C1q deficiency leads to the defective suppression of IFN-α in response to nucleoprotein containing immune complexes

RESULTS

Q: Does C1q change the binding and/or trafficking of SLE ICs within monocytes?

Figure 2. C1qD patient sera are defective at inhibiting IFN-α production by SLE IC-stimulated monocytes. (A) PBMCs were isolated from normal donors, and C1qD depleted (C1q dep) sera were added at indicated concentrations to SLE ICs from normal donors or to SLE ICs from a family with C1qD. (B) SLE ICs were added to PBMCs with (+) or without (-) serum/C1q. IFN-α was measured as in Fig. 1. (B) IFN-α production was quantified as above.

Figure 3. C1q inhibition of IFN-α production by pDCs requires CD14+ monocytes. (A and B) SLE ICs were added to purified pDCs (CD64+, CD8−) or CD64+ CD14+ monocytes. (B) IFN-α was quantified as above.

Figure 4. Monocytes "steal" IC containing C1q from pDCs and inhibit IFN-α production via cell-cell contact. (A) pDCs and monocytes were purified and pDCs were cultured alone or with monocytes at a 1:1 ratio. SLE ICs were added with or without C1q. (B) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (C) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (D) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (E) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (F) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (G) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (H) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (I) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (J) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (K) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (L) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (M) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (N) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (O) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (P) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (Q) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (R) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (S) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (T) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (U) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (V) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (W) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (X) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (Y) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production. (Z) SLE ICs were made with or without C1q, and C1qD patient sera were added to enhance IFN-α production.

Figure 5. The presence of C1q causes significantly more SLE IC to bind to monocytes and accumulate in early endosomes. (A) SLE ICs were added to monocytes or monocyte-depleted monocytes (CD14+). IFN-α was measured as in Fig. 1. (B) C1qD patient sera were added to PBMCs or monocytes at 2.5 or 25 μg/ml and detected on monocytes by flow cytometry after 2 h of binding. The mean fluorescent intensity (MFI) is plotted. *, P < 0.05; **, P < 0.01; ****, P < 0.0001. ICs were made as in B and added to purified monocytes for 4 h at 37°C. After fix and permeabilizing, early endosomes (EDU) or transmembrane (JAMM) were labeled and quantification of colocalization with SLE IC and image collection were done using an Alexa Imagestream®.

SUMMARY/CONCLUSIONS

- Deficiency in C1q leads to enhanced IFN-α production by pDCs, thus providing an additional explanation of why >90% of C1qD patients develop SLE
- C1q indirectly inhibits pDCs through CD14+ monocytes
- C1q causes preferential binding of ICs to monocytes and alters intracellular trafficking resulting in retention in early endosomes
- Monocytes suppress IFN-α production by pDCs through 2 mechanisms:
  a) "Stealing" IC containing C1q
  b) Cell contact through an inhibitory ligand