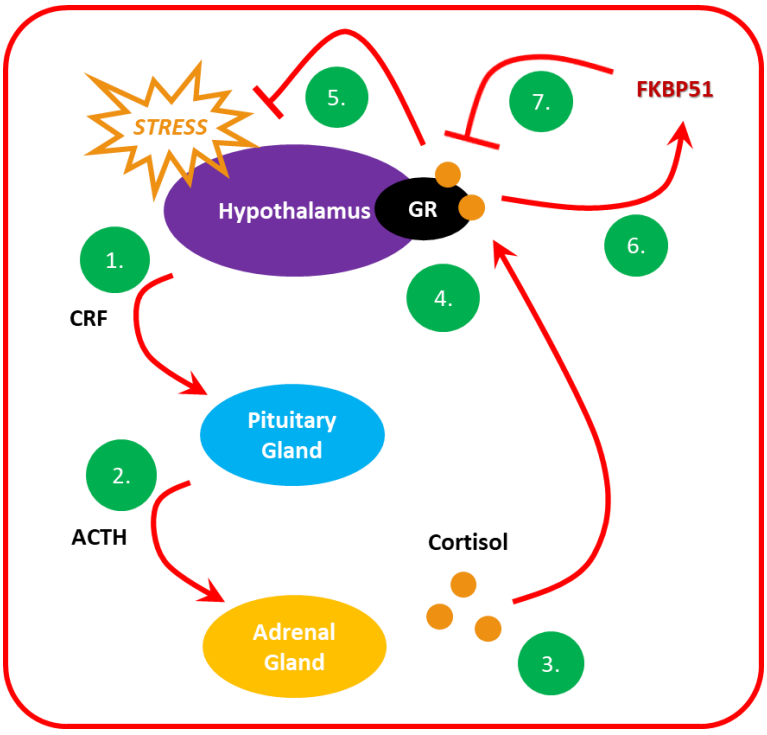

Figure 2