219 CD47 AND PHOSPHATIDYLSERINE CONTRIBUTE TO THE INTERACTION BETWEEN ANTIGEN PRESENTING CELLS AND THE ALLOGENEIC CELL-BASED RELAPSE VACCINE DCP-001

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Background DCP-001 is a cancer relapse vaccine derived from the DCOne® human leukemic cell line. During manufacturing, DCOne® cells are shifted towards a mature dendritic cell (mDC) phenotype, combining an endogenous tumor antigen repertoire (e.g. WT-1, RHAMM and PRAME) with a mDC costimulatory profile and providing the basis for the highly immunogenic vaccine DCP-001. In a phase I clinical study in acute myeloid leukemia (AML), DCP-001 demonstrated to be safe and to induce multifunctional antitumor immune responses.[1] It has also been reported that DCP-001 induces antitumor immunity against multiple myeloma cells in peripheral blood mononuclear cells (PBMC) from multiple myeloma patients and that DCP-001 antigenic material is transferred to host antigen presenting cells (APC), possibly via extracellular vesicles.[2] However, the possibility of direct interactions between DCP-001 and host APC has not yet been investigated.

Methods To further elucidate the mode of action of DCP-001, we studied the interactions of DCP-001 with human PBMC and isolated immature monocyte-derived DCs (iMoDC) in in vitro co-culture studies. A human skin explant model was used to determine uptake of DCP-001 by migrating skin DCs after intradermal injection.

Results We found that DCP-001 stimulates the secretion of various proinflammatory cytokines (IL-1β, GM-CSF, IFN-γ, IL-2, TNF-α, and IL-6) and chemokines (IL-8 and RANTES) in PBMC. In addition, we demonstrate that DCP-001 is efficiently taken up by iMoDC via direct cell-cell interactions and that this phagocytic process is influenced by ”eat-me” and ”don’t eat me” signaling pathways. Blocking of the ”eat-me” signals calreticulin and phosphatidylserine inhibited the uptake of DCP-001, whereas blockade of the ”don’t eat me” signal CD47 enhanced DCP-001 uptake. After intradermal injection of DCP-001 in an ex-vivo human skin model, its uptake by skin-emigrating DCs was demonstrated as well as simultaneous activation of these DCs.

Conclusions Our data suggest a key role for host antigen presenting cells in the triggering of immune responses upon DCP-001 vaccination. In addition, the data provide rationale for potential combination therapies based on DCP-001 and inhibitors of the CD47 pathway.

REFERENCES

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