

Myeloid-derived suppressor cell, arginase-1, IL-17 and cl-CD95L: an explosive cocktail in lupus?

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Myeloid-derived suppressor cells (MDSCs) (CD33⁺CD11b⁺) are a heterogeneous population derived from immature myeloid cells consisting of two main subsets: CD15⁺CD66b⁺ granulocytic (G-MDSCs) and CD14⁺HLA-DR⁻ monocytic (M-MDSCs) cells (1). G-MDSCs consist of relatively immature and pathologically activated neutrophils, whereas M-MDSCs are inflammatory monocytes (2). While MDSCs are associated with a poor clinical outcome in cancer, their role in chronic inflammatory diseases remains unclear probably because, among other explanations, the heterogeneity of this cellular population.

Systemic lupus erythematosus (SLE) is a disorder of largely unknown etiology whose pathogenesis can affect almost all organs and tissues. SLE is characterized by an autoimmune response with circulating autoantibodies secreted by B cells, which are aided by the CD4⁺ T cell subset, follicular helper T (T_{fh}) cells. A growing body of evidence in both human and murine studies confirm a pivotal role for IL17-secreting T-cells (Th17) cells in the progression of SLE disease [see (3) for a review] (4). Indeed, lupus-prone mice are partially protected from immunopathology by a reduction in renal Th17 cell accumulation (5). Therefore, modulation of Th17 cell migration and trafficking to inflamed organs is an attractive therapeutic option for reducing disease-related inflammation. However, the precise mechanism of Th17 cell accumulation in damaged SLE organs remains unclear.

Yang and colleagues team demonstrated that the

percentage of blood MDSCs is positively correlated with the SLE disease activity index (SLEDAI) in patients. Moreover, this team observed that IL-6 accumulation in SLE patients promotes the expression of arginase-1 (*Arg-1*) by G-MDSCs. Arg-1 enzymatically hydrolyzes the amino acid L-arginine (L-Arg) to ornithine and urea. Unexpectedly, while L-Arg depletion by MDSCs in tumors is responsible for the suppression of the immune response (1), this depletion in SLE patients causes inflammation by activating two kinases, general control nondepressible 2 (GCN2) and mTOR, through a molecular mechanism that depends on the increase in uncharged tRNA (6) and that triggers Th17 differentiation. Indeed, MDSCs promote Th17 development *in vitro* when co-cultured with naive healthy autologous CD4 T-cells. This effect is abrogated in the presence of the Arg-1 inhibitor, nor-NOHA. Using the same experimental set-up, Wu *et al.* demonstrated that MDSCs derived from SLE patients amplify the positive effect of co-culture on Th17 differentiation, again in an Arg-1-dependent manner. Using a humanized mouse model, in which injection of PBMCs from SLE patients into immunodeficient mice (NOD/SCID) gives rise to SLE-like disease, they showed an *in vivo* role for MDSC and Arg-1. Indeed, prior depletion of MDSCs from PBMCs or nor-NOHA-mediated inhibition of Arg-1 halts the development of disease and expression of *il-17a* in both the spleen and kidney. Strikingly, in their hands, MDSCs would appear to exacerbate the pathological role of Th17 cells in

SLE patients. This study emphasizes that although MDSCs block T-cell proliferation in lupus and cancer, these cells can also promote the differentiation of IL17-expressing CD4⁺ T-cells, fueling inflammation in lupus patients. Taking into account that IL-17 is known to promote the production of IL-6 and directly recruits MDSC in tumor environment (7), one can envision that Wu *et al.* highlighted an amplification loop that might cause acceleration of the pathogenesis in SLE patients.

A mechanistic link between MDSC, Arg-1 and Th17 cells has recently been reported (8). Indeed, Iwata *et al.* observed an increased number of MDSCs (CD11b⁺GR-1^{low}) in SLE patients and the percentage of these cells was correlated with the progression of the disease. Nonetheless, they did not evaluate the impact of MDSCs on T-cell differentiation but instead showed that the increased Arg-1 activity in these myeloid cells was responsible for the inhibition of T-cell proliferation in lupus-prone mice MRL^{Lpr}. These differences in the effects of Arg-1 on SLE outcome and progression could be due to the lupus-prone mouse models used in these studies—adoptive cell transfer in Wu *et al.*, versus genomic mutation in the *CD95* loci in Iwata *et al.*—or could be reconciled because disparate degrees of proliferation account for Th cell differentiation (9). A more established role for Arg-1 in suppression of Th2 function *in vivo* (10) and in promoting intracellular *T. gondii* survival have already been described (11).

Our group recently demonstrated that the tumour necrosis factor (TNF) member, CD95L (also known as FasL or CD178) aggravates the inflammatory process in SLE patients by recruiting Th17 cells in inflamed organs (12). The CD95L receptor, namely CD95 (also known as Fas), belongs to the death domain (DD)—containing members of TNF receptor superfamily (13). Regardless of accumulating evidence indicating that this plasma membrane receptor possesses non-apoptotic functions, CD95 is still considered as a death receptor (14). CD95L is expressed as a transmembrane “cytokine” (m-CD95L), whose extracellular domain is composed of a juxtamembrane stalk region and a TNF homology domain. This stalk region can be cleaved by metalloproteases (15) releasing a soluble CD95L into the bloodstream. In presence of m-CD95L, CD95 aggregates and forms a molecular complex consisting of FADD and caspase-8/10 that is called death-inducing signaling complex (DISC) (16). Metalloprotease-cleaved CD95L [cl-CD95L for cleaved CD95L to distinguish this ligand from its soluble, exosome-bound counterpart (17,18)] fails to form DISC but triggers

non-apoptotic signaling pathways such as NF- κ B (19) and PLC γ 1-driven Ca²⁺ response (20). In a pathophysiological standpoint, we showed that this soluble ligand, cl-CD95L, is accumulated in sera of lupus patients and promotes endothelial transmigration of activated T lymphocytes through the formation of a molecular complex designated MISC for motility-inducing signaling complex (20). Binding of cl-CD95L to CD95 triggers the recruitment of PLC γ 1 and the implementation of a Ca²⁺ signal promoting the endothelial transmigration of Th17 cells (12). PLC γ 1 recruitment occurs at the level of the juxtamembrane region of CD95, designated calcium-inducing domain (CID). A selective inhibitor consisting of the cell-penetrating domain of TAT fused to CID, namely TAT-CID, interacts with PLC γ 1 and prevents its recruitment to endogenous CD95. Moreover, injection of TAT-CID in lupus-prone mice (MRL^{Lpr/+}) blocks endothelial transmigration of Th17 cells and alleviates clinical symptoms. In this study, we did not investigate the effect of TAT-CID on the recruitment of MDSC cells in spleen and kidney of the lupus-prone mice MRL^{Lpr/-}. According to the study of Wu *et al.*, it would be interesting to address whether TAT-CID by preventing endothelial transmigration of Th17, could also inhibit the accumulation of MDSCs in damaged organs of lupus-prone mice indicating that either Th17 recruitment precedes MDSC accumulation or cl-CD95L exacerbates inflammation in SLE patients by recruiting simultaneously Th17 and MDSCs initiating the local amplification loop of the inflammatory process in these organs. Like IL-6 and IL-17, we cannot rule out that cl-CD95L, which is also increased in these patients (20), contributes to MDSC and/or Th17 differentiation in organs of SLE patients. Overall these findings raise the question whether MDSCs and cl-CD95L are biomarkers of lupus flare by promoting Th17 differentiation and trafficking, respectively. This question remains to be addressed to better understand the lupus etiology and propose novel and targeted treatments for clinicians to more efficiently treat this pathology.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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