Review

CellPress

Hypothalamic microinflammation: a common basis of metabolic syndrome and aging

Yizhe Tang, Sudarshana Purkayastha, and Dongsheng Cai

Department of Molecular Pharmacology, Diabetes Research Center, Institute of Aging, Albert Einstein College of Medicine, New York, NY 10461, USA

Chronic microinflammation is a hallmark of many aging-related neurodegenerative diseases as well as metabolic syndrome-driven diseases. Recent research indicates that chronic caloric excess can lead to hypothalamic microinflammation, which in turn participates in the development and progression of metabolic syndrome disorders such as obesity, glucose intolerance, and hypertension. Additionally, it was recently shown that increasing age after young adulthood can cause hypothalamic microinflammation independently of nutritional status, mediating a central mechanism of systemic aging. Taken together, these findings suggest that the hypothalamus has a fundamental role, via hypothalamic microinflammation, in translating overnutrition and aging into complex outcomes. Here we summarize recent work and suggest a conceptual model in which hypothalamic microinflammation is a common mediator of metabolic syndrome and aging.

Co-basis of metabolic syndrome and aging: hypothalamic microinflammation

Metabolic syndrome, defined as a family of interrelated pathophysiological consequences of metabolic dysfunctions – particularly including obesity, hyperglycemia, insulin resistance, hyperlipidemia, and hypertension – represents a pathogenic substrate for the development of debilitating chronic diseases such as type 2 diabetes (T2D) and cardiovascular disease (CVD). Also, importantly, metabolic syndrome is frequently associated with aging [1,2] and, moreover, can participate in the development of other aging-related diseases; for example, Alzheimer's disease (AD), Parkinson's disease (PD), and some types of cancer [3–6]. Conversely, caloric restriction (CR), a nutritional manipulation that improves metabolic homeostasis, is known to counteract aging and aging-related disorders [7,8]. Following from this close relationship between metabolic syndrome and aging, a major question is: could nutritional change and aging increase engage a common mechanism in the progression to their interconnected disease outcomes and, if so, which organs in the body play a leading role in this process?

The hypothalamus is a key neuroendocrine system known to regulate energy homeostasis via the orchestrated actions of neural pathways and neuroendocrine hormones that regulate energy balance and nutrient homeostasis [9–16]. Nutritional status exerts important effects on various types of hypothalamic signaling, such as insulin and leptin pathways, and hypothalamic dysfunction is a critical cause of metabolic syndrome and its related diseases [17–24]. For example, recent research has shown that chronic overnutrition induces inflammation-like changes in the hypothalamus [25–35] mediated by low-degree activation of proinflammatory nuclear factor kappa B (NF-κB) and the upstream IκB kinase β (IKKβ) [25–27,31–33,36–40]. These atypical neural inflammatory changes comprise hundreds of inflammatory genes, including classical inflammatory molecules such as tumor necrosis factor alpha (TNF-α) and interleukins (ILs), that are dynamically induced during disease development, many aspects of which remain to be characterized. In general, these molecular inflammatory changes in the hypothalamus are often a result of hypothalamic low-level NF-κB activation and hence are termed 'hypothalamic microinflammation'. This overnutrition-triggered, NF-κB-dependent hypothalamic microinflammation can interrupt the central regulation of energy balance, glucose homeostasis, and blood pressure and mediate the core features of metabolic syndrome

Glossary

Free radical theory of aging: also referred to as the 'oxidative stress' theory of aging; argues that accumulation of free radical damage causes the aging of an organism. Free radicals are molecules or atoms with unpaired electrons and are generated by intracellular redox reactions or from exogenous sources such as ionizing radiation. Highly reactive free radicals can oxidize other molecules and cause damage to biological structures, such as DNA crosslinking, which in turn leads to many biological changes during aging.

Inflammaging: aging-associated changes in inflammatory networks characterized by a chronic low-grade proinflammatory cellular status or microenvironment. The initial causes may include various intracellular stresses such as ER stress, RNA stress, and mitochondrial dysfunction. The term also refers to promotion of the aging process by these inflammatory changes.

Overnutrition: chronic uptake (weeks to months in rodents and a longer duration in humans) of excessive amounts of calories; for example, through overeating calorie-rich food such as a high-fat diet.

Prediabetes: a prodiabetic metabolic condition that often features glucose intolerance, insulin resistance, hyperlipidemia, and obesity and represents an early therapeutic window for prevention of the development of T2D.

Corresponding author: Cai, D. (dongsheng.cai@einstein.yu.edu).

0166-2236/
© 2014 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tins.2014.10.002

CrossMark

including obesity, glucose intolerance, and hypertension [25–27,31–33,36–40].

It should be noted that low-grade inflammation is also a hallmark of aging; the systemic level of inflammation is negatively correlated with human longevity [41–44]. Studies using rodent models have shown that certain proinflammatory signaling pathways mediated by, for example, NF-κB are activated in various tissues during aging [45–47]. In accordance with the 'free radical' theory of aging [48] (see Glossary), chronic inflammation is known to damage cellular functions, and the relationship between inflammation and oxidative stress may have a critical role in aging. In the central nervous system (CNS), neural inflammation is a feature of aging-related neurodegenerative diseases [49], and the antiaging effects of CR correlate with enhanced synaptic plasticity, neurogenesis, and related protection against neurodegeneration in AD, PD, Huntington's disease (HD), and stroke [50–52]. Interestingly, like chronic overnutrition, aging after young adulthood can cause hypothalamic microinflammatory changes, albeit in a manner that can be independent of nutritional status. Recently, studies have shown that hypothalamic microinflammation promotes systemic aging [36–38]. This work is in agreement with various rodent models (Table 1) that have linked neural, endocrine, or metabolic signals to influences on aging and/or longevity. Therefore, NF-κB-dependent hypothalamic microinflammation represents a shared means through which conditions of overnutrition and aging can mediate the consequent development of metabolic and aging-related diseases. In the following sections, we discuss the molecular and cellular mechanisms and physiological relevance of hypothalamic microinflammation in the context of overnutrition and aging.

Hypothalamic microinflammation via mitochondrial and endoplasmic reticulum (ER) dysfunction

Unlike classical inflammation manifested in disease conditions like infections, trauma, and certain cancers, overnutrition/aging-related inflammation is often related to an unbalanced nutrient influx that challenges intracellular organelles such as mitochondria and the ER. It is appreciated that mitochondrial oxidative stress, at least through a chronic excess of reactive oxygen species (ROS), causes damage to cells and is implicated in the pathophysiology of metabolic syndrome as well as aging-related diseases [53,54]. For example, overexpression of the genes encoding the antioxidants superoxide dismutase (SOD), catalase, or thioredoxin-1 was shown to delay aging-related physiological impairments or protect against aging-associated diseases in mice [55] and, conversely, knockout of the genes for antioxidants such as SOD, methionine sulfoxide reductase, and thioredoxin-2 in mice shortens lifespan and predisposes animals to deficits in normal aging or age-related diseases [55,56]. Furthermore, it was recently shown that ROS production, presumably at physiological levels, can have biological actions, including metabolic functions [57–59]. Along these lines, a few studies have reported that the aging process did not accelerate in $Sod2^{+/-}$ mice [60], $Sod3^{-/-}$ mice [61,62], or sod mutant worms [63]. Despite oxidative stress not being clearly elevated in these animals with defective SODs [61,63–65] – perhaps due to activation of stress resistance pathways [66] – this literature should prompt us to assess other alterations in mitochondrial stress. Besides the elevated production of ROS, aging is associated with a wide spectrum of changes in mitochondria, including disorganization of mitochondrial structure, accumulation of mitochondrial DNA mutations, and functional decline in mitochondrial oxidative phosphorylation – all of which compromise normal cellular functions [67–72]. Of the many mechanisms involved, inflammation is likely to be a significant link between dysfunctional mitochondria and organismal aging [73]. Defective mitochondria can directly drive the production of proinflammatory cytokines and, reciprocally, inflammation can disrupt mitochondrial homeostasis, thus leading to an intracellular vicious cycle that should eventually compromise cellular functions. Therefore, although the contribution of ROS to aging remains to be elucidated, the connection between dysfunctional mitochondria and inflammation seems to play a role in the development of aging and aging-related diseases.

ER stress is a local, intracellular stress response that is prototypically reactive to the unfolded protein response (UPR) of the ER. When activated, UPR downstream cascades can interact with inflammatory molecules, including the IKKβ/NF-κB and c-Jun N-terminal kinase (JNK)/activator protein 1 (AP1) pathways as well as oxidative stress pathways, all of which are known to influence metabolism [74]. Research has demonstrated that ER stress can occur in various peripheral tissues under conditions of overnutrition, participating in the mechanisms of metabolic syndrome [74]. More recently, it was revealed that ER stress is induced in the hypothalamus in overnutrition [27,75], promoting hypothalamic NF-κB inflammation [27], and this hypothalamic interaction between ER stress and inflammation is sufficient to cause central insulin and leptin resistance [27]. Consistent with these results, brain-specific deletion of X-box-binding protein 1 (XBP1), which results in loss of ER function leading to ER stress in the hypothalamus, was reported to lead to leptin resistance and obesity [75]. Furthermore, ER stress-promoted hypothalamic inflammation causes sympathetic upregulation, inducing glucose intolerance and hypertension [32]. In addition to metabolic diseases, ER stress may also play a role in aging. For example, in aging-related neurodegenerative diseases such as HD, AD, amyotrophic lateral sclerosis, and PD, abnormal protein degradation along with ER stress has been proposed to be mechanistically important [76–79]. Thus, brain ER stress can contribute to certain aspects of hypothalamic microinflammation, although it is unclear whether this mechanism is early enough to initiate inflammation. Also, it remains to be addressed whether ER stress in the brain is critical for normal aging as opposed to aging-related brain diseases.

Hypothalamic microinflammation via RNA stress response

The RNA stress response and the associated formation of stress granules in the cytoplasm regulate eukaryotic mRNA translation and decay in response to environmental dynamics [80]. RNA stress granules and their pathological

Download English Version:

https://daneshyari.com/en/article/4354185

Download Persian Version:

https://daneshyari.com/article/4354185

Daneshyari.com