Pathogenesis and therapy of inclusion body myositis

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Purpose of review
Inclusion body myositis (IBM) is a poorly understood progressive muscle disease of middle and later life. Its dual pathologies of autoimmunity and unexplained myofiber degeneration and loss have been enigmatic since its earliest descriptions over 40 years ago. No reliable effective therapy currently exists for IBM. This review provides an update of current issues in the pathogenesis and therapy of IBM.

Recent findings
Recent studies have further defined the clinical features of IBM, including natural history, pattern of muscle involvement, and role of MRI imaging. Further potential immune mediators have been identified. An autoantibody directed against a muscle antigen appears to have high specificity for IBM among muscle diseases. Further evidence for myonuclear degeneration has been reported.

Summary
IBM remains a poorly understood muscle disease, although understanding of the pathophysiological mechanisms continues to expand and is supporting new therapeutic approaches.

Keyword
inclusion body myositis, myositis, inflammatory myopathy, muscle atrophy

INTRODUCTION
Sporadic inclusion body myositis (IBM) is a progressive degenerative and inflammatory disorder of skeletal muscle of unknown cause. It has been recognized as a distinct disease for over 40 years, yet knowledge of its clinical features and course is still expanding. Although other forms of inflammatory myopathy had been described in the late 1800s, the distinctive pathological features of IBM were first described in 1967 [1]. The name of the disease entity derives from a 1971 case report of a patient who in retrospect did not have IBM [2]. The first clinical and pathological series was not published until 1978 [3].

The pathogenesis of IBM includes a marked antigen-stimulated autoimmune process, immune-mediated myofiber destruction accompanying nuclear degeneration, sarcoplasmic aggregation of many proteins, and myofiber loss. How these different pathologies are related is the key unknown question in IBM research. No drug has been demonstrated to have efficacy in the relatively few clinical trials that have been performed to date. Here, recent published reviews of the pathogenesis and therapy of IBM are updated [4,5].

EPIDEMIOLOGY
IBM prevalence per million has been estimated at 1.0 in Turkey [6], 4.7 in the Netherlands [7], 9.8 in Japan (a reported increase from 1.3 between 1991 and 2003) [8], 10.7 in Connecticut, USA [9], 14.9 in western Australia [10], and 71 in Olmsted County, USA [11]. Studies of non-Japanese Asian IBM remain rare [12,13]. Age 50 or greater prevalence estimates are approximately 50 per million in western Australia [14].

CLINICAL FEATURES
IBM is a slowly progressive muscle disease with a specific pattern of muscle involvement, evident clinically [7,15,16,17] and by MRI [18,19].
Delayed diagnosis (average time 5.2 years) [10,20] and misdiagnosis [14] are common. Quadriceps muscle weakness, resulting in difficulty walking and knee buckling, and finger flexor weakness (commonly worse on the nondominant side [10,21]) resulting in grip impairment, are distinctive features. Greater reliance on muscle biopsy features relative to clinical features contributes to misdiagnosis, with weakness of finger flexors, especially flexor digitorum profundus, often overlooked.

Muscle pathology in IBM is variable, with some patients showing intense widespread endomysial inflammation, some showing intense but very focal or multifocal endomysial inflammation, and some showing sparse inflammation. Rimmed vacuoles (Fig. 2), holes seen in hematoxylin and eosin, and Gomori trichrome stains, are variably present in 1–6% of myofibers and help to distinguish IBM pathologically from other inflammatory myopathies. True inclusion bodies are uncommonly seen (Fig. 2). Patients with typical clinical features and endomysial inflammation with invasion of nonnecrotic muscle fibers may meet the European Neuromuscular Centre research criteria for probable IBM even if rimmed vacuoles are absent [7].

PATHOGENESIS

Many theories of the pathogenesis of IBM have been put forth since the initial description of this disease in 1967 (Table 1). The large number of muscle molecular and pathological abnormalities that have been reported have suggested many hypotheses. Toxicity theories of various molecules have dominated the field and form the basis for at least 13 animal model publications (reviewed in [22]). Other theories have considered that IBM is of potential infectious origin or a mitochondrial disorder. Combined with absence of a genetically recognized cause and poor response to immunotherapy, there is little known of the key mechanisms involved in the disease. This review focuses on two aspects of IBM pathogenesis: autoimmunity and nuclear degeneration.

AUTOIMMUNITY

Of the inflammatory myopathies, IBM has the most highly refined adaptive immune response. The
adaptive immune system is an arm of the immune system capable of generating highly specific molecular targeting. Both T cells and B cells undergo affinity maturation, selection, and clonal expansion through high-affinity interactions of their receptors (the T-cell antigen receptor and B-cell surface immunoglobulin receptor) with target antigen. IBM adaptive autoimmunity includes roles for T cells, B cells, myeloid dendritic cells, and an IBM autoantibody.

T-cell adaptive immune response

The adaptive T-cell immune response in IBM has been the subject of numerous research studies (reviewed in [23]; Fig. 3). Cytotoxic T-cell invasion of myofibers has been emphasized since the mid 1980s [24–26]. Molecular analyses of the T-cell receptor (analysis of the sequences of the variable regions of their α and β chains) have demonstrated clonal restriction (a limited population of distinct T-cell receptor transcript sequences), providing circumstantial evidence of clonal expansion (that T cells have been activated by antigen and proliferated). In IBM muscle, T cells have been stimulated by antigen and developed through successive

### Table 1. Concise history of theories of inclusion body myositis pathogenesis

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Theory</th>
<th>Summary</th>
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<tbody>
<tr>
<td>1967/1977</td>
<td>Viral infection</td>
<td>EM demonstration of ‘myxovirus-like structures’</td>
</tr>
<tr>
<td>1985/1986</td>
<td>Slow virus infection; mumps virus</td>
<td></td>
</tr>
<tr>
<td>1968/1978</td>
<td>Nuclear degeneration (early history)</td>
<td>Light microscopic pathology suggested nuclear degeneration</td>
</tr>
<tr>
<td>1994/1996</td>
<td>Failure to verify βAPP transcript reported by others; instead a sarcoplasmic nucleic acid-binding protein is demonstrated</td>
<td></td>
</tr>
<tr>
<td>1984-1988</td>
<td>Antigen-directed T-cell response</td>
<td>IHC and EM characterization of immune cell types identified cytotoxic T-cell invasion of myofibers</td>
</tr>
<tr>
<td>1991</td>
<td>Amyloidogenic proteins or prion disease</td>
<td>Congophilic material identified in IBM myofibers; the specific proteins constituting this material are unknown</td>
</tr>
<tr>
<td>1992/1993/1994</td>
<td>Molecular toxicity: β amyloid and tau</td>
<td>Studies of specific βAPP transcript overproduction led to βAPP transcript overproducing animals as IBM models; subsequent studies contradict specific βAPP transcript overproduction in IBM</td>
</tr>
<tr>
<td>to present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993/1995/</td>
<td>Mitochondrial disorder</td>
<td>Morphological abnormalities in mitochondria</td>
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<tr>
<td></td>
<td></td>
<td>Multiple mitochondrial DNA deletions</td>
</tr>
<tr>
<td>2005/2007/2011</td>
<td>Antigen-directed autoantibody response</td>
<td>Humoral-mediated autoimmunity with intramuscular immunoglobulin transcription identified by microarray studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intramuscular immunoglobulin production antigen driven</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local maturation of B cells into plasma cells in muscle</td>
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<tr>
<td></td>
<td></td>
<td>Identification of anti-IBM43, an IBM autoantibody</td>
</tr>
<tr>
<td>2006/2008/2009</td>
<td>Sarcoplasmic nucleic acid-binding proteins/nuclear degeneration</td>
<td>Nuclear proteins line rimmed vacuoles (e.g., emerin, lamin A/C, histone H1)</td>
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<tr>
<td></td>
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<td>Abnormal localization of TDP-43 in sarcoplasm</td>
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</table>

APP, amyloid precursor protein; EM, electron microscopy; IBM, inclusion body myositis; IHC, immunohistochemistry.
generations highly specific antigen-directed T-cell receptors. Multiple lines of study have suggested that there are one or more antigens eliciting a T-cell adaptive immune response, but no study has yet identified an autoantigen that T cells are directed against in IBM.

Some current models propose that the common final pathway by which the immune system injures IBM muscle is cytotoxic T-cell invasion of myofibers. However, the majority of immune system cells in IBM muscle biopsy cross-sections appear to surround but not invade myofibers. Attention has also been focused on the potential for soluble molecules produced by the immune system, such as cytokines, to injure myofibers.

Cytokines

The study of cytokines in myositis muscle has a long history [27–32]. Published studies of cytokines in inflammatory myopathy muscle samples date to 1986 [31]. Cytokine protein immunohistochemical detection in myositis muscle has been inconsistent and confounded by a number of technical and biological limitations, first outlined in 1989 [32], such as nonspecific immunoreactivity in human muscle biopsy samples. For example, cytokine immunoreactivity seen with a multilayer alkaline phosphatase method, as used in [31], was found to be identical to immunoreactivity seen with control immunoglobulin IgG1 antibodies [32]. Biological factors limiting histochemical detection of cytokines in muscle that have been noted include their low concentration even in cells producing them and their transient expression [32]. Additionally, secreted cytokines are soluble molecules that may be washed out of muscle sections during processing for immunohistochemical reactions.

What appears to be more robust than cytokine detection is the detection of either cytokine or cytokine-inducible transcripts. A large number of cytokines can be reliably inferred to be upregulated in IBM muscle from detection of their transcripts or gene transcripts specifically induced by them, including interferon-gamma [33]. Increases in interferon-gamma-inducible transcripts are present globally [33] and can be demonstrated segmentally within myofibers by a combined laser capture microdissection and PCR method [34]. Upregulation of tumor necrosis factor-like weak inducer of

**FIGURE 3.** T cells in inclusion body myositis muscle. (a–d) CD3 staining highlights T cells. (a) Diffuse endomysial inflammation. (b) Multifocal endomysial inflammation. (c) Deep invasion of nonnecrotic muscle fiber. (d) Intense inflammation surrounding a myofiber, invasion of that myofiber, and an adjacent nodular collection of T cells. [Copyright S.A.G., courtesy of the Inclusion Body Myositis Foundation, Inc. (http://www.ibmfoundation.org/ibm-picture-gallery/t-cells/)].
apoptosis (TWEAK) and its inhibition of mesoangio-blast differentiation has recently been reported [35].

B-cell adaptive immune response
A highly refined adaptive immune B-cell response in IBM muscle and blood has been identified over the last decade (Fig. 4) [33,36–38]. B cells (identified by the surface markers CD19 and CD20) were identified as sparse or absent from IBM muscle in the mid-1980s [39]. Microarray studies reported in 2002 showed that the most abundantly present transcripts in IBM muscle samples compared with normal muscle were immunoglobulin transcripts, unique to the B-cell lineage [33]. Subsequent studies demonstrated abundant plasma cells [38] with immunoglobulin gene rearrangements, characteristic of clonal expansion in response to local antigen stimulation [36], and a permissive environment for ectopic lymphoid structures, suggestive of local maturation of B cells in muscle [37]. The differentiated B cells develop into clonally expanded, highly refined antigen-directed plasma cells that produce and secrete immunoglobulins within IBM muscle.

The consequences of such antibody production are unknown, and there is no evidence that the immunoglobulins produced injure myofibers. Because of the principle of linked recognition (B-cell aided maturation of T cell requires that both B-cell immunoglobulin and T-cell receptor recognize the same molecular complex), these discoveries provide a technical approach to identifying antigens against which both T and B cells may be directed.

An inclusion body myositis autoantibody
Autoantibodies associated with polymyositis and dermatomyositis have been recognized and testing for these is frequently part of clinical management.

FIGURE 4. Highly refined B-cell adaptive immune response in inclusion body myositis muscle. (a) Microarray studies disclosed marked upregulation of immunoglobulin transcripts in IBM muscle (arrowheads). (b) Staining of IBM muscle for CD138 demonstrates plasma cells. (c) Laser capture microdissection of individual plasma cells followed by single cell PCR of immunoglobulin genes demonstrates plasma cell clonality, with cells 6.1 and 8 belonging to the same clone. (d) Identification of an IBM serum autoantibody against an unknown 43 kDa muscle protein. DM, dermatomyositis; IBM, inclusion body myositis; PFA, perifascicular atrophy; PM, polymyositis. Portions reproduced with permission from [33], [37], and [38]. [panel (d) copyright by S.A.G.].
of patients (reviewed in [40,41]). Recognition that a B-cell-specific response was present in IBM muscle and characterization of this response suggested that a search for circulating IBM autoantibodies might be fruitful. In 2011, an autoantibody to an approximately 43 kDa human muscle protein was identified in 52% (13 of 25) of IBM samples, 0% (0 of 25) of other autoimmune myopathy samples, and 0% (0 of 15) of normal samples [42**]. The identity of this approximately 43 kDa protein has not been established.

Inclusion body myositis muscle has become an immune cell host

As noted in a previous review [5], IBM muscle has become an immune cell host, a place in which B cells mature into plasma cells and myeloid dendritic cells (mDCs) activate T-helper cells [39], providing rationale for targeting molecules involving mDC/ T-cell and T-cell/B-cell interactions in IBM therapeutic trials. Nodular collections of immune cells studied by serial sections and laser capture microdissection demonstrates the presence of plasma cells producing immunoglobulins with the same antigen specificity, therefore derived from a common precursor, developing in an environment rich in T-helper cells and the cytokine B-cell activating factor. Skeletal muscle is probably not well suited to function as both a force-generating contractile tissue and a lymphoid tissue supporting an environment for immune-cell interaction and maturation.

NUCLEAR DEGENERATION

Nuclear degeneration is a prominent aspect of IBM pathology (Fig. 5). Histochemical evidence of nuclear degeneration in IBM myofibers was reported between 1967 and 1996 [1,2,45], reviewed in [4]. Studies reported in 1994 [46] found the presence of nucleic acid-binding proteins lining vacuoles in IBM. These investigators were attempting to confirm a previous study [47] that β-amyloid precursor protein mRNA was visibly increased in in-situ histochemical experiments in IBM myofibers. Although these investigators did find binding of probes to β-amyloid precursor protein mRNA in IBM myofibers, they also found similar binding of their nucleic acid control probes, indicating the presence of an aberrantly localized sarcoplasmic protein with the capacity to nonspecifically bind nucleic acids.

Independent laboratories have since identified the nucleic acid-binding protein TDP-43 in IBM nonnuclear sarcoplasm [44,48–50]. TDP-43 is a predominantly nuclear heterogeneous ribonucleoprotein that undergoes nucleocytoplasmic shuttling and associates with translation machinery in the cytoplasm. TDP-43 has two RNA-recognition motifs (RRMs) capable of binding both DNA and RNA. Recent studies in a Drosophila model, targeting TDP-43 to cytoplasm by mutating its nuclear localization signal, resulted in cellular cytotoxicity that was rescued after additionally mutating TDP-43’s RRM nucleic acid-binding domain [51]. These studies suggest that accumulation of extranuclear TDP-43 is toxic through its binding to RNA.

Rimmed vacuoles are an essential aspect of IBM muscle for diagnosis, and are seen in a number of other disorders, including myopathies due to mutations in valosin-containing protein, desmin, and titin. A majority of IBM rimmed vacuoles contain nuclear proteins and are, thus, derived from or highly associated with nuclei. Immunohistochemical evidence that rimmed vacuoles are lined with the nuclear membrane proteins lamin A/C and emerin was reported in 2006 [43]. Lining of these vacuoles with histone H1 and with emerin was reported in 2008 [52] and with histone 2AX and DNA repair regulatory components (DNA-dependent protein kinase, Hu70, and Hu80) in 2011 [53*]. Whether this nuclear degeneration relates to TDP-43 accumulation in sarcoplasm is not known.

PROTEIN AGGREGATION

At least 80 proteins have been reported to form abnormal sarcoplasmic aggregates in IBM muscle, as viewed in immunohistochemical studies. Abnormal protein aggregation does likely occur in IBM muscle, but understanding of its causes and consequences remains very limited. Attempts to categorize protein abundance on a large scale using proteomic methods have provided incremental but not deep insight into IBM pathogenesis [54–56].

THERAPY

IBM is a highly refractory disease. The case literature suggests that very few patients increase their strength or function in response to any medication therapies, although there have been some reported, particularly with Sjögren’s syndrome [57,58*]. Improvements in strength in a well documented case series of six patients with IBM and Sjögren’s syndrome were temporary, lasting 6–24 months [58*]. Uncontrolled exercise therapies have reported short-term increases in strength in patients with IBM [59–61,62*]. The IBM clinical trials’ published literature and trials registration databases include 16 completed
trials (eight open-label, eight placebo-controlled), and three in-progress trials (one open-label and two placebo-controlled) (Table 2). Immunotherapies that have been studied in placebo-controlled trials include intravenous immunoglobulin (IVIG), IVIG with prednisone, methotrexate, antilymphocyte globulin, and β-interferon.

Two placebo-controlled trials have been directed at reversing muscle atrophy. Oxandrolone had borderline or slightly positive statistically significant effects on several strength outcome measures after 12 weeks of treatment [63]. An investigational drug currently in placebo-controlled studies is BYM338, a protein therapeutic intended to improve muscle atrophy [64].

Caution regarding interpretation of efficacy from open-label trials is warranted. Enthusiastic responses seen in one early open-label IVIG trial [65], but not another early open-label trial [66], were not confirmed by subsequent placebo-controlled trials [67–69]. Similarly, improvement has occurred in strength outcome measures in natural history studies of IBM [70] and in placebo arms of IBM clinical trials [63]. In a 6-month IBM prospective natural history study [70], four of 11 patients had increased muscle strength measured by quantitative myometry. Other important considerations for trial design have been reviewed [71] and include the use of practical and meaningful outcome measures [72].

**FIGURE 5.** Inclusion body myositis myonuclear pathology. (a, b) Rimmed vacuoles typically are lined with nuclear membrane proteins, such as emerin (shown here) and lamin A/C. (c1–3) TDP43 sarcoplasmic deposits in a myofiber whose nuclei are devoid of TDP43 (white arrowheads). Panels (a) and (b) reproduced with permission from [43]. Panels (c1–3) reproduced with permission from [44].
CONCLUSION

Studies of IBM disease pathogenesis have suggested targeting the immune system or muscle atrophy pathways might have efficacy, although immunotherapies in placebo-controlled trials to date have failed. Understanding the mechanisms underlying myofiber and nuclear degeneration and the immune reaction present are likely essential to therapeutic development.

Acknowledgements

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Conflicts of interest

S.A.G. is a Principal Investigator for BYM338 clinical trials in inclusion body myositis sponsored by Novartis and has served on a Novartis Scientific Advisory Board. He is a Director of the nonprofit Inclusion Body Myositis Foundation, Inc.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


Table 2. Clinical trials of inclusion body myositis

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<th>Therapeutic</th>
<th>Year</th>
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<th>Number</th>
<th>Duration (months)</th>
<th>Placebo controlled</th>
<th>Outcome measures</th>
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ATL, anti-T-lymphocyte globulin; AZA, azathioprine; IFN, interferon; IVIG, intravenous immunoglobulin; MMT, manual muscle testing; MTX, methotrexate; NSS, neuromuscular symptom score; QMT, quantitative muscle testing; Quest, questionnaire. [Copyright S.A.G., adapted from the Inclusion Body Myositis Foundation, Inc. (http://www.ibmfoundation.org/trials/)].
Pathogenesis and therapy of inclusion body myositis


43. IBM has historically been viewed as having no significant humoral autoimmune component. A series of studies over the last 10 years have defined IBM humoral autoimmunity, and this publication is the first to identify a circulating IBM autoantibody with high sensitivity and specificity.


Neuromuscular disease: muscle


This study provides an extensive review of the small literature on exercise in IBM. It includes a review of the unblinded and uncontrolled clinical studies of exercise in IBM.


The authors define a potential role for surrogate biomarkers potentially suitable for use in IBM clinical trials. The use of measures of quadriceps strength as potential surrogates for function in particular are described.