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The retroviral engineering of a human plasmacytoid dendritic cell-based vaccine allowed the priming and expansion of multispecific viral and tumor antigen-specific T-cells in multiple HLA contexts.

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Text
Because dendritic cells are crucial to prime and expand antigen-specific $CD8^+$ T-cells, several strategies are designed to use them in therapeutic vaccines against infectious diseases or cancer. In this context, off-the-shelf allogeneic dendritic cell-based platforms are more attractive than individualized autologous vaccines tailored to each patient. We have previously shown that a unique dendritic cell line (PDC*line) platform of plasmacytoid origin, was able to prime and expand tumor-specific $CD8^+$ T cells in vitro and in vivo in a first-in-human clinical trial with melanoma patients. The aim of the present study was to improve the PDC*line platform using retroviral engineering. The transduced PDC*line cells were cocultured with either Peripheral blood mononuclear cells (PBMCs) or antigen-specific T-cell clones. The antigen presentation efficiency was displayed by the expansion of antigen-specific $CD8^+$ T cells present in PBMCs or the secretion of cytokines by T-cell clones measured using flow cytometry. We demonstrated that the clinical-grade PDC*line transduced with genes encoding whole viral or tumoral proteins efficiently processed the transduced antigens and stably presented the derived peptides to specific $CD8^+$ T cells both in HLA-A*02:01 and HLA-B*07:02 molecules expressed by PDC*line. When PDC*line cells were transduced with retroviral constructs encoding a polyepitope composed of four HLA-A*02:01-restricted peptides from the tumoral or viral antigens, the cells were able to mount a multispecific $CD8^+$ T-cell response against peptides of the polyepitope. We also demonstrated that the addition of a part of the sequence of the Lysosome-associated membrane protein-1 (LAMP-1) to the whole protein or to the polyepitope greatly improved the presentation of some peptides. Lastly, we used retroviral transduction to express a new HLA class I molecule, HLA-B*35:02, in PDC*line. After loading with HLA-matched peptides, this new PDC*line successfully presented the peptides in the endogenous HLA-A*02:01 or in the new HLA-B*35:02 molecules. The HLA-A*24:02 allele was also of interest as the Asian population expresses it more than the Caucasian population. The PDC*line transduced with HLA-A*24:02 and loaded with the HLA-matched peptide from the HIV protein Nef was able to prime and expand specific $CD8^+$ T-cells (unpublished results). The retroviral engineering can thus benefit a broadened population of patients through the easy addition of new HLA class I molecules. The demonstration of the effective retroviral transduction of PDC*line cells strengthens and broadens the scope of the PDC*line antigen presentation platform, which can be used in adoptive or active immunotherapy.

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