SELECTIVE EXPANSION OF ANTIGEN-SPECIFIC CD8 T CELLS WITH ENGINEERED ANTIGEN PRESENTING EXOSOME

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Background Exosomes are vesicular granules of about 100 nm and are secreted by many types of cells. Exosomes contain various proteins, lipids, and RNAs that are transported to target cells which induce functional and physiological changes. Exosomes are promising nano-vesicles for clinical application, owing to their high biocompatibility, low immunogenicity, and high drug delivery efficacy. Recent studies have demonstrated that exosomes from tumor cells or antigen presenting cells (APCs) regulate immune responses. Tumor derived exosomes express PD-L1 on their surface and suppress tumor immunity systemically. On the other hand, mature dendritic cells derived exosomes exert immune activation, and tumor immunotherapy using DCs exosome has been developed. However, few studies have been found to exert a significant effect on cancer treatment, may be because of low expression of costimulatory molecules and lack of cytokines on DCs derived exosomes.

Methods It has been demonstrated that GFP can be conveyed into exosomes by conjugating GFP with tetraspanins, exosome-specific surface proteins. First, we generated a tetraspanin fusion protein with a single-chain MHC I trimer (scMHC I). IL-2 is inserted on the second extracellular loop of CD81, allowing robust and functional expression of IL-2 on the exosome. We collected exosomes from HEK293 cells culture, which stably express scMHC I-CD81-IL2 and CD80-MFGE8, and used as Antigen-presenting exosome(AP-Exo).

Results AP-Exo expresses high expression of MHC I-peptide complex, costimulatory molecule, and cytokine, activating cognate CD8 T cells as dendritic cells do. AP-Exo selectively delivered co-stimulation and IL-2 to antigen-specific CD8 T cells, resulting in a massive expansion of antigen-specific CD8 T cells without severe adverse effects in mice. AP-Exo can expand endogenous tumor-specific CD8 T cells and induce the potent anti-tumor effect.

Conclusions Our strategy for building engineered exosomes that work like APCs might develop novel methods for cancer immunotherapy.

Ethics Approval All mice were housed in a specific pathogen-free facility, and all animal experiments were performed according to a protocol approved by Kanazawa University, Kanazawa, Japan.

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