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CD169 defines activated CD14$^+$ monocytes with enhanced CD8$^+$ T cell activation capacity

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Monocytes are antigen-presenting cells (APCs) that play diverse roles in promoting or regulating inflammatory responses, but their role in T cell stimulation is not well defined. In inflammatory conditions, monocytes frequently show increased expression of CD169/Siglec-1, a type-I interferon (IFN-I)-regulated protein. However, little is known about the phenotype and function of these CD169$^+$ monocytes. Here, we investigated the phenotype of human CD169$^+$ monocytes in different diseases, their capacity to activate CD8$^+$ T cells, and the potential for a targeted-vaccination approach. Using spectral flow cytometry, we detected CD169 expression by CD14$^+$ CD16$^-$ classical and CD14$^+$ CD16$^+$ intermediate monocytes, and unbiased high-dimensional analysis showed that they were distinct from dendritic cells, including the recently described CD14-expressing DC3. CD169$^+$ monocytes expressed higher expression of co-stimulatory- and HLA-molecules, suggesting an increased activation state. IFNα treatment highly upregulated CD169 expression on CD14$^+$ monocytes and boosted their capacity to cross-present antigen to CD8$^+$ T cells. Furthermore, scRNA-seq and flow cytometry analyses showed that CD169$^+$ monocytes were present in the blood and bronchoalveolar lavage fluid of COVID-19 patients, and in the blood of patients with five different types of cancers. Finally, we evaluated two CD169-targeting nanovaccine platforms, antibody- or liposome-based, and we showed that CD169$^+$ monocytes efficiently presented tumor-associated peptides gp100 and WT1 to antigen-specific CD8$^+$ T cells. In conclusion, our data indicate that CD169$^+$ monocytes are activated monocytes with enhanced CD8$^+$ T cell stimulatory capacity and that they emerge as an interesting target in nanovaccine strategies, because of their presence in health and different diseases.