Comment on: Mitochondrial abnormalities in idiopathic inflammatory myopathies by Torri *et al.*: a short reader guide

Sirs,

We congratulate Torri *et al*. for their comprehensive narrative review (1), which aims to consolidate current knowledge on the mechanisms and effects of mitochondrial dysfunction in inflammatory myopathies (IM), as well as insights into present and future therapeutic options targeting this aspect, drawing on the analysis of 27 papers.

We would like to point out that, in place of several seminal studies in the field, Torri *et al*. have provided references in which we were unable to find evidence supporting their statements. We therefore wish to offer a brief reader guide to this review.

We agree that recent evidence suggests that inflammation, oxidative stress, impaired mitophagy, mitochondrial DNA damage, and protein aggregation interact in a vicious cycle that sustains muscle weakness and degeneration. However, we were unable to find data supporting this statement in references 10-12 provided by the authors. Rather, in a recently published article that is not cited, it has been shown in a mouse model of IM that mitochondrial dysfunction precedes inflammation, that targeting mitochondrial abnormalities with N-acetylcysteine improves inflammation, and that targeting inflammation with JAK inhibitors prevents mitochondrial dysfunction (2).

In dermatomyositis (DM), human, murine and *in vitro* data indicate that interferon (IFN)-β drives mitochondrial dysfunction, which in turn sustains inflammation (3). Although the authors acknowledge this mechanism, reference 13 provided by Torri *et al*. does not support this concept, while the seminal evidence for it remains uncited.

In addition, in inclusion body myositis (IBM), mitochondrial dysfunction is associated with mitochondrial dilation, which drives inflammation. While the authors also describe this mechanism, references 15 and 17 do not support their statements, and the article by Kleefeld *et al*. (4) is not cited.

The observation regarding HARAKIRI involvement by Nagaraju and colleagues is also not correctly referenced (ref. 16).

We further agree that, at the histological level, mitochondrial abnormalities characterise both IBM and DM, albeit with two distinct patterns: patchy abnormalities in IBM and perifascicular distribution in DM. However, references 16 and 17 provided by the authors do not contain evidence for this statement, and the seminal observations are absent from the bibliography.

In the therapeutic section, the authors state that glucocorticoids, DMARDs, and targeted therapies reduce mitochondrial abnormalities. Yet, none of the referenced studies support this view. Although scarce, data supporting a metabolic effect of immunomodulatory drugs do exist (5), but are not included in the references.

Finally, the authors hypothesise that proteasome inhibition might have an effect and cite an unpublished study that does not report any mitochondrial outcome. We have recently demonstrated, in experimental *in vitro* and *in vivo* models of myositis, that proteasome inhibition restores mitochondrial function in muscle (6).

In conclusion, we once again congratulate the authors and fully support their perspective. We hope that this complementary letter will assist readers in locating the seminal references underpinning the statements made by Torri *et al*.

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