Activation of anti-SARS-CoV-2 human CTLs by extracellular vesicles engineered with the N viral protein

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November 15, 2021

Abstract

We investigated an innovative anti-SARS-CoV-2 immune strategy finalized to oral administration of extracellular vesicles (EVs) inducing an anti-SARS-CoV-2 N CD8+ T cytotoxic lymphocyte (CTL) immune response. We previously reported that the SARS-CoV-2 N protein can be uploaded at high levels in EVs upon fusion with Nefmut, i.e., a biologically inactive HIV-1 Nef mutant incorporating into EVs at quite high levels. Here, we analyze the immunogenic properties in human cells of EVs engineered with SARS-CoV-2 N fused at the C-terminus of either Nefmut or a deletion mutant of Nefmut referred to as NefmutPL. Analysis of in vitro produced EVs proven the uploading of N protein also when fused with truncated Nefmut. Mice injected with DNA vectors expressing each fusion protein developed robust SARS-CoV-2 N-specific CD8+ T cell immune responses. When ex vivo human dendritic cells were challenged with EVs engineered with either fusion products, the induction of a robust N-specific CTL activity, as evaluated by both CD107a and trogocytosis assays, was observed. Through these data we achieved the proof-of-principle that engineered EVs can be instrumental to elicit anti-SARS-CoV-2 CTL immune response in human cells. This achievement represents a mandatory step towards the upcoming experimentations in pre-clinical models.

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