Phenotypic and functional characterization of HPV positive tumour lysate or recombinant human SPAG9 primed dendritic cell vaccines in cervical cancer

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Abstract

India, ranking number one globally in terms of cervical cancer burden, has an estimated 134,420 new cases of cervical cancer every year and 72,825 deaths occur due to this disease. These necessitate an emergence of novel adjuvant immunotherapeutic strategies to trigger a potent antitumour response. Dendritic cells (DCs) are one such immune cell that triggers both adaptive and innate immune cells which result in tumour suppression or regression. Our study showed the presence of tumour lysate as the antigen source increased the maturation marker with the significant migratory capacity of tumour lysate primed DCs (TLDCs) towards the gradient of chemokine ligands. The functionality of TLDCs was also improved in stimulating Th1 response with a significant rise in IL12 and IFNγ in autologous co-cultures. Also, our study for the first time showed the possibility of generating the sperm associated antigen 9 (SPAG9) primed DCs invitro with 750ng of SPAG9 as the optimised dosage for priming. The phenotypic and functional assays also imply the SPAG9 primed DCs in producing a comparable immune response to TLDCs. Further, the intervention of chemotherapeutic regimen-cisplatin on TLDCs and SPAG9 primed DCs did not hamper the phenotypic as well as the functionality of DCs at the 200µM concentration (equivalent to the clinical dose). In conclusion, our study standardised and set up the quality control criteria for DC vaccine which acts as the potential therapeutic vaccine treatment along with the standard chemotherapeutic agent cisplatin for the ongoing phase II clinical trial in cervical cancer.

Dendritic cells have emerged as important cell based therapeutic adjuvants due to their ability to cross present antigens to the host immune system and express ample co-stimulatory molecules. However,choice of tumour antigens has posed the biggest challenge to DC vaccine production. Hence the use of cancer testis antigen (CTA), due to their unique expression, have made them attractive peptide vaccine candidates, particularly MAGE-A and NY-ESO1 which have been used as therapeutic entities in several clinical trials. Recent studies showed that restricted NY-ESO-1 immunogenic peptides in combination with various adjuvants exhibited potent anti-tumour response. However, two other phase II trials with a single MAGEA3 peptide did not show an improvement in disease free survival. In contrast to peptides or peptide mixtures, whole protein CT antigens may be suitable for peptide processing and presentation across several HLA types when used for priming autologous DCs. Recently, sperm associated antigen 9 (SPAG9) has been shown to be expressed in various cancer types such as epithelial ovarian cancer (EOC- 90%), renal cell carcinoma (RCC- 88%), colorectal cancer (74%), breast cancer (88%) and cervical cancer (82%). Studies on SPAG9 also showed that it is associated with cellular proliferation, migration and invasion of cancer cells, and is capable of eliciting humoral immune responses in a majority of epithelial ovarian cancers (67%), breast cancer (80%), cervical cancers (80%), renal cell carcinoma (77%), colorectal cancer (74%) and hepatocellular carcinoma. However its antigenicity in invoking a cell mediated immune response has not been studied until now. Combinatorial regimens utilizing chemotherapy and immunotherapy may decrease the tumour burden as well as the immunosuppressive cells in the tumour microenvironment facilitating pronounced synergistic effects. Several clinical trials conducted in solid tumours also showed an increased overall survival of patients when cell based immunotherapy with DC vaccines was combined with chemotherapy regimens. Hence evaluating the ecacy of dendritic cells and DC stimulated T cells in the presence of chemotherapeutic agents may be necessary to account for any difference in such functionality linked to specic antigens affecting their antigenicity.

This is the rst study to assess the potential of SPAG9 protein as an antigenic source for dendritic cell priming. We primed immature DCs with increasing dosage of rhSPAG9 and determined the optimal priming dose. The ecacy of rhSPAG9 primed DCs (SPDC) was examined using immunophenotyping and functional assays. Our earlier studies in-vitro and in phase I cervical cancer trials, we have demonstrated the ecacy of autologous tumour lysate pulsed DCs (TLDC). Hence, autologous TLDCs from the same patient were compared with SPDCs to assess their functional characteristics. In addition,the ability of SPDCs to elicit a Th1 response in combination with cisplatin at various concentrations was also assessed. Our present study has laid down the foundation for undertaking Phase II cervical cancertrials employing rhSPAG9 protein as an antigenic source for DC based vaccines.

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