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Recent advances and current status of gm-Csf as an adjuvant in DNA vaccines for viral diseases

Abstract

Here, I update the recent advances and current status of Granulocyte macrophage colony-stimulating factor (GM-CSF), since we have reported for the first time that porcine GM-CSF gene in a DNA vaccine formulation exerted immuno-adjuvant and protective effects against Aujeszky's (Pseudorabies)viral disease to the natural host pigs with a single vaccination. GM-CSF has been broadly used as an adjuvant in preclinical DNA vaccine studies for cancer and viral diseases. Currently, GeoVax Labs, Inc. reported a recombinant HIV vaccine (GEO-D03) that co-expresses the human GM-CSF and non-infectious HIV-1 virus-like particles (VLPs) is being evaluated in HIV infected young adults in several Phase I studies (NCT01571960). In addition, we summarized here the outcomes of the use of GM-CSF in DNA vaccine for other viral diseases. Further, phase 3 studies reported that GM-CSF showed an improvement in patient outcome when applied in combination with suitable anti-tumor vaccines. However, GM-CSF in excessive levels may expand myeloid suppressor cells that were shown to dampen adaptive immune responses.

Keywords: granulocyte macrophage colony-stimulating factor, gm-Csf, genetic adjuvant, DNA vaccine, viral disease, cancer, clinical trial

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Abbreviations: GM-CSF, granulocyte macrophage colony-stimulating factor; HIV, human immunodeficiency virus; SIV, simian immunodeficiency virus

Introduction

Here, I update the recent advances and current status of Granulocyte macrophage colony-stimulating factor (GM-CSF), since we have reported for the first time[1,2] that a DNA vaccine formulation with porcine GM-CSF gene exerted immuno-adjuvant effects and protected the natural host pigs against Aujeszky's (Pseudorabies) viral disease with single vaccination. The hematopoietic cytokine GM-CSF has been shown as an efficient adjuvant in DNA vaccine preclinical studies for cancer and viral diseases. Xiang Z et al.[3] first reported that GM-CSF is a genetic adjuvant for DNA vaccine.

GM-CSF as a genetic adjuvant for HIV DNA vaccine in human clinical trials

A recombinant HIV vaccine (GEO-D03) that co-expresses the human GM-CSF and non-infectious HIV-1 virus-like particles (VLPs) is being currently evaluated in HIV infected young adults in several Phase I studies (NCT01571960- 2015).[4,5] This trial will determine whether this vaccine will provide excellent protection in humans as in macaques by simian immunodeficiency virus (SIV)-prototype (NCT01909414-2013).[6] Lai et al.[7] 2011 reported that the SIV vaccine co-expressing GM-CSF achieved significantly higher reduction in risk of infection and protected more SIV challenged macaques in preclinical studies. In addition, this vaccine elicited both anti-viral T cells and antibody. The vaccine-induced prevention of infection was shown to increase from 25% to 71% in the presence of GM-CSF.[7] The Outcomes of the use of GM-CSF as genetic adjuvant in DNA vaccine for other viral diseases is given in Table 1.

Use of GM-CSF in cancer

GM-CSF was found the most efficient adjuvant for cancer cell vaccines in early preclinical screens of retroviral-expressed cytokines.[27] Further, the ability of the fused GM-CSF to elicit anti-tumor immune responses and boost vaccine efficiency is found in the first licensed cancer vaccine, Provenge.[28] Despite, a number of studies demonstrating cytokines can act as adjuvants in tumor vaccines, the cost prevent their widespread use, except for the GM-CSF. More recently, GM-CSF has shown improved patient outcome in phase 3 studies when applied in combination with suitable anti-tumor vaccines.[29] In addition, GM-CSF is licensed to use as an adjuvant in a fusion protein for a dendritic cell therapy for prostate cancer and for recovery and replacement of white blood cells following bone marrow transplantation and chemotherapy.[30] However, GM-CSF in excessive levels may expand myeloid suppressor cells that were shown to dampen adaptive immune responses.[31–33]

Table 1 Efficacy and outcomes of GM-CSF as genetic adjuvant in DNA vaccines for viral diseases

Virus	Efficacy/Outcome of GM-CSF	Reference
Porcine Circovirus Type-2	Pigs immunized with Cap-GM-CSF subunit vaccine showed significantly higher levels of PCV2-specific antibodies and neutralizing antibodies and higher average daily weight gain than pigs receiving immunized with the Cap subunit vaccine and a commercial vaccine (Ingelvac CircoFLEX; P<0.05) after wild-type PCV2 challenge.	8

Table continued...

Virus	Efficacy/Outcome of GM-CSF	Reference
Flaviviridae Virus	Reported as complex and diverse, ranging from enhancement to suppression, depending on the immunogen of Flaviviridae virus DNA vaccine candidates.	9
Simian ImmunoDeficiency Virus	The co-expressed GM-CSF increased vaccine-induced prevention of infection from 25% to 71% in simian immunodeficiency virus in macaques.	7
	GEO-D03, a DNA vaccine that expresses human GM-CSF and non-infectious HIV-1 virus-like particles .entered into human trials.	4
HIV/AIDS	A phase 1 study of the safety and immunogenicity of DNA/MVA immunizations with co-expressed GM-CSF in HIV-1 infected young adults with suppressed viremia on HAART.	5,6
Foot and Mouth Disease	Efficacy of the DNA vaccine with GM-CSF was improved further in reducing the clinical disease and virus excretions by electroporation.	10
Japanese Encephalitis Virus	Reported no protection	11
HIV	Induced long-lived humoral and cell mediated immune memory responses.	12
Dengue Virus	DV1 challenged mice showed long-term IgG response, strong cytotoxic T lymphocyte activity, produced high levels of splenocyte-secreted interferon-γ and interleukin-2 and sufficient protection after immunization with pCAG-DV1-GM-CSF immunization than pCAG-DV1/E alone	13
	Induced stronger immunogenicity and protection from virus challenge in Aotus monkeys.	14
Influenza Virus	GM-CSF gene enhanced systemic and mucosal immunogenicity of the HA DNA vaccine in Rhesus macaque	15
Hepatitis B Virus	HBV-S gene fused with GM-CSF strengthened the immune effects of the HBV DNA vaccine in HBV-transgenic mice	16
Bronchitis Virus	pVAX-chGM-CSF and pVAX-S1 provided more protection against IBV challenge in chickens than pVAX-S1 vaccination alone.	17
Feline Immuno Deficiency Virus	Preserved global CD4 T lymphocyte function after the challenge..	18
Porcine Reproductive and Respiratory Syndrome Virus	Significantly enhanced the humoral and cellular immune responses and protection against PRRSV challenge in pigs	19
Hepatitis C Virus	Reported no change in the Th1/Th2 balance as compared with simultaneous IL-23 administration.	20
	Co-immunization with Flt3-L and GM-CSF shown promise in the development of an effective antiviral HCV vaccine	21
Simian-Human Immuno Deficiency Virus	Enhanced IgA response was associated with the best protection, but did not achieve significance.	22
HIV-1 Gag	Demonstrated strong antibody and CTL responses and a protective response against infection with recombinant vaccinia virus expressing HIV-1 Gag.	23
Equine Herpes Virus	DNA vaccine with GM-CSF, formulated in DMRIE-DOPE significantly improved virus neutralizing antibody responses to EHV-1.	24
HIV-1 Env	The adjuvant treated group showed significantly better control to the challenge than the non-GMCSF group.	25
	Bicistronic DNA vaccines containing GM-CSF elicited remarkably potent CD4(+) T cell responses	26
Aujeszky's (Pseudorabies) Viral Disease.	We demonstrated that the Porcine GM-CSF gene in a DNA vaccine formulation exerted immuno-adjuvant and protective effects with single vaccination in the natural host pigs against Aujeszky's disease.	1

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Conflict of interest

Author declares that there is no conflict of interest.

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