Biochimica et Biophysica Acta 1852 (2015) 633–643

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Sporadic inclusion-body myositis: A degenerative muscle disease associated with aging, impaired muscle protein homeostasis and abnormal mitophagy☆,☆☆

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ARTICLE INFO

Article history:
Received 7 August 2014
Received in revised form 9 September 2014
Accepted 10 September 2014
Available online 18 September 2014

Keywords:
Inclusion-body myositis
Aging
Mitophagy
Autophagy
Multiprotein aggregates
Amyloid-β42

ABSTRACT

Sporadic inclusion-body myositis (s-IBM) is the most common degenerative muscle disease in which aging appears to be a key risk factor. In this review we focus on several cellular molecular mechanisms responsible for multiprotein aggregation and accumulations within s-IBM muscle fibers, and their possible consequences. Those include mechanisms leading to: a) accumulation in the form of aggregates within the muscle fibers, of several proteins, including amyloid-β42 and its oligomers, and phosphorylated tau in the form of paired helical filaments, and we consider their putative detrimental influence; and b) protein misfolding and aggregation, including evidence of abnormal myoproteostasis, such as increased protein transcription, inadequate protein disposal, and abnormal posttranslational modifications of proteins. Pathogenic importance of our recently demonstrated abnormal mitophagy is also discussed. The intriguing phenotypic similarities between s-IBM muscle fibers and the brains of Alzheimer and Parkinson's disease patients, the two most common neurodegenerative diseases associated with aging, are also discussed. This article is part of a Special Issue entitled: Neuromuscular Diseases: Pathology and Molecular Pathogenesis.

1. Introduction

Sporadic inclusion-body myositis (s-IBM) is the most common muscle disease of older persons. The onset of clinical weakness is age-related, slowly progressive and leading to severe disability. There is no sustainable treatment available. Initially, s-IBM was considered a rare muscle disease, but during the last two decades, due to both physicians' greater awareness of this disease and the existence of more reliable pathological markers of s-IBM muscle biopsies, diagnosis of s-IBM has become more prevalent.

The pathogenesis of sporadic inclusion-body myositis (s-IBM) is complex and involves multidimensional pathways, and several critical issues are still unresolved.

The known muscle-fiber degeneration aspects and mononuclear-cell inflammation are components of the s-IBM pathology, but which is precedent and how they interrelate are not certain [1–5]. There is growing evidence that aging of the muscle-fiber, associated with intra-muscle-fiber accumulation of several conformationally-modified proteins, plays a primary and major pathogenic role leading to muscle-fiber destruction and clinical weakness.

s-IBM muscle-fiber degeneration is characterized by vacuolization and intra-muscle-fiber accumulation of misfolded, ubiquitinated, congophilic, multiple-protein aggregates [1–3]. We suggest that multiple postranslationally-modified proteins (see below) accumulated within the s-IBM aging muscle fibers may be eliciting the T-cell inflammatory reaction. This may be similar to some older patients with *hereditary* IBM (h-IBM) caused by missense mutations in the UDP-N-acetylglucosamine-2 epimerase/N-acetylmannosamine-kinase (GNE) gene, whose muscle biopsies exhibit several similarities to s-IBM biopsies and have various degrees of lymphocytic inflammation [6–8], even though that form of h-IBM is considered not basically immune-mediated [9]. We propose that in older h-IBM patients, the "aging" muscle-fiber environment, and perhaps other individual intrinsic muscle fiber abnormalities, make some of the accumulated proteins interpreted as "foreign" by the immune system, thereby inducing the component of T-cell lymphocytic inflammation. Another hint that inflammation might be secondary in human s-IBM is provided by an alleged mouse "model of s-IBM" based on overexpression of mutated gelsolin D187N [10]. In that model, within the myofibers of aged mouse there were intra-myofiber accumulations of misfolded and

☆ Research described in this review was supported by grants (to VA) from the National Institutes of Health (AG 16768 Merit Award), the Muscular Dystrophy Association, The Myositis Association, and the Helen Lewis Research Fund. None of the authors has conflict of interest.
☆☆ This article is part of a Special Issue entitled: Neuromuscular Diseases: Pathology and Molecular Pathogenesis.
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http://dx.doi.org/10.1016/j.bbadis.2014.09.005

congophilic proteins, including Aβ and gelsolin; in addition, there was perivascular and endomysial lymphocytic infiltration, suggesting that inflammation in that mouse model was secondary to the overexpressed abnormal mutant protein or other proteins accumulated within the muscle-fiber. The possibility that in s-IBM the inflammation might be a secondary to the ongoing degeneration and production of abnormal proteins within the muscle-fibers could explain why s-IBM patients, in contrast to polymyositis patients, whose muscle biopsies express similar inflammatory repertoire, do not satisfactorily respond to various anti-dysimmune/anti-inflammatory treatments that have been extensively tried [4,11–13]. There is a possibility, not yet convincingly proven, that various cytokines and other putatively toxic products released from the inflammatory cells may contribute to s-IBM pathogenesis and aggravate the existing degenerative component — a concept proposed by others [14,15]. Another aspect involves a reported genetic predisposition to s-IBM involving the HLA-DRB1 genotype, as well as association of the HLA-A haplotype with earlier disease onset [16,17]. A recent paper reported that polymorphism in the *TOMM40 gene* influences the risk of developing s-IBM, as well as the age of disease onset [18]. *TOMM40* encodes the mitochondrial pore protein Tom40, which is involved in the transport of Aβ and other proteins into mitochondria [19], and its elongation has been postulated associated with the pathogenesis of AD [20]. Even though still requiring confirmation, those studies might contribute to better understanding of mitochondrial abnormalities in s-IBM, and add to the possible importance of Aβ in s-IBM pathogenesis.

An increase of non-organ-specific auto-antibodies, as well as association of some autoimmune disorders with approximately 27% of s-IBM patients was reported [16,21,22]. Auto-antibodies against 5′-nucleotidase have also been reported in s-IBM patients [23,24], but their pathogenic significance is not yet known.

Here we describe several molecular abnormalities occurring in s-IBM muscle fibers, which, in our opinion, importantly contribute to the s-IBM pathogenesis. These include: 1. Abnormal accumulation within s-IBM muscle fibers of multiprotein congophilic aggregates, which apparently result from a) increased transcription of several proteins, b) their abnormal posttranslational modifications and misfolding, and c) inadequate protein disposal. These phenomena indicate abnormalities of muscle protein homeostasis, also called "myoproteostasis" [25]. We propose that abnormal myoproteostasis might be provoked or aggravated by an aging intracellular milieu. 2. Consequences of impaired autophagy leading to accumulation of Aβ42 and its oligomers. 3. Abnormalities of mitophagy putatively have a pathogenic role contributing to the mitochondrial abnormalities. Fig. 1 illustrates our current proposed cascade of s-IBM pathogenesis.

Experimental evidence indicating strong relationships among various pathologic pathways were recently described in detail [25], stressing the complex, interwoven pathogenic cascade of s-IBM.

Interesting phenomena involving degeneration of s-IBM muscle fibers are several similarities to the complex neuronal degenerations occurring both in Alzheimer (AD) and Parkinson (PD) brain diseases. These include: a) abnormal accumulations of many of the same putatively pathogenic proteins; b) similar posttranslational modifications of the accumulated proteins; c) similarly defective mechanisms of protein disposal, including inhibition of both the 26S proteasome and autophagy; and d) mitochondria abnormalities (detailed and referenced in [2,26,27]).

Accordingly s-IBM, similarly to AD and PD, is considered a "conformational disorder", caused by protein unfolding/misfolding and associated with the formation of ubiquitinated multiprotein inclusion-bodies (aggregates) (reviewed and referenced in [2,5,26]).

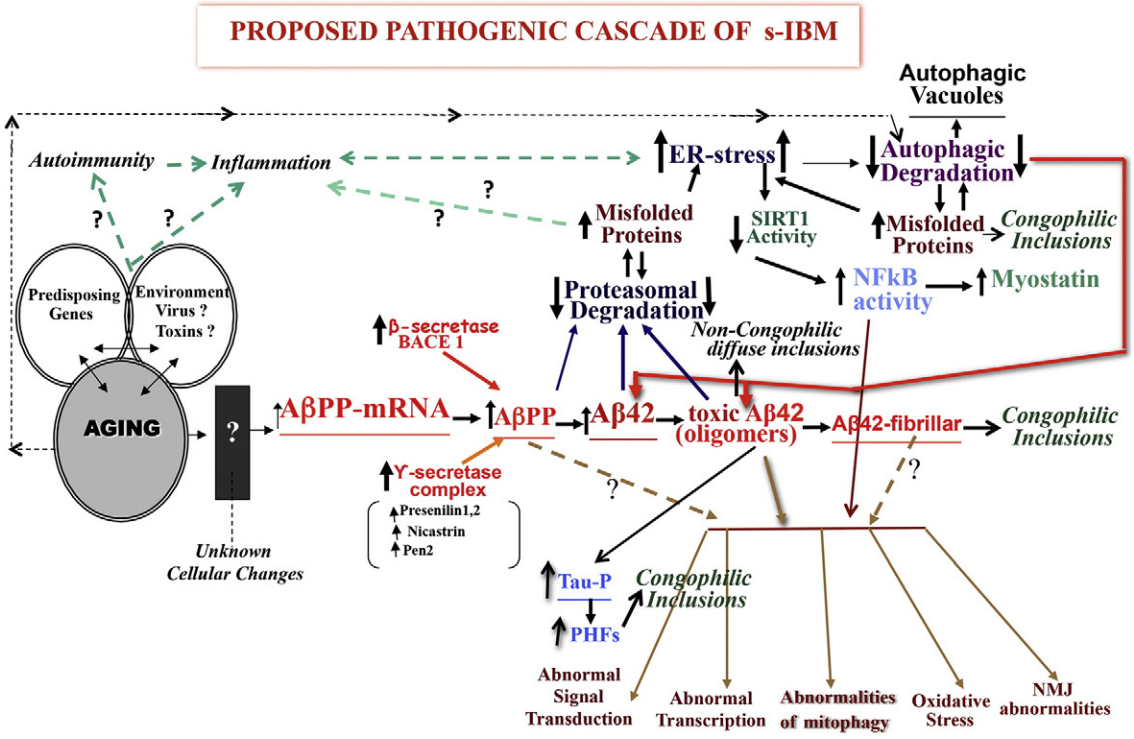

Fig. 1. Proposed pathogenic cascade of s-IBM. We propose that aging of the muscle fiber intracellular milieu, predisposing genes, and possibly some other aspects of the muscle-cell milieu, lead to still unknown molecular changes within the muscle fiber (indicated in the diagram as a black box with a question mark). This subsequently leads to several detrimental events, namely: a) existence of several abnormal mechanisms of protein transcription and processing; and b) accumulations of several proteins. These constitute the typical profile of s-IBM muscle fiber abnormalities (details in the text). We also propose that Aβ42 and its oligomers, as well as an inhibition of protein-disposal and mitochondrial abnormalities are key factors leading to muscle fibers atrophy, weakness, and death (details in the text).