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Targeting the DCIR Receptor with a TLR7 Agonist Specifically Activates Monocytes and DCs

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Purpose: Tumor immune escape is a major reason for cancer manifestation and progression. Monocytes and dendritic cells (DCs) are central to both innate and adaptive immune responses, but often become inactivated or actively immunosuppressive in the tumor tissue. Providing activated monocytes and DCs to the tumor tissue could therefore be a way to break the immune suppression and reinstate cancer immune surveillance [1,2]. We have developed a delivery system consisting of liposomes targeted to the Dendritic Cell Immunoreceptor (DCIR), which is highly expressed on monocytes and DCs. We coupled DCIR specific antibodies to liposomes formulated with the TLR7 agonist TMX-202 and examined targeting to monocytes, myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) in PBMC culture as well as activation of the targeted cells.

Methods: Maleimide-functionalized Rhodamine B labeled liposomes containing TMX-202 were prepared using the lyophilization method. Anti-DCIR Antibodies were thiolated and conjugated to the liposomes. Peripheral blood mononuclear cells (PBMCs) were isolated from buffy coats from healthy donors. PBMCs were incubated with buffer, free drug or liposomes and liposome uptake was analyzed by flow cytometry. After stimulation, the PBMCs were further cultured for 1-5 days and on each day the secretion of key cytokines indicative of activation of monocytes and/or DCs was analyzed using Meso Scale Discovery cytokine assays.

Results: DCIR liposomes showed strong preferential association to monocytes and mDCs over the combined population of T, B and NK cells, as well as significant targeting to pDCs (Fig. 1A). Analysis of culture supernatants from stimulated PBMCs demonstrated potent secretion of cytokines, which support activation of monocytes, mDCs and pDCs and/or are associated with anti-cancer effects (Fig. 1B-D). Targeted liposomal delivery was superior at inducing secretion of anti-cancer cytokines compared to the free drug.

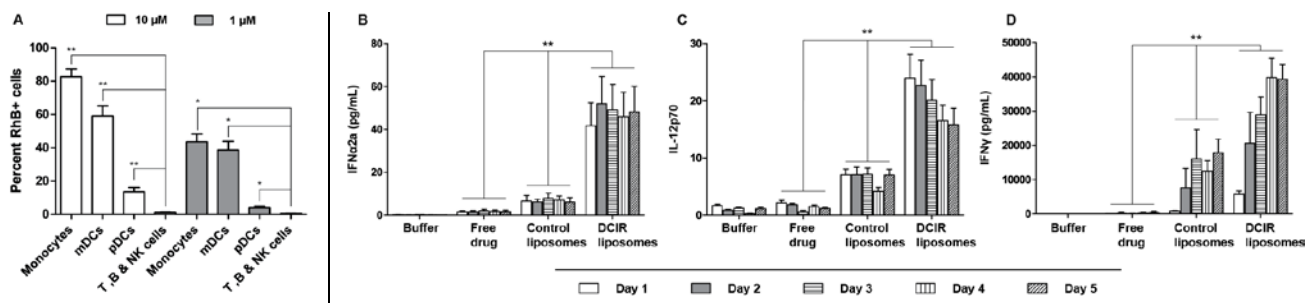


Figure 1. (A) DCIR liposomes preferentially associate to monocytes and mDCs (1 and 10 μM TMX-202). (B-D) Stimulation of PBMCs (1 μM TMX-202) leads to secretion of anti-cancer cytokines such as IFNα2a (B), IL-12p70 (C) and IFNγ (D). ** $p < 0,0001$, * $p < 0,005$, t-test, $n = 9$, Error bars = S.E.M.

Conclusions:

The presented delivery system targeted monocytes and DCs with high specificity over lymphocytes, potentially activated the targeted cells and was superior to the free drug at activating DCs and monocytes. This delivery system could be a way to improve cancer treatment either as a vaccine or as immunotherapy to boost antigen-presentation in combination with other types of treatment such as chemotherapy or radiotherapy

References:

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2. Cook J., Hagemann T. Curr. Opinion Pharm. 2013 (12) 595-601