Response to: 'Monocyte type I interferon signature in antiphospholipid syndrome is related to pro-inflammatory monocyte subsets, hydroxychloroquine and statin use' by van den Hoogen *et al*

Primary antiphospholipid syndrome (APS) is an autoimmune disorder of unknown cause, characterised by not only thrombotic events and pregnancy morbidity but also accelerated atherosclerosis. We reviewed with great interest the letter by van den Hoogen *et al*,[1] which comments on our recent paper.[2] In our study, we discovered a defect in endothelial progenitor function in patients with primary APS—such defects have been described as predecessors to atherosclerosis. We subsequently revealed a type I interferon (IFN) signature in peripheral blood mononuclear cells of the same patients. Importantly, inhibition of the type I IFN receptor restored normal differentiation of endothelial progenitors into endothelial cells in vitro. Further, we detected the IFN signature not only in our local primary APS cohort but also in a cohort of patients from Mexico.

van den Hoogen *et al*[1] have now detected a type I IFN signature in a third cohort of patients with primary APS, this one recruited in the Netherlands. Going further, they reanalysed publicly available data from a recent study of primary APS monocytes, which had initially seemed to point away from an IFN signature in primary APS.[3] The reanalysis revealed overexpression of type I IFN-responsive genes, at a level just below the threshold the authors had used for their pathway analysis.[3] With this replication of our work, we can now definitively say that exaggerated type I IFN expression is a feature of at least some patients with primary APS.

While our study characterised the IFN signature of total peripheral blood mononuclear cells, van den Hoogen *et al* specifically assessed purified monocytes. In parallel, they also scored monocytes as classical (CD16-negative), intermediate (CD16-positive), and non-classical (CD16-positive, with down-regulation of CD14). They saw enrichment of the latter two inflammatory subsets in patients with a more robust type I IFN signature and pointed out that such subsets have been associated with preclinical cardiovascular disease in both lupus and rheumatoid arthritis. To this important analysis, we would also mention a point discussed in detail in our manuscript,[2] namely that endothelial progenitors are a heterogeneous population of cells that include cells sometimes labelled as 'circulating angiogenic cells' or CACs. CACs are CD14-positive and presumably derived from the myeloid lineage. We speculate that the shift in monocytes away from classical subtypes would actually correlate very well with the defect we described in endothelial progenitor function. In fact, these may be two different strategies for characterising the exact same phenotype. Future studies should ask whether type I IFNs mechanistically shift monocytes towards these inflammatory subsets or whether the subsets themselves may actually be a source of type I IFNs.

van den Hoogen *et al* importantly characterise the type I IFN signature of a large number of patients with systemic lupus erythematosus (SLE) in parallel to primary APS. They find a more robust signature in SLE as compared with primary APS and speculate that IFN expression may mark a subset of patients with APS who will develop more lupus features over time. We demonstrated a similar trend in our cohort, although were underpowered to detect statistically significant differences between SLE and APS. Regarding the possible clinical transition from primary APS to SLE over time, we speculated similarly in our manuscript, but importantly (and like van den Hoogen *et al*) did not find clinical features of SLE in the patients with primary APS at the time of analysis. Longitudinal cohorts will be required to address these questions further.

Finally, we would highlight their interesting subgroup analysis regarding potential medication effects. In our study, we had relatively few patients taking hydroxychloroquine and did not capture data regarding statins. Given what we know about antimalarials like hydroxychloroquine in lupus, it is certainly appealing to think that antimalarial use in primary APS can reduce the IFN signature. In addition to their role in mitigating signalling through Toll-like receptors, antimalarials also reduce neutrophil extracellular trap release, at least in vitro.[4] Given the recent work of both our group and that of van den Hoogen *et al* in showing aberrant neutrophil activity in patients with primary APS,[5 6] antagonising neutrophil extracellular traps is a potential mechanism by which antimalarials reduce type I IFN expression in primary APS.

In summary, now that the type I IFN signature has been detected in multiple relatively small primary APS cohorts (and with appealing drugs in development that target these pathways), it will be important to further assess the IFN signature in larger cohorts, where clinical correlations can be more appropriately assessed. Anticoagulation is not effective for all patients with primary APS (nor is it effective for many of the non-thrombotic manifestations of the disorder). It is therefore of paramount importance to understand whether targeting inflammatory pathways has a role as adjuvant therapy for patients with primary APS.

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