The pathogenic role of these 2 autoantibodies remains to be established, but it is known that immunization of mice with a Ro peptide recapitulates many signs and symptoms of SS (4), associated with increased IL-12 expression in the salivary glands (Yin H, et al: unpublished observations). Finally, we completely agree with the conclusion that SS may comprise different pathogenetic entities leading to shared clinical manifestations.

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Contribution of myeloid dendritic cells to type I interferon–induced cytokines and chemokines: comment on the article by Bilgic et al

To the Editor:

Type I interferons (IFNs) play a critical role in the pathogenesis of several autoimmune rheumatic diseases and inflammatory conditions (1–4). We read with interest the recent report by Bilgic et al, who evaluated the capacity of type I IFN–dependent peripheral blood gene and chemokine signatures and levels of proinflammatory cytokines to serve as biomarkers for disease activity in adult and juvenile dermatomyositis (DM) (4). The authors found that prominent type I IFN signatures, such as serum interleukin-6 (IL-6) levels and IFN-driven chemokine levels, correlated strongly with DM disease activity (4). We conducted a study to explore how innate immune cells, and in particular myeloid dendritic cells (DCs), contribute to type I IFN–induced elevations in levels of inflammatory cytokines and chemokines. DCs secrete a wide range of inflammatory mediators that are critically involved in the pathogenesis of autoimmune diseases including DM (5).

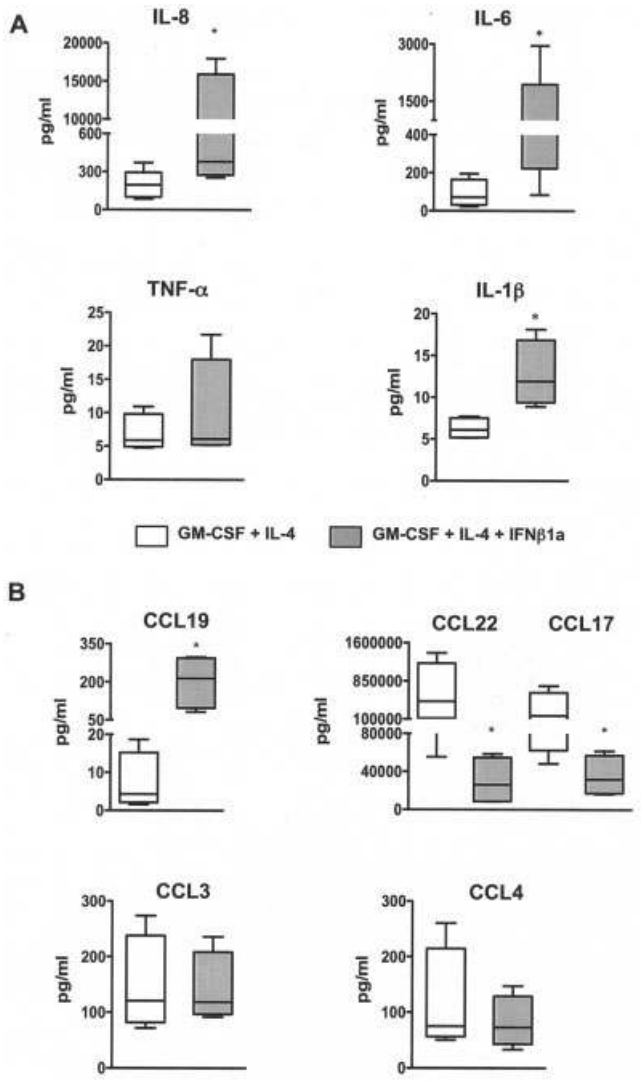

Figure 1. Secretion of cytokines and chemokines by human myeloid dendritic cells (DCs) upon stimulation with type I interferon (IFN). Monocytes from peripheral blood mononuclear cells of healthy donors were isolated using CD14 beads (Miltenyi Biotech). CD14+ monocytes were differentiated for 6 days in the presence of granulocyte–macrophage colony-stimulating factor (GM-CSF; 1,000 IU/10^6 cells) and interleukin-4 (IL-4; 500 IU/10^6 cells) (open bars) or a combination of GM-CSF, IL-4, and type I IFN (IFN-β1a; 1.5 ng/10^6 cells) (shaded bars) (all from ImmunoTools). **A,** Levels of inflammatory cytokines in cell-free culture supernatants of DCs differentiated for 6 days, as analyzed by cytometric bead array assay (BD Biosciences). **B,** Levels of chemokines in cell-free culture supernatants of DCs differentiated for 6 days, as analyzed by enzyme-linked immunosorbent assay (R&D Systems). Data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and the lines outside the boxes represent the minimum and maximum values. Results are from 4–5 donors. $* = P < 0.05$ versus cultures without type I IFN, by Mann-Whitney test.

DCs were generated by culturing monocytes for 6 days in the presence of granulocyte–macrophage colony-stimulating factor (GM-CSF) and IL-4 (conventional DCs) or a combination of GM-CSF, IL-4, and type I IFN (IFN-DCs). As shown in Figure 1A, type I IFN significantly enhanced the secretion of the inflammatory cytokines IL-8, IL-6, and IL-1β, and moderately enhanced the secretion of tumor necrosis factor α, by DCs. The results thus indicate that DCs are the possible cellular source of the enhanced IL-6 levels observed in patients with DM. Further, we found that type I IFN significantly enhanced secretion of CCL19 (macrophage inflammatory protein 3β), an IFN-inducible chemokine that has many inflammatory properties, by DCs (Figure 1B). Ectopic expression of CCL19 can retain mature and activated DCs in target tissue and can mediate the influx of CCR7-expressing T cells, macrophages, and B cells, culminating in inflammation-mediated tissue damage and formation of extrafollicular germinal center–like structures at the site of chronic inflammation. However, type I IFN did not modulate the secretion of CCL3 (MIP-1α) or CCL4 (MIP-1β), suggesting that myeloid DCs do not contribute to secretion of the latter type I IFN–induced chemokines.

Interestingly, type I IFN significantly down-regulated the secretion of CCL17 and CCL22, the chemokines that recruit Treg cells via CCR4, by DCs (Figure 1B). Treg cells are suppressor cells and play a critical role in down-modulating the inflammatory process by inhibiting the functions of innate cells and effector T cells (6,7). Our findings thus suggest that by reducing DC secretion of CCL17 and CCL22 and thus limiting Treg cell recruitment, type I IFN enhances inflammation, leading to unabated activation and function of both innate cells and T cells. Taken together, our results indicate that myeloid DCs are one of the major sources of cells involved in type I IFN induction of cytokines and chemokines in DM and other autoimmune rheumatic diseases. In addition, DCs may contribute to inflammation by modulating the recruitment of other immune cells to the site of inflammation.

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Reply

To the Editor:

In their letter, Dr. Maddur et al describe their experiments examining potential cellular sources of inflammatory cytokines and chemokines. Their results suggest that under conditions of stimulation with type I IFN, myeloid DCs may produce proinflammatory molecules implicated in the pathogenesis of DM. Maddur and colleagues found that type I IFN significantly enhanced the secretion of IL-8, IL-6, and IL-1β, and moderately enhanced tumor necrosis factor α (TNFα) production by cultured human myeloid DCs in vitro. These results complement our observation of elevated IL-6 levels in DM sera and identify myeloid DCs as a possible cellular source of the enhanced concentrations of IL-6 in DM patients. However, in contrast to the results obtained by Maddur et al, we observed decreased serum IL-8 and TNFα levels in our adult DM cohort. In addition, DM patient sera displayed increased levels of the type I IFN-regulated chemokine CCL3, while in Maddur and colleagues' study the in vitro–derived myeloid DCs did not elaborate this molecule. These data suggest that the regulation of proinflammatory cytokine subsets and type IFN–driven molecules in DM may involve additional cellular mechanisms.

Plasmacytoid DCs constitute one such potential contributing population. Investigators in our group recently reported that muscle biopsy specimens from patients with juvenile DM contained largely plasmacytoid DCs rather than myeloid DCs; these tissue-resident plasmacytoid DCs expressed several proinflammatory chemokines (Lopez de Padilla CM, Vallejo AN, McNallan KT, Vehe R, Smith SA, Dietz AB, et al. Plasmacytoid dendritic cells in inflamed muscle of patients with juvenile dermatomyositis. Arthritis Rheum 2007; 56:1658–68). Future in vivo and tissue-based studies will help define the extent to which such cells contribute to type I IFN–driven chemokine production in DM and other autoimmune diseases.

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