Al collegio docenti del Dottorato in Medicina Molecolare

Dott.ssa Giulia Braccagni
Ciclo XXXV **Tutor** Prof.ssa Carla Gambarana

Attività svolta nel secondo anno di Dottorato, Anno Accademico 2020/2021

Introduction: Neurosteroids orchestrate stress responses and represent key factors in resilience or vulnerability to development of major depression (MD). 5α-Reductase (5αR) is the rate-limiting step of neurosteroid synthesis. We previously showed that acute stress increases 5αR2 expression in the prefrontal cortex (PFC), while chronic stress decreased 5αR2 levels in PFC and nucleus accumbens (NAc), two key areas regulating stress responses. Thus, I investigated how region-specific changes in 5αR2 expression regulate depressive-like behaviors.

Methods: Adeno-associated virus (AAV) harboring shRNA for 5αR2 (AAV-5αR2-shRNA) was used to downregulate 5αR2. AAV-5αR2-shRNA-GFP or control AAV-scrambled-shRNA-GFP were stereotaxically injected in PFC and NAc of male rats. AAV spreading was analyzed by immunofluorescence and 5αR2 expression levels by immunoblotting. Two weeks after AAV injection, 5αR2 knock-down (KD) rats were tested in the forced swim test (FST) and sucrose preference test (SPT). In the FST rats are forced to swim in an inescapable tank, providing a measure of behavioral despair, reminiscent of the difficulty to cope with stressful situations. In the SPT rats can choose between a palatable sucrose solution or water, providing a measure of hedonic responses, impaired in MD.

Results: AAV-mediated 5αR2 down-regulation in PFC induced a depressive-like phenotype in male rats. Indeed, PFC 5αR2 KD rats, compared to control group rats, showed decreased latency to immobility and increased immobility time in the FST, decreased sucrose preference in the SPT, indicating the presence of anhedonia. Conversely, 5αR2 down-regulation in NAc did not induce the development of a depressive phenotype. Immunofluorescence analysis confirmed GFP expression limited to the PFC and NAc and immunoblotting demonstrated a significant decrease in 5αR2 levels in both regions in the KD group.
These results provide further information on the possible region-specific role of 5αR2 expression in conferring vulnerability to the development of a depressive phenotype. Thus, 5αR2 represents the "positive" internal control for the next RNA-Seq analysis of transcriptional patterns in the rat models of MD that aims to identify molecular targets that may be useful for MD prevention, diagnosis, and therapy.