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OAO5-04. Gp96-Ig-SIV vaccines induce predominant immune responses at mucosal sites

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Background

We have developed a vaccine design that utilizes the unique property of the endoplasmic reticulum chaperon, heat shock protein (HSP) gp96, to bind antigenic peptides and deliver them to APCs. Cell-based gp96-Ig vaccines, by prolonged in vivo secretion of gp96-Ig peptide, imitate viral replication and provide immune stimuli comparable to attenuated viruses. In model systems in mice we have shown that gp96-Ig transfected, antigen expressing cells secrete gp96-Ig *in vivo* and stimulate both systemic and strong mucosal immunity. The aim of our study was to evaluate safety and systemic and mucosal SIV-immunity with secreted gp96-Ig-SIV vaccines in non-human primates.

Methods

Gp96-Ig was generated by replacing the ER retention sequence KDEL with the IgG1-Fc tag. HEK-293 cells were transfected with gp96-Ig and with the cDNAs encoding the SIV antigens gag, pol, env and retanef. Irradiated, transfected 293 cells that secrete 1, 5 or 50 micrograms gp96-Ig-SIV-peptide complexes in 24 h, were injected intraperitoneally in Mamu-A*01+ macaques at 0, 4 and 25 weeks.

Results

After the third immunization the SIV-specific CD8 response was boosted to very high levels in the rectum and jejunum (30 – 50% tetramer positive cells in the CD8 gate in LPL and IEL). In vaginal IEL gag-specific CD8 responses reached 4%. Tetramer+ cells expressed appropriate functional (granzymeB) and migration markers (CD103). Control macaques immunized with 293 cells not secreting gp96, showed only background tetramer binding. The mucosal CD8+ and CD4+ T cells from lamina propria and intraepithelial compartment secrete IL-2 or IFN-gamma or both simultaneously in response to peptide stimulation.

Conclusion

We conclude that the cell secreted gp96-Ig-SIV vaccine is safe and can induce strong poly-specific, multifunctional and predominant CD8 responses in mucosal compartments that are thought to be critical for protection from SIV/HIV infection.

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