3 CONTRIBUTION OF IMMATURE MUSCLE PRECURSORS TO MYOSITIS PATHOGENESIS: A SOURCE OF TYPE I INTERFERON AND A POSSIBLE TARGET OF THE IMMUNE ATTACK

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Objectives To investigate the contribution of immature muscle precursors to the adaptive and innate immune responses in inflammatory myopathy.

Method Muscle biopsies from eight patients with polymyositis and dermatomyositis were investigated for the expression of CD56, a marker of immature muscle precursors, HLA class I, known to be overexpressed in myositis, and interferon β (IFNβ), a type I IFN, inducer of HLA class I and possibly involved in the pathogenesis of myositis. Muscle inflammatory infiltrates were further characterised for the presence of myeloid dendritic cells (mDCs) and their associated C type lectin receptors (CLRs), which play a critical role in initiating adaptive immune response, and for the products of activated DCs, IL12 and IL23. In vitro, the production of IFNβ by human myoblasts was assessed after stimulation with the TLR3 agonist Poly(I:C), IFNγ and IL17. The expression of HLA class I by myoblasts was determined by FACS after TLR3 stimulation and IFNβ neutralisation.

Results Positive IFNβ staining was detected in seven of the eight myositis patients whereas no positive staining was detected in the five controls. Although rare IFNβ expression was observed in mononuclear cells, a strong staining was observed in muscle fibers with a perifascicular pattern in DM and an intrafascicular pattern in PM. Staining of serial PM and DM sections identified IFNβ-positive muscle fibers as immature muscle precursors expressing CD56 and HLA class I. In contrast to controls, expression of DC-SIGN, MMR, ASGPR, the main CLRs associated with DCs, was broadly observed in myositis with an endomysial pattern in PM and a perivascular pattern in DM. Overexpression of CLRs was associated with the presence of CD11c+mDCs and with the presence of IL12 and IL23 cytokines. Serial immunostaining performed in five patients showed that inflammatory infiltrates with CD11c-positive DCs expressing CLRs were associated with the presence of CD56- and HLA class I-positive muscle fibers. In vitro, IFNβ production was induced when TLR3 activation was combined with IFNγ stimulation. TLR3 activation up-regulated HLA class I expression which was decreased after IFNβ neutralisation.

Conclusion In myositis muscle tissue, immature muscle precursors were identified as a local source of type I IFN. In turn, such a local production of IFNβ could be implicated in HLA class I overexpression on muscle cells. Moreover, immature muscle precursors may represent the target of an immune response involving activated DCs, with expression of CLRs and production of IL12 and IL23 cytokines implicated in the Th1 and Th17 polarisation.