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HIV-1 gp120-carrying polyion complex nanoparticles induce potent adaptive immunity via dendritic cell maturation

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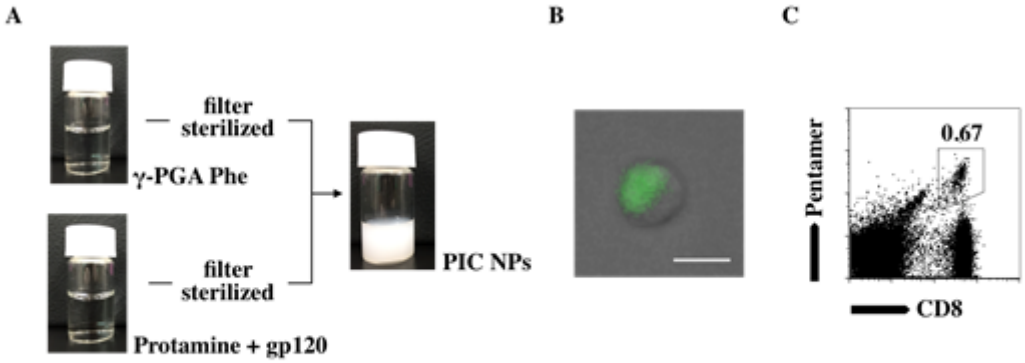
Background: The development of safe and effective vaccines against human immunodeficiency virus type 1 (HIV-1) is important for prevention of the global AIDS pandemic. The induction of HIV-1-specific CD8+ T cells and antibodies have been reported in controlling disease progression thorough the inhibition of viral replication. We have created polyion complex nanoparticles (PIC NPs) using the anionic polymer poly(γ-glutamic acid) (γ-PGA) and the cationic protein protamine. Both of them are biodegradable. Antigen-carrying PIC NPs can be simply prepared by mixing γ-PGA with protamine in PBS containing antigens. In this study, we have examined the effect of HIV-1 gp120-carrying PIC NPs on the induction of innate and adaptive immune responses in mice.

Material/methods: Filter-sterilized protamine was mixed with gp120 or FITC-labeled gp120. The mixture was added to an equal volume of filter-sterilized γ-PGA to yield gp120-carrrying PIC NPs. Bone marrow-derived dendritic cells (DCs) were incubated with PIC NPs. After incubation, cell-associated fluorescence, cell signaling pathways, cell surface molecules, and cytokine production were measured by a fluorescence microscope, western blotting, flow cytometry, and ELISA, respectively. Mice were immunized subcutaneously with gp120-carrying PIC NPs on days 0 and 7. On day 14 after the final immunization, spleen cells were harvested and analyzed for their gp120-specific responses.

Results: The PIC NPs showed a monodispersed size distribution with a mean diameter ranging from 200 to 300 nm. FITC-labeled gp120-carrying PIC NPs were efficiently taken up into DCs. PIC NPs

upregulated surface CD86 expression and IL-12p40 production through MAPK-mediated NF-κB signaling pathway in DCs. The immunization of mice with gp120-carrying PIC NPs resulted in robust induction of IFN-γ- and TNF-α-producing gp120-specific CD8+ T cells. In contrast, no such induction was obserbed, when mice were immunized with gp120 alone or gp120 plus commercial adjuvants such as aluminum or incomplete Freund's adjuvant.

Conclusions: In addition to the simple method for preparation of PIC NPs, PIC NPs have not only antigen-carrying capacity but also potent activity of inducing innate and adaptive immune responses. Therefore, PIC NPs may have great potential as an effective vaccine adjuvant against HIV-1.



(A) Preparation of gp120-carrying PIC NPs, (B) uptake of PIC NPs by DCs, and (C) Induction of antigen-specific CD8+ T cells in mice immunized with gp120-carrying PIC NPs.