Selected annotated bibliography 2015 on sIBM.

This is a highly selected sampling of the research that I felt was significant annotated with direct quotations and figures from the articles.

**Key points for patients:**

- Respiratory involvement is a critical factor that should be investigated as soon as an sIBM diagnosis is made. Respiratory dysfunction can be identified, treated and monitored. The most common causes of death in sIBM patients are complications due to respiratory failure and aspiration pneumonia (associated with both weak respiration and dysphagia – weakness in swallowing). Therefore, ongoing monitoring and awareness of these issues is highly recommended to both the patient and his or her physicians.

- The basic cause of sIBM is still unclear and until a cause can be isolated direct treatments are effectively stymied.

- The defective mechanisms that are being discovered associated with sIBM involve the very fundamental, basic mechanisms of the cell’s functions (for example, mitochondrial dysfunction).

- Again this year, the literature is divided between the ideas that sIBM is caused by protein abnormalities that trigger the immune system versus an abnormal immune response that then triggers muscle protein damage.

- A possible link to genetics – isolating a genetic susceptibility – continues to be researched.

- A blood test is in the pipeline but faces a number of obstacles among them, as of yet, there is no consistent and standard method agreed on for measuring the exact chemical they are looking for (anti-cN-1A auto-anti-bodies).

- An indirect treatment is being investigated and looks somewhat promising. This drug, Bimagrumab, increases overall muscle mass with the idea that having more muscle produced may help increase function in spite of the ongoing harm done by sIBM mechanisms.


In a subset of patients with sIBM, insidious onset dysphagia creates swallowing difficulties and choking. As with the initial muscle wasting, early signs of dysphagia can be overlooked as aging related choking or coughing associated with eating or drinking. In 40%–50% of patients, however, dysphagia becomes quite debilitating later in disease progression. Interestingly, although sIBM is more common in men, there is some evidence suggesting that dysphagia is more commonly the initial presenting symptom in women.

Cardiac function appears to be spared in sIBM, although case studies have been published reporting various cardio-myopathies coexisting in patients with sIBM. While heart function may be preserved, there are reports of sleep disordered breathing being identified primarily
later in disease progression, although not necessarily correlated to severity of peripheral muscle weakness. Respiratory decline has also been reported as the most common cause of death in a long-term follow-up of patients with sIBM.

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Figure 1 Progress of drug development and testing in IBM on a scale from not currently supported or recommended based on best available evidence to full approval. Abbreviations: TNF, tumor necrosis factor; IBM, inclusion body myositis; X, not supported by current evidence, no current studies underway.

Bimagrumab acts to inhibit activin type II receptors in the myostatin pathway to potentially increase muscle size in patients with sIBM. . . . A pivotal trial in 240 subjects with sIBM is currently ongoing to evaluate changes in the distance walked on the 6MWT after 52 weeks.


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.

In conclusion, s-IBM is a degenerative muscle disease in which aging appears to be a key risk factor. Several molecular mechanisms responsible for multiprotein aggregation and accumulation within s-IBM muscle fibers were reviewed. Since anti-dysimmune treatments are generally not effective, and were even reported to be detrimental for s-IBM patients [12], it is not likely that s-IBM is a primary dysimmune/inflammatory disease. But as we have been proposing, accumulation of posttranslationally modified, misfolded proteins in the aging milieu of s-IBM muscle fibers might be perceived by the patient's immune system as “foreign” (not “self”) and be responsible for inducing T-cell inflammation in the s-IBM muscle. Accordingly, we feel that therapeutic approaches should be directed toward decreasing degenerative components of the s-IBM pathogenesis. Unfortunately, thus far the source of a Fountain of Myo-Youth has not yet been identified.

Controversy reigns as to whether sIBM is primarily an inflammatory or a degenerative myopathy, the distinction being vitally important in terms of directing research for effective specific therapies. We review here the pros and the cons for the respective hypotheses. A possible scenario, which our experience leads us to favour, is that sIBM may start with inflammation within muscle. The rush of leukocytes attracted by chemokines and cytokines may induce fibre injury and HLA-I overexpression. If the protein degradation systems are overloaded (possibly due to genetic predisposition, particular HLA-I subtypes or ageing), amyloid and other protein deposits may appear within muscle fibres, reinforcing the myopathic process in a vicious circle.

Pneumonia, secondary to immobility, respiratory muscle weakness and aspiration due to dysphagia, is a common terminal event.

Two major aspects to pathology:

1). Amyloid component of sIBM.

Amyloids are insoluble fibrous protein aggregates sharing specific structural traits. They are insoluble and arise from at least 18 inappropriately folded versions of proteins and polypeptides present naturally in the body. These misfolded structures alter their proper configuration such that...
they erroneously interact with one another or other cell components forming insoluble fibrils. They have been associated with the pathology of more than 20 serious human diseases.


Accumulation of [abnormal protein] aggregates seems to be related to proteasome and autophagy dysfunctions, but with what pathophysiological consequences?

2). Inflammatory component of sIBM

The second pathological hallmark of sIBM is the presence of inflammatory infiltrates. These infiltrates are rich in lymphocytes (mostly CD8+ T cells) and macrophages, while CD4+ T cells and B lymphocytes are less abundant. CD8+ T cell- and macrophage-rich infiltrates are regularly observed invading non-necrotic fibres.

Fig. 5 A possible scenario for the pathogenesis of sIBM is that it may start with inflammation within muscle (the different actors are represented in red). The rush of leukocytes attracted by chemokines and cytokines may induce fibre injury and HLA-I overexpression. If the protein degradation systems are overloaded (due to genetic predisposition, particular HLA-I subtypes or ageing), amyloid and other protein deposits (represented in green) may appear within muscle fibres, reinforcing the myopathy in a vicious circle. The opposite scenario where amyloid deposits come first leading to a secondary inflammatory reaction is less probable since (apart some rare exceptions) neither hereditary inclusion body myopathy nor animal models of forced amyloid deposits (with proteasomal and/or autophagosomal pathway deficiencies) are accompanied by inflammation.

A possible scenario for the pathogenesis of sIBM, and one that we favour, is that it may start with inflammation within muscle (of unknown aetiology but postulates include viral infections and muscle micro-trauma by eccentric exercise) with the histological features long considered the hall-mark of
polymyositis (inflammatory cells, invasion of non-necrotic muscle fibres, necrotic and regenerating muscle fibres, but without vacuoles or amyloid). . . . The rush of leukocytes, attracted by chemokines and cytokines, may induce fibre injury, mitochondrial dysfunction and HLA class I overexpression through, presumably, components of pro-inflammatory cell stress mechanisms such as nitric oxide production. If the protein degradation systems are overloaded (perhaps failing to cope because of genetic predisposition, particular HLA class I subtypes or ageing), amyloid and other protein deposits may appear within muscle fibres, reinforcing the myopathy in a vicious circle, which is clinically manifest as progressive muscle weakness. Figure 5 tries to summarize these hypothetical physiological pathways starting from inflammation: the egg, if we accept that it came first! The opposite scenario, where amyloid deposits come first, leading to a secondary inflammatory reaction, is in our opinion, less probable since (apart some rare exceptions) neither hereditary inclusion body myopathy nor animal models of forced amyloid deposits (with proteosomal and/or autophagosomal pathway deficiencies) are accompanied by inflammation.


Genes located within the MHC region remain the strongest genetic association with sIBM. Some candidate genes/geno types have also been evaluated, building on previous studies, including the APOE-TOMM40 genotypes, mtDNA rearrangement and mitochondrial-related nuclear DNA. Genes related to hIBM and diseases with clinico-pathological features resembling sIBM are providing important clues to sIBM genetic research. Of note, rare variants in the VCP and SQSTM1 genes have for the first time been identified in sIBM patients.


This is the largest cohort where the influence of the APOE and TOMM40 genes in sIBM disease risk and features has been investigated. Concerning APOE, our findings confirmed that the APOE ε4 allele is not a susceptibility factor for developing sIBM, which is consistent with the previous studies (Needham et al., 2008). APOE alleles were also not significantly associated with the age of onset of the disease. In addition, our findings did not replicate a previously reported association between APOE-TOMM40 and risk of developing sIBM (Mastaglia et al., 2013). However, we observed that carriage of a VL repeat allele was significantly associated with a later age of onset of symptoms. This effect was even more pronounced among those also with the APOE ε3/ε3 genotype. This suggests that the TOMM40 VL polyT repeat has a disease-modifying effect on sIBM by delaying the onset of symptoms, and the APOE ε3/ε3 genotype enhances this effect. Although the association between APOE and TOMM40 and sIBM risk was not confirmed in our study, the finding of an association between the TOMM40 VL polyT repeat and a later age of onset of sIBM may justify further gene expression studies in the future.

In this cross-sectional analysis of patients with sIBM we asked whether patients with seropositive and seronegative sIBM have different disease phenotype. Our data suggests that seropositive sIBM with antibodies to NT5c1A may represent a more aggressive disease, with more severe motor and functional deficits and a higher incidence of bulbar and respiratory involvement.

Dysphagia is a known complication in sIBM: reported in 10% of patients with sIBM at onset and in 40% at the time of diagnosis.

Respiratory dysfunction in sIBM has been reported previously in the context of aspiration pneumonia and primary respiratory failure. It remains the predominant cause of mortality in long-term follow-up of patients with sIBM.

- Females have higher odds of being seropositive.
- Participants with seropositive sIBM took significantly longer to get up and stand.
- There were no significant differences between the two groups in terms of distance covered on a six minute walk.
- Seropositive participants were more likely to require assistive devices such as a walker or wheelchair for mobility.
- Participants with the NT5c1A antibody were significantly more likely to have symptoms of dysphagia.
- Facial weakness occurred in 50% of seropositive participants while it was only seen in 14% of seronegative participants. Researchers concluded that even the small sample showed those positive to the NT5c1A antibody are likely to have greater motor and functional disability. [from The Outlook, Summer, 2015]


Anti-cN-1A auto-antibodies represent the only serum biomarker for sIBM and highlight a potential role for adaptive immunity in sIBM pathogenesis. . . . the presence of anti-cN-1A auto-antibodies could be detected in up to 72% of sIBM sera, [blood] but in less than 5% of polymyositis and dermatomyositis sera. . . . they are not specific for sIBM. Rather, we also frequently detected anti-cN- 1A auto-antibodies in the sera of patients with Sjogren’s syndrome (SjS; 37%) and systemic lupus erythematosus (SLE; 20%).
Musculoskeletal Diseases and Conditions: Studies from Sir Charles Gairdner Hospital Further Understanding of Inclusion Body Myositis (Sleep disordered breathing and subclinical impairment of respiratory function are common in sporadic inclusion body myositis). (2015 Feb. 23).
Gastroenterology Week, p. 307. Retrieved from http://go.galegroup.com/ps/i.do?id=GALE%7CA406465309&v=2.1&u=ucalgary&it=r&p=AONE&sw=w&asid=83b078ac683217a8a1bb60d3c9e708ef

This is a medical news article reporting on this: Rodríguez Cruz, P. M., Needham, M., Hollingsworth, P., Mastaglia, F. L., & Hillman, D. R. (2014). Sleep disordered breathing and subclinical impairment of respiratory function are common in sporadic inclusion body myositis. Neuromuscular Disorders : NMD. http://doi.org/10.1016/j.nmd.2014.08.003

According to the news editors, the research concluded: "This suggests respiratory function testing, including sleep study, should be performed routinely in sIBM, irrespective of peripheral muscle function or other disease severity parameters."


HMGB1 [high mobility group box 1 protein released by necrotic cells]
RAGE [receptor for advanced glycation end products] the receptor of HMGB1, is crucial for β-amyloid-associated neurodegeneration.

mRNA-expression levels of HMGB1 and RAGE were upregulated [increased] in muscle biopsies of patients with sIBM and PM, but not in muscular dystrophy or non-myopathic controls.

Upregulation of RAGE on the cell surface was [also seen].

The findings strengthen the concept of unique interactions between degenerative and inflammatory mechanisms and suggest that HMGB1 / RAGE signaling is a critical pathway in sIBM pathology.

Collectively, our results indicate that HMGB1 uniquely contributes to the interplay of inflammation and degeneration in sIBM. In spite of beneficial effects of the HMGB1 antagonist BoxA in animal models of sepsis and arthritis (Yang et al., 2004; Kokkola et al., 2003), the HMGB1-RAGE- axis could be an interesting target for future therapeutic strategies in diseases with chronic inflammatory cell stress in conjunction with accumulation of β-amyloid such as in sIBM and several neurodegenerative disorders.


Endoplasmic reticulum (ER) plays a critical role in processing, folding, and exporting newly synthesized normal and unfolded/misfolded proteins into the secretory pathway. Accumulation of the unfolded/misfolded proteins in the ER lumen leads to ER stress, which subsequently elicits the unfolded protein response (UPR), a mechanism by which cells attempt to both protect themselves against the ER stress and restore their folding capacity.

Here we demonstrate for the first time that UPR [unfolded protein response] is activated in s-IBM muscle biopsies . . . In contrast, we did not find similar evidence of the UPR induction in GNE-h-IBM patient muscle

In summary, our results demonstrate a coordinated activation of 3 branches of the UPR in s-IBM muscle fibers. The lack of UPR, implying no ER stress, in GNE-h-IBM suggests that different intracellular mechanisms might be associated with very similar pathologic phenotypes.

[3 branches of the UPR: (a) protein kinase RNA (PKR)-like ER protein kinase (PERK); (b) activating transcription factor 6 (ATF6); and (c) inositol-requiring enzyme 1 (IRE1)]


We identified respiratory-deficient fibres at different stages of mitochondrial dysfunction, with downregulated [decreased] expression of complex I of mitochondrial respiratory chain being the initial feature. We detected mitochondrial DNA rearrangements in the majority of individual
respiratory-deficient muscle fibres. There was a strong correlation between number of T lymphocytes and macrophages residing in muscle tissue and the abundance of respiratory-deficient fibres. Moreover, we found that respiratory-deficient muscle fibres were more likely to be atrophic compared with respiratory-normal counterparts. Conclusions: Our findings suggest that mitochondrial dysfunction has a role in sIBM progression.

Discussion

Mitochondrial dysfunction is common and often very prominent in muscle from sIBM patients. We demonstrate that there are abnormalities in the expression of individual mitochondrial respiratory complexes, and propose that a protocol combining mitochondrial respiratory subunit expression and COX/SDH activity provides a clearer picture of the mitochondrial changes in sIBM. We have explored the nature of the mitochondrial defect in individual muscle fibres and, in accordance with previous reports, we show that some of them accumulate high level of clonally expanded mtDNA deletions. We also show that respiratory-deficient fibres are more prone to atrophy indicating that the mitochondrial defect has a direct effect on muscle wasting. In addition, there is a clear correlation between the overall percentage of respiratory-deficient fibres and the degree of T lymphocyte infiltrate. Thus there seems to be a direct link between the inflammation present in muscle environment and the mitochondrial defect.

[The eukaryotic cell's most efficient path for production of ATP is aerobic respiration that takes place in mitochondria. Cellular respiration is the set of metabolic reactions and processes that take place in the cells of organisms to convert biochemical energy from nutrients into adenosine triphosphate (ATP), and then release waste products.

\[
\text{Glucose} + \text{Oxygen} \rightarrow \rightarrow \rightarrow \text{Water} + \text{Carbon dioxide} + \text{Chemical energy (ATP)}
\]

The reactions involved in respiration are catabolic reactions, which break large molecules into smaller ones, releasing energy in the process, as weak so-called "high-energy" bonds are replaced by stronger bonds in the products. Respiration is one of the key ways a cell gains useful energy to fuel cellular activity. Cellular respiration is considered an exothermic redox reaction which releases heat. The overall reaction occurs in a series of biochemical steps, most of which are redox reactions themselves. [[redox: a process in which one substance or molecule is reduced and another oxidized; oxidation and reduction considered together as complimentary processes: redox reactions involve electron transfer.]] Although technically, cellular respiration is a combustion reaction, it clearly does not resemble one when it occurs in a living cell due to slow release of energy from the series of reactions. Nutrients that are commonly used by animal and plant cells in respiration include sugar, amino acids and fatty acids, and the most common oxidizing agent (electron acceptor) is molecular oxygen (O2). The chemical energy stored in ATP (its third phosphate group is weakly bonded to the rest of the molecule and is easily broken allowing stronger bonds to form, thereby transferring energy for use by the cell) can then be used to drive processes requiring energy, including biosynthesis, locomotion or transportation of molecules across cell membranes. Cellular respiration. (2015, December 14). In Wikipedia, The Free Encyclopedia. Retrieved 01:16, December 20, 2015, from

Our findings reflect the rareness of the disease and the existing uncertainty in understanding the causes and pathogenesis of sIBM. Only a few controlled trials have focused exclusively on the treatment of sIBM.

So far, there is no evidence indicating that any specific treatment for sIBM is effective, and further high-quality research is needed on the topic. Acknowledgements


In conclusion, patients with a muscle biopsy showing endomysial cell infiltration with invasion of non-necrotic muscle fibers most probably have sIBM, regardless of clinical and other pathological features. Women lack typical features more often than men.


We performed targeted sequencing of 38 “high probability” genes associated with clinical syndromes having phenotypic and pathogenic similarities to sIBM, in 78 patients with sIBM; making it the largest genetic study performed to date for sIBM.

The future of research and clinical treatment for acquired muscle diseases such as sIBM is rapidly evolving and will dramatically change with the advent of inexpensive and comprehensive genetic testing. Moreover, clinical trials and therapeutic interventions for sIBM are currently in development. The identification of potential genetic risk factors, genetic modifiers or genetic elements associated with treatment response for sIBM will be of equal value to that of properly genetically diagnosing sIBM patients. Our study offers an initial glimpse into the genetic variation seen in clinically reported sIBM patients.