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Age-Dependent Neuroimmune Modulation of IGF-1R in the Traumatic Mice

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Abstract

Background: Age-dependent neuroimmune modulation following traumatic stress is accompanied by discordant upregulation of Fyn signaling in the frontal cortex, but the mechanistic details of the potential cellular behavior regarding IGF-1R/Fyn have not been established.

Methods: Trans-synaptic IGF-1R signaling during the traumatic stress was comparably examined in wild type, Fyn (−/−) and MOR (−/−) mice. Techniques included primary neuron culture, in vitro kinase activity, immunoprecipitation, Western Blot, sucrose discontinuous centrifugation. Besides that, [^{3}H] incorporation was used to assay lymphocyte proliferation and NK cell activity.

Results: We demonstrate robust upregulation of synaptic Fyn activity following traumatic stress, with higher amplitude in 2-month mice than that in 1-year counterpart. We also established that the increased Fyn signaling is accompanied by its molecular connection with IGF-1R within the synaptic zone. Detained analysis using Fyn (−/−) and MOR (−/−) mice reveal that IGF-1R/Fyn signaling is governed to a large extent by mu opioid receptor (MOR), and with age-dependent manner; these signaling cascades played a central role in the modulation of lymphocyte proliferation and NK cell activity.

Conclusions: Our data argued for a pivotal role of synaptic IGF-1R/Fyn signaling controlled by MOR downstream signaling cascades were crucial for the age-dependent neuroimmune modulation following traumatic stress. The result here might present a new quality of synaptic cellular communication governing the stress like events and have significant potential for the development of therapeutic approaches designed to minimize the heightened vulnerability during aging.

Keywords: IGF-1R, Fyn, Synapse, Neuroimmune modulation, MOR

Background

It has shown that surgery depresses several aspects of immune functions, including decreased splenocyte proliferation and natural killer cell activity [1], impaired T cell proliferation [2] and bactericidal activity [3], reduced production of a number of cytokines [4,5]. Aging was recently was identified as an exaggeration for several stress responses by decline of proteostasis, DNA damage repair networks and mitochondrial respiratory metabolism [6,7]. Our previous observation confirmed this realization that when challenged with traumatic stress, 1-year rats displayed deteriorated immuno-suppression and prolonged recovery than 3-month counterpart. The major hypothesis has been proposed Fyn, a member of Src-family protein tyrosine kinase, as an explanation, whose age-dependent expression was responsible for the related cellular responses induced by traumatic stress, and presumed to be crucial for the resolution of this stressful event [8].

It has been well defined that Fyn is localized to the lipid rafts microdomain, emerging as distinct entry portals of signal compartment and played an essential role in cell migration, proliferation, gene expression, metabolism, and cytoskeletal architecture. Specifically, Fyn was presumed to be required for activation of growth factors [9,10]. It is now firmly established that stress-induced

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Functional capability of IL-15-Akt signaling in the denervated muscle

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ABSTRACT

Introduction: Denervation of skeletal muscles results in timely muscle–T cell cross-talk, but the mechanistic details of the orchestrated local circuits, as well as the potential regulatory link to the muscular function have not been established.
Methods: We used a combination of techniques to measure: (i) timely expression of IL-1β-ERK1/2 and IL-15-Akt signaling and (ii) celluar events controlled by IL-15-Akt signaling. Techniques included gastrocnemius strip, satellite cell culture, real time PCR, immunoprecipitation, Western blotting and subcellular fractionation. Besides that, muscle cell survival was determined by MTT assay.
Results: We found that there were two events: rapid IL-1β-ERK1/2 ⟨1 day⟩ and the later IL-15-Akt signaling ⟨7 day⟩ were selectively triggered by sciatic nerve injury. IL-15-Akt signaling was mostly targeted on CD2 phosphorylation and strengthened CD2–CD48 adhesion within gastrocnemius lipid rafts, in the same time, it exerted a restriction on TAB2 via miR155 pathway, thereby prevented muscle cell from inflammatory damage.
Conclusions: Our results suggested that IL-15-Akt signaling harbored the complex signals for muscle–T cell interaction, the regulatory networks have significant potential for the restriction on IL-1β inflammatory signaling. These results are likely to provide new insights into the therapy of neuromuscular injury.

1. Introduction

Skeletal muscle, which comprises up to 40% of human body mass, is a highly ordered, structurally stable tissue, whose function is dependent on intact nerve supply, as reported, sciatic nerve injury not only causes profound structural and functional changes, including rapid loss of muscle mass and contractile force [1–5], but also local immune response [6,7]. Recently, it was shown that in the denervated muscle, muscle cells were able to exchange membrane components with T cells and gained an important capacity for trogocytosis [8,9]. As such, skeletal muscle is also an immunologic micro-environment, wherein many positive and negative muscle-derived regulators were characterized to be responsible for immune interactions [10,11].

As a confirmation, our previous study demonstrated that inflammatory response is the first line of host defense in response to the sciatic nerve injury, which was represented by production of IL-1β [12]. As reported, IL-1β family has emerged as the primary evolutionarily sensors of pathogen-associated molecular patterns, which could shape and enhance the later adaptive immune responses [13–15]. Therefore, the presence of IL-1β signaling cascades in the early stage of muscle denervation was proposed to recruit and activate branches of macrophages and dendritic cells, the events might ultimately result in exaggerated cell damage [16,17]. Importantly, we also identified that, with prolonged muscle denervation, IL-1β signaling was gradually defected, while muscle–T cells interaction within the lipid rafts was preferentially initiated and mainly accomplished by IL-15, then, we assumed that homeostatic mechanisms might be implicate in maintaining T cell compartment during muscle denervation.

Accumulating evidence documented that CD48 and lymphocyte function related antigen-2 (LFA-2/CD2) tend to accumulate in the central region of immunological synapse, their adhesion is prerequisite for T cells targeting on antigen presenting cells (APCs) [18,19]. During this process, IL-15 could exceptionally modulate CD2 expression, by which played a critical role in T cell development [20,21]. Intriguingly, IL-15 and IL-1β were inversely modulated at the later stage of sciatic nerve injury [12], then, whether there was local network implicating in restriction muscular inflammation? Notably, among several classes of negative regulators of inflammatory response, microRNA 155, an evolutionarily conserved class of endogenous 22-nt noncoding RNA, was reported

Abbreviations: IL-1β, interleukin-1β; IL-1a, IL-1β receptor antagonist; IL-15, interleukin-15; CD48, LFA-3, cluster of differentiation 48; CD2, cluster of differentiation 2; APC, antigen present cell; TCR, T cell receptor; MTT, 3-(4,5-cimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; TAB2, TAK-1 binding protein 2; miR155, microRNA 155.

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