

Mini Review

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RIP140 in Stress Response of the Brain

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ABSTRACT

Receptor interacting protein 140 (RIP140), gene named Nuclear receptor interacting protein 1 (*Nrip1*), is a transcription co-regulator of numerous nuclear receptors and transcription factors that are important for various biological processes. RIP140 is highly expressed in various cell types of the brain, especially cortex and hippocampus. Increasingly, studies have begun to reveal its multiple functional roles in maintaining brain health. In particular, there appears to be an intimate relationship between RIP140 and neurodegenerative diseases, such as reduced RIP140 expression in Alzheimer's Disease (AD) postmortem brain and impaired cognitive functions in RIP140 knockout mice. The different functional roles of RIP140, mediated by distinct mechanisms, coordinately contribute to the execution of stress response of the brain to Endoplasmic Reticulum (ER) stress, heat shock (HS) stress, oxidative stress and psychological/behavioral stress. In this review, we describe the roles of RIP140 in three brain cell types (neurons, microglia, and astrocytes) stressed by pharmacological agents or behavioral manipulation. These results demonstrate physiological integration of various functional roles of RIP140 in different brain cells to facilitate survival and recovery from stress. The results also suggest a potential, preventive and/or therapeutic strategy by targeting RIP140 in managing neurodegenerative diseases.

Keywords: RIP140; NRIP1; Brain; Psychological stress; ER stress; Heat shock response; Neuron; Microglia; Astrocyte; Protein degradation; Post-translational modification.

Introduction

Receptor interacting protein RIP140 (RIP140, gene name *Nrip1*) is a versatile transcriptional co-regulator of numerous nuclear receptors and transcription factors^{1,2}. RIP140 can function as a co-activator or co-repressor, and is detected in various tissues including brain, liver, adipose, muscle and immune cells. As a co-repressor, RIP140 recruits histone deacetylases (HDACs), C-terminus binding protein (CtBP) and other chromatin remodeling proteins to regulate gene expression². In adipocyte, RIP140 suppresses genomic response to hormones such as thyroid hormone and retinoic acid³⁻⁵. Animal and cell culture studies have demonstrated that lipid accumulation, fatty acid oxidation, energy dissipation, and glucose uptake can be regulated by RIP140 in adipocyte^{6,7}. In hepatocyte, RIP140 reduces phosphoenolpyruvate carboxykinase (PEPCK) levels to suppress gluconeogenesis by acting as a liver X receptor (LXR) co-repressor⁸. RIP140 also represses E2F transcription factor to affect tumor growth^{9,10}. As a co-activator, RIP140 interacts with LXR to enhance the expression of sterol regulatory element-binding protein 1 (SREBP-1) and fatty acid synthase to promote lipogenesis in the liver⁸. In inflammatory (M1) macrophage, RIP140 acts as co-activator of NFκB to increase inflammatory response¹¹.

In the brain, RIP140 is expressed in neurons, microglia and astrocytes, indicating extensive functional roles for RIP140 in

maintaining brain health. Molecular studies have shown extensive protein modification and context-dependent distribution/transport of RIP140 under various physiological/pathological conditions (see section 2 below), supporting the complexity of RIP140's multiple functional roles. Its ultimate role, on a system level, is most likely to reflect the collective actions of its multiple biological activities in various cell types rather than a simple cell-autonomous activity. To this end, this review focuses on RIP140's functional roles in three major brain cell types, neurons, microglia and astrocytes. Established molecular mechanisms of RIP140's action in the brain, mostly implicated in stress responses, are also reviewed.

Molecular features of RIP140

The first interesting molecular feature of RIP140 is its extensively context-dependent post-translational modifications (PTMs) such as phosphorylation, methylation, acetylation, methylation, PLP conjugation, SUMOylation and ubiquitination.^{2,12,13} These PTMs, elicited individually or in combination in response to various stimuli, modulate sub-cellular localization, stability and activity of RIP140. For instance, RIP140 undergoes specific arginine-methylation to initiate its nuclear-cytoplasmic export during adipocyte maturation/expansion¹⁴, which can also play out in stressed neurons (see later). In macrophages, in lipopolysaccharide induced inflammatory response, RIP140 is not only degraded via spleen protein kinase (Syk)-mediated tyrosine phosphorylation to tone down inflammatory response¹¹ but also exported to the cytoplasm to activate STAT6 signaling and enhance M2 anti-inflammatory response¹⁵.

Secondly, RIP140 also exerts specific extra-nuclear activities in various cell types, besides its widely reported co-regulatory activities in gene transcription. In fat-accumulating, expanding adipocyte, RIP140 gradually translocate to the cytoplasm and interacts with AS160 (Akt substrate of 160 kDa), thereby reducing further uptake

of glucose and insulin vesicles, which contributes insulin resistance⁷. In macrophage, RIP140 is exported to the cytoplasm of activated cell to enhance M2 polarization in anti-inflammatory stage¹⁵. The extra-nuclear activity of RIP140 is also observed in stressed neurons (see below).

Thirdly, in adult brain, RIP140 is detected in multiple cell types including neurons, microglia, and astrocytes¹⁶⁻¹⁹. In neurons, it can also be distributed to the nucleus and/or cytoplasm, depending upon the states/conditions of the cells^{19,20}. Further, its biological activity, protein stability and dynamics in neurons are context-dependent, which have been investigated in cultures and, to a lesser extent, in animals. Below we review the results of studies concerning RIP140 in these three brain cell types, and its physiological/pathological relevance to stresses in the brain. **Table 1** lists reports that are related to RIP140's activities and behavior in brain cells *in vitro*, as well as the implication of RIP140 in stress responses of the brain *in vivo*.

RIP140 in neurons

Nuclear RIP140 regulates heat shock factor 1 (HSF1) and HSR in stressed neurons

HSR is a highly conserved mechanism that protects organisms from different stressors, such as HS, heavy metals, oxidative stress, and ER stress^{21,22}. These stressors induce HSF1, the key transcription factor for HSR, which then dissociates from the chaperone complex and translocates into the nucleus. The active HSF1 forms phosphorylated trimers as an active transcription factor by binding to HS element (HSE) to promote the expression of HSR genes that are necessary for protein homeostasis and survival of stressed cells. In neurons derived from Huntington Disease (HD) patients' brain, downregulating HSF1 induces the accumulation of toxic misfolded protein which is involved in neurodegeneration^{23,24}. On the contrary, the presence of active HSF1 can prevent polyglutamine (polyQ) aggregate formation and attenuate neurodegeneration in cellular,

Table 1. The roles of RIP140 in various brain regions, cell subtypes and CNS diseases.

Author(s) and year	Cell subtype or Brain area	Stress/diseases model studied	Role of RIP140
Chuang et al, 1997 ⁶⁶	GHFT1-5 pituitary progenitor cell line	N/A	Thyroid hormone receptor/ estrogen receptor related gene regulation
Schaufele, 1999 ⁶⁷	GHFT1-5 pituitary progenitor cell line	N/A	Estrogen receptor related gene regulation
Duclot et al, 2012 ¹⁷	Cortex and hippocampus	Alzheimer's disease and depression	Cognitive learning and memory as well as stress response.
Flaisher-Grinberg et al, 2014 ⁵⁰	Hypothalamus	Forced swimming stress	Emotional regulatory
Feng et al, 2014 ²⁰	Neuron in hippocampus	ER stress	Neuron protection
Feng et al, 2015 ¹⁶	Astrocyte; cortex, hippocampus, and hypothalamus	Behavioral stress for mice; ER stress for astrocyte	Brain cholesterol homeostasis
Blondrath et al, 2016 ¹⁸	Hippocampus, cortex, cerebellum	Alzheimer's disease	Regulation of gene involved in Ab generation
Lin et al, 2017 ¹⁹	Neuron in hippocampus	Heat shock stress/oxidative stress	Co-repressor of HSF1 and regulation of HSR

mouse, worm, and fly models²⁵⁻²⁷. The protective role of HSF1 activation is mediated by its induction of heat shock proteins (HSPs). Over-expression or pharmacological activation of HSPs is sufficient to suppress proteinopathic neurodegeneration^{21,28}. All these studies demonstrate that HSF1-mediated HSR plays a crucial role in the development/progression of neurodegenerative diseases.

To this end, we have found that RIP140 is protective for hippocampal neurons in response to different stresses and cell death induction by acting as a co-repressor of HSF1 to down-regulate HSR in stressed hippocampal neuron¹⁹. In these neurons, HS rapidly (20 min at 41°C; 10 min at 43°C) induces HSF1 activation to elevate HSR. It appears that nuclear RIP140 can be associated with HSF1 as a corepressor when HSF1 enters the nucleus in stressed neurons. Following stress induction, rapid degradation of nuclear RIP140, which is otherwise associated with HSF1 as a corepressor, relieves HSF1 from repression and allows HSF1 to timely switch to an activator. Oxidative stress induced by sodium arsenite (As) at a concentration higher than 40 μ M also induces RIP140 degradation and subsequent HSF1-mediated HSR. In primary and HT22 hippocampal neurons, silencing RIP140 can enhance HSR, rescue spine density, and protect neurons from As-induced oxidative stress¹⁹. *In vivo* experiments have shown that chronic As treatment causes significant hippocampal-dependent learning defects in mice. Chronic knockdown of RIP140 in hippocampus by lentivirus-delivery of RIP140-silencing RNA (shRIP140) efficiently rescues the defects in As-treated mice, and dramatically increases HSR¹⁹. These animal experiments suggest that RIP140, possibly acting as a corepressor of HSF1, may function to safe guard neurons from accidental HSR under a normal condition; but in stressed neurons, early degradation of RIP140 may be

crucial for neurons to activate HSF1 and subsequent HSR in order to adapt to the stressful conditions and survive. Thus, we propose a model that, timely reducing nuclear RIP140 level in neurons is important for the execution of HSR in stressed neurons, ultimately protecting the brain from stressful insults (Figure 1).

In this context, rapid RIP140 degradation provides a timely, cell-autonomous protective mechanism, enabling proper HSF1 activation in hippocampal neurons¹⁹. Molecularly, we have determined that HS and As-stress activates RIP140 degradation, mediated by a specific proteasome dependent protein degradation that involves Syk elicited phosphorylation on three specific Tyr residues (Tyr 364, 418, 436) of RIP140. Interesting, inflammatory stress in macrophages also induces RIP140 degradation via the same Syk-mediated Tyr-phosphorylation¹¹, suggesting that Syk-mediated RIP140 degradation pathway may provide a common stress sensing mechanism in multiple cell types including neurons.

Cytoplasmic RIP140 protects neurons from ER stress via regulating IP3R

Eukaryotic cells employ a protein quality control important for cellular survival and function. Disrupting this system usually results in ER stress and the activation of unfolded protein response (UPR). ER stress is also closely related to Ca^{2+} homeostasis including its uptake and efflux through various transporters and ion channels on the ER membrane²⁹. Depleting Ca^{2+} storage in ER by blocking Ca^{2+} pumps or disrupting Ca^{2+} release results in ER stress and cell death²⁹. The control of intracellular Ca^{2+} via ER is contributed by two major ion channels/receptors - inositol 1,4,5-trisphosphate (IP3) receptor (IP3R) and ryanodine receptors (RyRs)³². IP3R on the ER

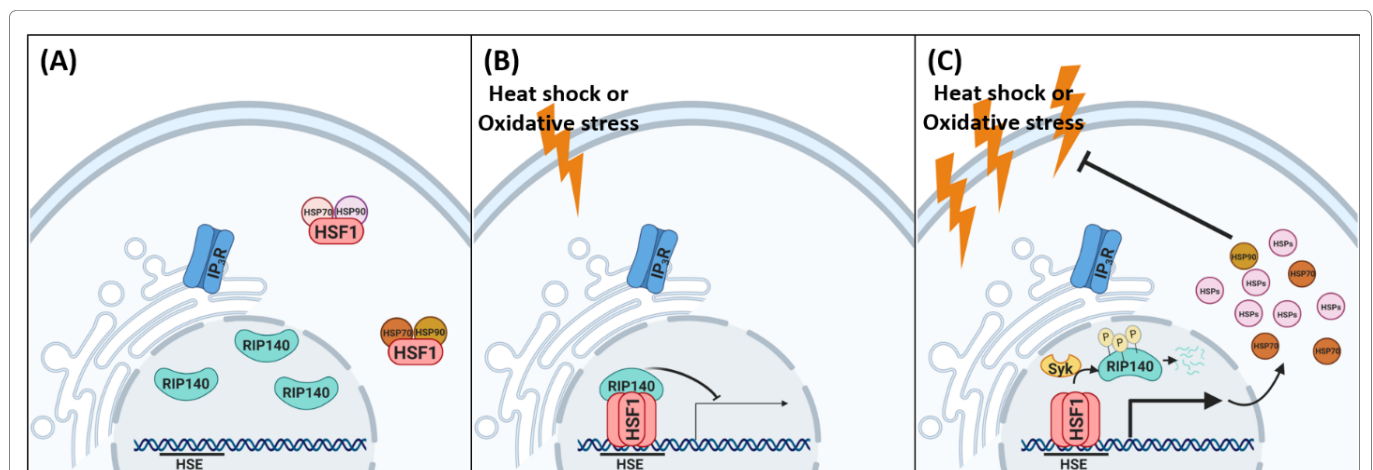


Figure 1: A scheme showing RIP140 modulating HSR under different stressful conditions in neuron. (A). In unstressed cells, HSF1 is localized in the cytosol and RIP140 is localized in nucleus. (B) During mild stress, HSF1 translocates to the nucleus to bind HSE and activate its chromatin targets; but RIP140 associates with HSF1 to repress (tone-down) HSF1's transcriptional activity. (C) In severely stressed cells, Syk is activated to phosphorylate RIP140 for its degradation; the repression of HSF1 is thus relieved, enabling a full scale HSR that facilitates adaptation and recovery.

is the main Ca^{2+} -release channel^{30,31}. Importantly, overtly activating IP3Rs usually triggers pathological processes and apoptosis, and knockout IP3R1 enhances neuronal vulnerability to ER stress³⁰. Moreover, stimulation of ER Ca^{2+} channels accelerates thapsigargin-induced ER calcium depletion and apoptosis and reducing Ca^{2+} release from ER by pharmacologically blocking IP3R-mediated Ca^{2+} release can attenuate ER stress and improved cell survival³². These studies demonstrate complicated regulation of IP3R in normal and stressed conditions.

We have found that, in neurons, ER stress inducers, such as thapsigargin (ER membrane Ca^{2+} pumps blocker), dithiothreitol (reducing agent), brefeldin A (collapse of the Golgi into ER), and amyloid beta ($\text{A}\beta$) all rapidly (within 15 min) induce nuclear RIP140 export and translocation to the cytoplasm²⁰. In the cytoplasm, RIP140 binds specifically to the IP3R, but not RyRs, on ER membrane, thereby inhibiting IP3R-mediated Ca^{2+} release from ER and protecting hippocampal neuron from excitatory neurotoxicity and cell death²⁰. We have further employed an animal model of ER stress (intraperitoneal injection of Tg) to validate the functional role for RIP140 *in vivo*³³. In this study, RIP140 was knocked down in hippocampal CA1 region, resulting in enhanced ER stress and apoptosis markers following Tg treatment, as compared to the control animals (without RIP140 silencing)²⁰. These results together support a functional role for RIP140 in neuroprotection against ER stress *in vitro* and *in vivo*.

At the molecular level, we have determined that the RD4 domain, residing at the carboxyl terminus of RIP140, directly interacts with the C-terminal gate-keeper domain of IP3R, which disrupts the “head-tail” interaction of IP3R necessary for its activation, thereby inhibiting channel open and Ca^{2+} release. Interestingly, introducing the RD4

fragment of RIP140 into hippocampal neurons is sufficient to decrease the formation of endogenous RIP140/IP3R complex and reduce Ca^{2+} release²⁰, suggesting a potential therapeutic strategy by targeting RIP140 in managing neuronal diseases associated with ER stress (Figure 2).

These studies illustrate at least two functional roles for RIP140 in protecting neurons from ER stress, mediated by its nuclear form (interacting with HSF1) and cytoplasmic form (interacting with IP3R). These neuron cell-autonomous protective mechanisms can contribute to the brain health. Their dysfunction may contribute to certain stress-related brain diseases as implicated in clinical data that show correlation with abnormal expression of RIP140¹⁸.

RIP140 in microglia

The Immune system and the central nervous system (CNS) interact closely to constitute the neuro-immune axis, which plays an important role in the development and homeostasis of the nervous system^{34,35}. Emerging studies have demonstrated that maintaining the crosstalk within this axis is pivotal to various neurophysiological processes^{36,37}. Due to physical blood-brain barrier, immune responses within the CNS are different from those in the periphery including the peripheral nervous system (PNS)^{38,39}. In the brain, tissue-resident macrophages, microglia cells, are one of the essential cell populations involved in defensive immune responses including sensing environmental changes and neuroprotection³⁴. Therefore, neuro-immune dysregulation can cause microglia cells to lose neuroprotective functions and trigger neurotoxicity, leading to various neurological diseases^{40,41}. For instance, during neuronal inflammation, microglia cells could activate astrocytes, causing amplification and sustention of inflammatory status and further leading to neurotoxicity

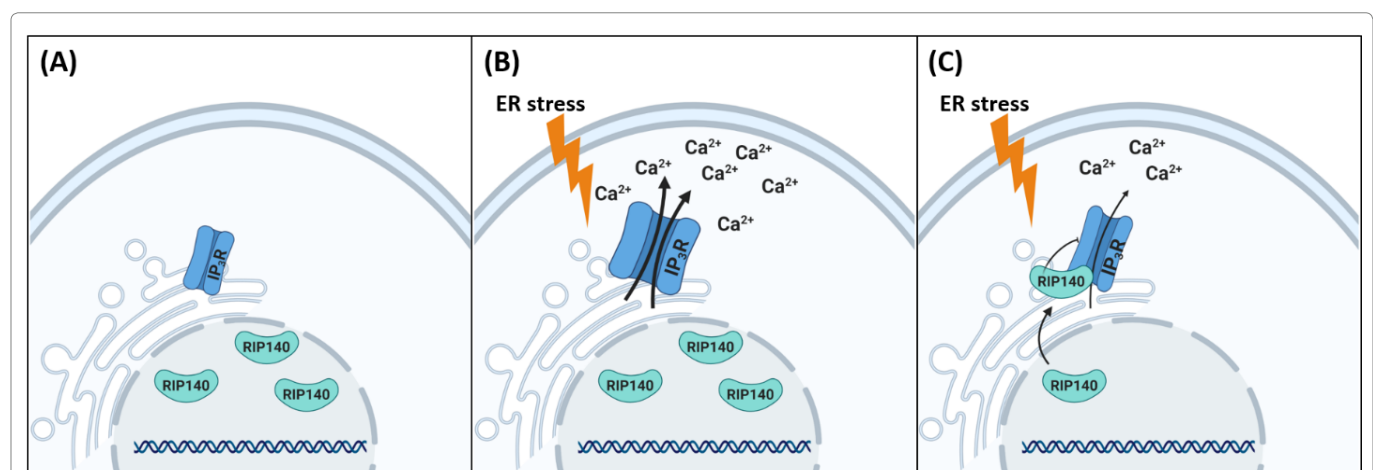


Figure 2: A scheme showing RIP140 modulating ER (cytosolic) stress via interacting with IP3R. (A). In unstressed cells, RIP140 is localized in nucleus. (B) During ER stress, IP3Rs are activated and Ca^{2+} is released from ER, which results in cell apoptosis. (C) To facilitate cell survival, RIP140 is rapidly translocated to the cytoplasm, specifically interacting with IP3R on the ER membrane, to reduce over-stimulation of IP3R-mediated Ca^{2+} release, thereby protecting neuron from ER stress-induced cell death.

⁴²⁻⁴⁴. In AD, microglia cells also play an important role in cleaning A β deposition through phagocytosis and endocytosis⁴⁵. In brain development, microglia are critical for synapse pruning; importantly, they can be reactivated in disease conditions including AD⁴⁶⁻⁴⁹.

In our lab, using a monocyte-specific RIP140 knockdown (MfRIP140KD) mouse model¹¹ where microglia RIP140 level is also reduced, we have found that MfRIP140KD mice have increased anxiety- and depressive-like behaviors⁵⁰. Interestingly, in MfRIP140KD mice where RIP140 expression is reduced in microglia, there appears to be a significant reduction in neuropeptide Y production in astrocyte. It is tempting to speculate that augmenting RIP140 levels in microglia, and thus brain inflammatory status, can also affect brain neurochemistry and contribute to neurological disorders. To this end, as increasingly recognized, microglia dysregulation can be highly associated with neurological diseases especially those related to chronic stress in the brain. In this context, RIP140's action in microglia can potentially contribute to stress response in the brain on a system level.

RIP140 in astrocyte

Clinical and basic studies both have demonstrated that stressful experiences can result in psychological and neurological disorders including depression^{51,52}. Forced swimming stress (FSS) test is the most popular test for depression-like behaviors in rodents, and is widely used as an antidepressant screening tool in rodents modeling human psychological stress⁵³.

MfRIP140KD mice show a significant increase in immobility when challenged with FSS, indicating a role for RIP140 in depressive like stress response¹⁷. While FSS can trigger a wide range of changes such as the sympathetic nervous system⁵⁴, the HPA axis (increased the stress hormone, corticosterone)^{54,55}, and neurotransmitters such as dopamine, serotonin, and GABA in the brain^{56,57}; of interest is that FSS also significantly reduces RIP140 level in the brain and increases its cholesterol content, which is associated with increased ER stress markers such as Bip in mouse brain¹⁶. Using primary astrocyte cell cultures as experimental systems, we have found that ER stress directly inhibits RIP140 mRNA expression via increasing microRNA 33 (miR33)¹⁶ which targets the mRNA's 3'-untranslated region of RIP140⁵⁸. Further, lowering RIP140 levels in astrocytes disrupts the expression of cholesterol metabolic genes and accelerates cholesterol exportation from astrocytes and uptake by neurons¹⁶. Presumably, these are attributable to the co-regulator (such as for the expression of cholesterol metabolizing genes) function of nuclear RIP140 in astrocyte.

While preliminary, these studies indicate that RIP140 in astrocyte can affect brain cholesterol homeostasis, which

may also modulate depressive-like stress in animals, and, probably, psychological stress-related conditions and other neurological disorders like AD in humans. Studies have also indicated that RIP140 can be involved in A β plaque formation^{18,58,61}. To this end, Apolipoprotein E4 has been shown as a key player in cholesterol regulation and A β plaque formation, and is a known risk factor of AD^{59,60}. It would be interesting to examine if and how RIP140 may be related to the regulation ApoE. Rigorous mechanistic studies of RIP140 action in astrocyte, *in vitro* and *in vivo*, await to be carried out.

Discussion and Perspectives

Because of the complicated PTMs of RIP140, which affects its protein localization, stability and functionality, and the extremely context-dependent nature of RIP140's activity/behavior, it requires extensive studies to carefully dissect and integrate the physiological and/or pathological pathways in specific brain cell types/circuitries where RIP140 plays roles in the face of stressful condition. It is also important to take into account the sequence of these events happening in a specific physiological or pathological processes. For example, ER stress and inflammation both can induce oxidative stress and HSR. However, ER stress induced by thapsigargin, dithiothreitol, and brefeldin A promotes rapid RIP140 translocation to cytoplasm in hippocampal neurons where it is required for toning down the extent of ER stress-induced IP3R activity, thus protecting cells from apoptosis²⁰. But HS, As-induced oxidative stress in hippocampal neurons can rapidly trigger nuclear RIP140 degradation, allowing HSF1 activation and thus execution of HSR program¹⁹. These represent neuron cell-autonomous protective mechanisms in the face of stress, mediated by both the nuclear and the cytoplasmic forms of RIP140. In astrocyte, ER stress reduces RIP140 mRNA and protein level¹⁶, which can alter brain neurochemistry and ultimately contributes to the modulation of brain health. In microglia, RIP140 modulates inflammatory response for both inflammatory and anti-inflammatory phases. This also is crucial to brain function and the maintenance of brain health. Given these multiple functions of RIP140 in various brain cells, it is important to understand the precise mechanism regulating RIP140 behavior/activity in these various brain cell types, and to what extent RIP140 is involved in these various processes in the context of whole brain. How these potentially synergistic or additive functional roles of RIP140 in various brain cells may integrate in the face of a specific type of stress, and whether any malfunction of RIP140 in any of these cells may contribute to the pathological processes of brain diseases are important questions to be further examined.

In the context of whole animal, the role of RIP140 specifically attributable to its actions in the brain has just begun to be understood. The facts that RIP140 is

expressed in multiple cell types of the brain and that it can function, differently, in the nucleus vs. the cytoplasm would indicate very complicated, multiple mechanisms of action. Accumulated data have mostly revealed its ultimate action in modulating brain stress response. This can be mediated by its cell autonomous action, such as in directly modulating neuronal stress, or by its action in non-neuronal cells like microglia and/or astrocyte that ultimately contribute to the overall health of the brain. In adult brain, RIP140 is most prominently detected in the cortex and hippocampus^{18,62}. This is also consistent with the finding that whole body RIP140 knockout mice indeed exhibit impaired cognitive function including deficits in hippocampus-dependent memory and learning, as well as an increased response to FSS challenges¹⁷. More interestingly, RIP140 expression in the brain is reduced during aging⁶³ and in AD postmortem brains¹⁸. In RIP140 transgenic (*Nrip1* knockout or over-expressing human RIP140) mice and cell lines, it has been found that RIP140 can regulate the expression of AD related genes, including β -site APP cleaving enzyme 1 (BACE1) and glycogen synthase kinase-3 (GSK3)¹⁸. Finally, the human *Nrip1* gene is located on chromosome 21⁶⁴ (an extra copy would cause Down's syndrome), and in the hippocampus of Down's syndrome patients, RIP140 level is elevated⁶⁵. All these experimental cell and animal studies, as well as clinical data, indicate that RIP140 can be intimately related to the development and/or progression of certain brain disorders, most notably stress-related neurodegenerative diseases such as AD and developmental disorders like Down's syndrome.

Many neurodegenerative diseases involve inflammation and protein misfolding and/or aggregation, such as A β and tau in AD, α -synuclein in Parkinson's disease, Huntingtin in HD, and superoxide dismutase in Amyotrophic lateral sclerosis. As described above, RIP140 exerts protective functions to attenuate, or adapt to, the stress condition in stressed cells, depending upon various specific signaling pathways (which can be triggered by environmental factors and/or cellular state that elicits PTMs). Therefore, it may be feasible to identify specific compounds that can trigger specific RIP140 translocation and/or degradation, thereby activating specific protective mechanism. Physiologically, stress responses are essential but proper and timely execution of different stress responses must be tightly regulated and coordinated in order to achieve the ultimate goal of animal survival and maintaining health. Given the high specificity of RIP140's functions and relevant signaling pathways, RIP140 should provide a highly potential and selective target for designing therapeutic strategy in the future. This requires careful dissection of the complicated and integrated functional roles of various forms of RIP140 in particular cell types in future studies.

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