UNIVERSITÀ DEGLI STUDI DI MILANO

D-MEM PhD-UNIMI | Doctorate program Milan EXPERIMENTAL MEDICINE

PROJECT TITLE

Maladaptive expression of memory as important determinant of Post-Traumatic Disorders

TUTOR and co-Tutor

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PROJECT DESCRIPTION

Post-traumatic disorders are widespread in western countries, representing individual, healthcare and societal burden whose largely elusive pathomechanisms limit therapeutic options. In our laboratory, we recently characterized a physiological neuroepigenetic mechanism involved in contrasting memory consolidation. We hypothesize that the ensemble of psychiatric symptoms that a person who underwent traumatic experiences may develop, is intimately linked to an exaggerated “contextual” strength of the traumatic memory. As such, enduring bad feelings, ectopic anxiety arousal and excessive manifestation of discomfort could be related to a sort of “short circuit” in which non-harmful, seemingly neutral contextual cues potently recall traumatic memories even when months and even years have passed. These psychiatric symptoms can be interpreted as maladaptive expression of memory underlying fear memory overgeneralization one of the prominent post-traumatic symptoms. In order to develop this line of research, the candidate will exploit different in vivo, in vitro and genetic approaches. In particular, she/he will center his/her investigations on Lysine Specific Demethylase 1 (LSD1), a remarkable homeostatic regulator of neuroplastic transcription. The candidate will test the hypothesis that LSD1 acts as an epigenetic guardian involved in the process of limiting negative (long lasting, psychiatric) effects of trauma (thereby promoting resilience) by restraining contextual fear/traumatic memory. Our research previously showed that only in response to trauma, a mammalian hippocampus-restricted splicing event increases the level of LSD1 in excitatory neurons. In association with Histone Deacetylase 2 (HDAC2), LSD1 possibly cooperates to limit contextual memory “on demand” via reducing trauma-induced transcription. The candidate will exploit different strategies to pharmacologically increase or decrease LSD1 level in the brain before administering paradigms of trauma, aiming respectively at a negative and positive modulation of contextual fear memory (scored by contextual fear conditioning test) and trauma resiliency (scored by social defeat stress).

As second aim of the project, the candidate will research for possible LSD1 gene variants as contributor to stress vulnerability in humans. In particular she/he will analyze a genetic contribution to the trauma-induced shift in LSD1/neuroLSD1 ratio resulting from splicing-mediated regulation of LSD1 exon E8a, whose inclusion generates neuroLSD1. The candidate will functionally characterize known human haplotypes (unpublished data from the lab) mapping at neuroLSD1 exon E8a cis-regulatory elements, to verify if they might functionally modify splicing. This analysis will allow to predict a differential efficiency in the trauma-induced shift in LSD1/neuroLSD1 in the human brain, representing a novel vulnerability spot. A differential association of the identified LSD1 haplotype/s in cohorts of psychiatric patients vulnerable to post-traumatic stress disorders will help to further validate LSD1 as stress-response modulator.

The deliverables of this project include new knowledge on a possible trauma-protective LSD1 role, mediated by its selective and efficient reduction of trauma-associated contextual fear memory opening new avenues of intervention in the pharmacological treatment of PTSD. In addition, the project has the ambition to provide a solid molecular rationale to those psychological therapies aimed at remodeling the specific trauma-associated contextual memories, reducing the distance between psychological and pharmacological approaches to post-traumatic disorders.

CANDIDATE SPECIFIC REQUIREMENTS

The ideal candidate is already expert in most molecular biology techniques. Preferential skills include experience with in vivo experiments, behavioral analyses and pharmacological approaches.
Buone conoscenze di biologia molecolare saranno considerate come titolo preferenziale così come una documentata esperienza con sperimentazione in vivo, analisi del comportamento ed approcci farmacologici.

MOST RELEVANT PUBLICATIONS FOR THE PROJECT

1. Evolution Increases Primates Brain Complexity Extending RbFOX1 Splicing Activity to LSD1 Modulation. Forastieri C, Italia M, Toffolo E, Romito E, Bonasoni MP, Ranzani V, Bodega B, Rusconi F, Battaglioli E. J Neurosci. 2022 Mar 28:JN-RM-1782-21. doi: 10.1523/JNEUROSCI.1782-21.2022. Online ahead of print. PMID: 35351830
2. NeuroLSD1: Splicing-Generated Epigenetic Enhancer of Neuroplasticity.Rusconi F, Grillo B, Toffolo E, Mattevi A, Battaglioli E.Trends Neurosci. 2017 Jan;40(1):28-38. doi: 10.1016/j.tins.2016.11.002. Epub 2016 Dec 13.PMID: 27986293 Review.
3. LSD1/KDM1A mutations associated to a newly described form of intellectual disability impair demethylase activity and binding to transcription factors. Pilotto S, Speranzini V,

Marabelli C, Rusconi F, Toffolo E, Grillo B, Battaglioli E, Mattevi A. Hum Mol Genet. 2016 Jun 15;25(12):2578-2587. doi: 10.1093/hmg/ddw120. Epub 2016 Apr 19. PMID: 27094131

4. LSD1 modulates stress-evoked transcription of immediate early genes and emotional behavior. Rusconi F, Grillo B, Ponzoni L, Bassani S, Toffolo E, Paganini L, Mallei A, Braida D, Passafaro M, Popoli M, Sala M, Battaglioli E. Proc Natl Acad Sci U S A. 2016 Mar 29;113(13):3651-6. doi: 10.1073/pnas.1511974113. Epub 2016 Mar 14. PMID: 26976584 Free PMC article.

5. LSD1 Neurospecific Alternative Splicing Controls Neuronal Excitability in Mouse Models of Epilepsy. Rusconi F, Paganini L, Braida D, Ponzoni L, Toffolo E, Maroli A, Landsberger N, Bedogni F, Turco E, Pattini L, Altruda F, De Biasi S, Sala M, Battaglioli E. Cereb Cortex. 2015 Sep;25(9):2729-40. doi: 10.1093/cercor/bhu070. Epub 2014 Apr 15. PMID: 24735673