Receptor interacting protein (RIP140) is a transcription coregulator highly expressed in macrophages to regulate inflammatory and metabolic processes. However, its implication in neurological, cognitive and emotional conditions, and the cellular systems relevant to its biological activity within the central nervous system are currently less clear. A transgenic mouse line with macrophage-specific knockdown of RIP140 was generated (MΦRIPKD mice) and brain-region specific RIP140 knockdown efficiency evaluated. Mice were subjected to a battery of tests, designed to evaluate multiple behavioral domains at naïve or following site-specific RIP140 re-expression. Gene expression analysis assessed TNF-α, IL-1β, TGF-1β, IL1-RA and neuropeptide Y (NPY) expression, and in vitro studies examined the effects of macrophage's RIP140 on astrocytes' NPY production. We found that RIP140 expression was dramatically reduced in macrophages within the ventromedial hypothalamus (VMH) and the cingulate cortex of MΦRIPKD mice. These animals exhibited increased anxiety- and depressive-like behaviors. VMH-targeted RIP140 re-expression in MΦRIPKD mice reversed its depressive- but not its anxiety-like phenotype. Analysis of specific neurochemical changes revealed reduced astrocytic-NPY expression within the hypothalamus of MΦRIPKD mice, and in vitro analysis confirmed that conditioned medium of RIP140-silnenced macrophage culture could no longer stimulate NPY production from astrocytes. The current study revealed an emotional regulatory function of macrophage-derived RIP140 in the VMH, and secondary dysregulation of NPY within hypothalamic astrocyte population, which might be associated with the observed behavioral phenotype of MΦRIPKD mice. This study highlights RIP140 as a novel target for the development of potential therapeutic and intervention strategies for emotional regulation disorders [1)].

Feng et al. show that the unfolded protein response (UPR) in neurons induces rapid translocation of nuclear receptor-interacting protein 140 (RIP140) to the cytoplasm. In the cytoplasm, RIP140 localizes to the ER by binding to the IP3R. The carboxyl-terminal RD4 domain of RIP140 interacts with the carboxyl-terminal gate-keeping domain of the IP3R. This molecular interaction disrupts the IP3R's 'head-tail' interaction, thereby suppressing channel opening and attenuating IP3R-mediated Ca(2+) release. This contributes to a rapid suppression of the ER stress response and provides protection from apoptosis in both hippocampal neurons in vitro and in an animal model of ER stress. Thus, RIP140 translocation to the cytoplasm is an early response to ER stress and provides protection against neuronal death [2)].

Lin et al. found that RIP140, a wide-spectrum cofactor of nuclear hormone receptors, acts as a co-repressor of heat shock factor 1 (HSF1) to suppress HSR in healthy neurons. When neurons are stressed such as by heat shock or sodium arsenite (As), cells engage specific proteosome-mediated degradation to reduce RIP140 level, thereby relieving the suppression and activating HSR. RIP140 degradation requires specific Tyr-phosphorylation by Syk that is activated in stressful conditions. Lowering RIP140 level protects hippocampal neurons from As stress, significantly it increases neuron survival and improves spine density. Reducing hippocampal RIP140 in the mouse rescues chronic As-induced spatial learning deficits. This is the first study elucidating RIP140-mediated suppression of HSF1-activated HSR in neurons and brain. Importantly, degradation of RIP140 in stressed neurons relieves this suppression, allowing neurons to efficiently and timely engage HSR programs and recover. Therefore, stimulating RIP140 degradation to activate anti-stress program provides a potential preventive or therapeutic strategy for neurodegeneration diseases [3)].

1)

Flaisher-Grinberg S, Tsai HC, Feng X, Wei LN. Emotional regulatory function of receptor interacting protein 140 revealed in the ventromedial hypothalamus. Brain Behav Immun. 2014 Aug;40:226-34.

doi: 10.1016/j.bbi.2014.03.019. Epub 2014 Apr 13. PubMed PMID: 24726835; PubMed Central PMCID: PMC4102625.

2)

Feng X, Krogh KA, Wu CY, Lin YW, Tsai HC, Thayer SA, Wei LN. Receptor-interacting protein 140 attenuates endoplasmic reticulum stress in neurons and protects against cell death. Nat Commun. 2014 Jul 28;5:4487. doi: 10.1038/ncomms5487. PubMed PMID: 25066731; PubMed Central PMCID: PMC4200015.

3)

Lin YL, Tsai HC, Liu PY, Benneyworth M, Wei LN. Receptor-interacting protein 140 as a co-repressor of Heat Shock Factor 1 regulates neuronal stress response. Cell Death Dis. 2017 Dec 12;8(12):3203. doi: 10.1038/s41419-017-0008-5. PubMed PMID: 29233969.