CPEB3-dowregulated *Nr3c1* mRNA translation confers resilience to developing PTSD-like behavior in fear-conditioned mice

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Background
Posttraumatic stress disorder (PTSD) is a trauma-induced psychiatric disorder, which depends on not only the intensity of trauma but also genetic risk factors; the latter may result in enhanced fear memory formation and/or impaired fear extinction after exposure to trauma reminders. A significant number of individuals with PTSD do not respond well to exposure therapy, which modifies fear memory through extinction learning. Therefore, the risk alleles that influence the development and treatment of PTSD must be identified. However, the genetic predisposition to PTSD is difficult to determine because an extensive trauma is necessary to trigger its development, and healthy controls can carry PTSD risk alleles in the absence of over-threshold trauma exposure.

Aims & Objectives
Susceptibility or resilience to PTSD depends on one's ability to appropriately adjust synaptic plasticity for coping with the traumatic experience. Activity-regulated mRNA translation synthesizes plasticity-related proteins to support long-term synaptic changes and memory. Hence, cytoplasmic polyadenylation element-binding protein 3-knockout (CPEB3-KO) mice, showing dysregulated translation-associated synaptic rigidity, may be susceptible to PTSD-like behavior. In this study, we addressed the involvement of CPEB3 in PTSD.

Methods
A context-dependent auditory fear conditioning and extinction paradigm was used to evaluate fear responses in mice. A genome-wide screen, gene ontology and GEO analyses, western blotting, calcium imaging and pharmacological rescue experiments were used to determine the role of CPEB3-controlled translation in fear extinction.

Results
We found that CPEB3-KO mice exhibited traumatic intensity-dependent PTSD-like fear memory. A genome-wide screen of CPEB3-bound transcripts revealed that *Nr3c1*, encoding glucocorticoid receptor (GR), was translationally suppressed by CPEB3. Thus, CPEB3-KO neurons with elevated GR expression exhibited increased corticosterone-induced calcium influx and decreased mRNA and protein levels of brain-derived neurotrophic factor (*Bdnf*). Moreover, the reduced expression of BDNF was associated with increased GR level during fear extinction in CPEB3-KO hippocampi. Intracerebroventricular delivery of BDNF before extinction training mitigated spontaneous fear intrusion in CPEB3-KO mice during extinction recall. Analysis of two GEO datasets revealed decreased transcriptomic expression of *CPEB3* but not *NR3C1* in peripheral blood mononuclear cells of humans with PTSD. Collectively, this study reveals that CPEB3, as a potential PTSD-risk gene, downregulates *Nr3c1* translation to maintain proper GR-BDNF signaling for fear extinction.

Discussion & Conclusion
Bi-directional control of synaptic efficacy is instrumental for dynamic and adaptive changes of memory and behaviors. Because PTSD is precipitated by the failure to appropriately adjust synaptic plasticity after severe trauma, KO or transgenic mice showing enhanced memory consolidation and/or impaired extinction should be more prone to PTSD-like behavior with increased intensity of the traumatic experience as we have demonstrated here that CPEB3 is a novel regulator of GR-mediated stress signaling for coping with traumatic experiences. We proposed that such mouse models (e.g. CPEB3-KO mice) could simulate the contribution of genetic risk factors to PTSD and resilience in response to exposure therapy and thus facilitate the molecular underpinnings of PTSD.