Curvature-sensing peptides

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Exosome-disrupting peptides for cancer immunotherapy

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A curvature-sensing peptide is used to disrupt exosomes for enhanced cancer immunotherapy.

Immune checkpoint blockade therapies that target the programmed cell death protein 1(PD-1)/programmed death-ligand 1 (PD-L1) axis have revolutionized cancer therapy[1]. These therapies, mainly comprising monoclonal antibodies, can specifically block PD-1/PD-L1 interactions between T cells and cancer cells and thus prevent T cells from resultant exhaustion and inactivation, preserving a strong anti-tumour immune response[2]. Several anti-PD-1/PD-L1 antibodies have already been approved by the US Food and Drug Administration and a large number of candidates are in clinical and pre-clinical studies[1]. However, although anti-PD-1/PD-L1 therapies have been shown to be effective in some patients, the overall response rate is low and a large proportion of patients do not respond to such therapies[3]. According to recent studies[4,5], one of the main contributing factors of the limited response to immune checkpoint blockade therapies is the tumour cells' secretion of large amounts of extracellular vesicles (mainly exosomes). The PD-L1 membrane protein expressed on tumour-derived exosomes (T-EXOs) can hamper anti-PD-1/PD-L1 therapies by binding to T cells to induce T cell exhaustion or act as a decoy to consume anti-PD-L1 (ref. 5). Thus, inhibition of T-EXOs could be a potential strategy for improving anti-PD-1/PD-L1 cancer immunotherapy.

The mechanism underlying exosome secretion by tumour cells is not fully understood. Studies have shown that exosome secretion is controlled by many factors such as the Ras-related protein Rab27a, sphingomyelinase and proton pumps[6]. Many strategies that target these pathways have been developed to decrease the level of T-EXOs. For example, studies have shown that knockdown of *Rab27a* using small interfering RNA (siRNA) greatly decreased exosome secretion[7]. Others have demonstrated that small-molecule inhibitors for sphingomyelinase and proton pumps can suppress T-EXO production[6]. However, the clinical translation of these therapies is challenging. *Rab27a* is expressed across normal cells and cancer cells, so siRNA against *Rab27a* could also affect normal cell functions. Synthetic inhibitors for sphingomyelinase and proton pumps lack tumour cell specificity,

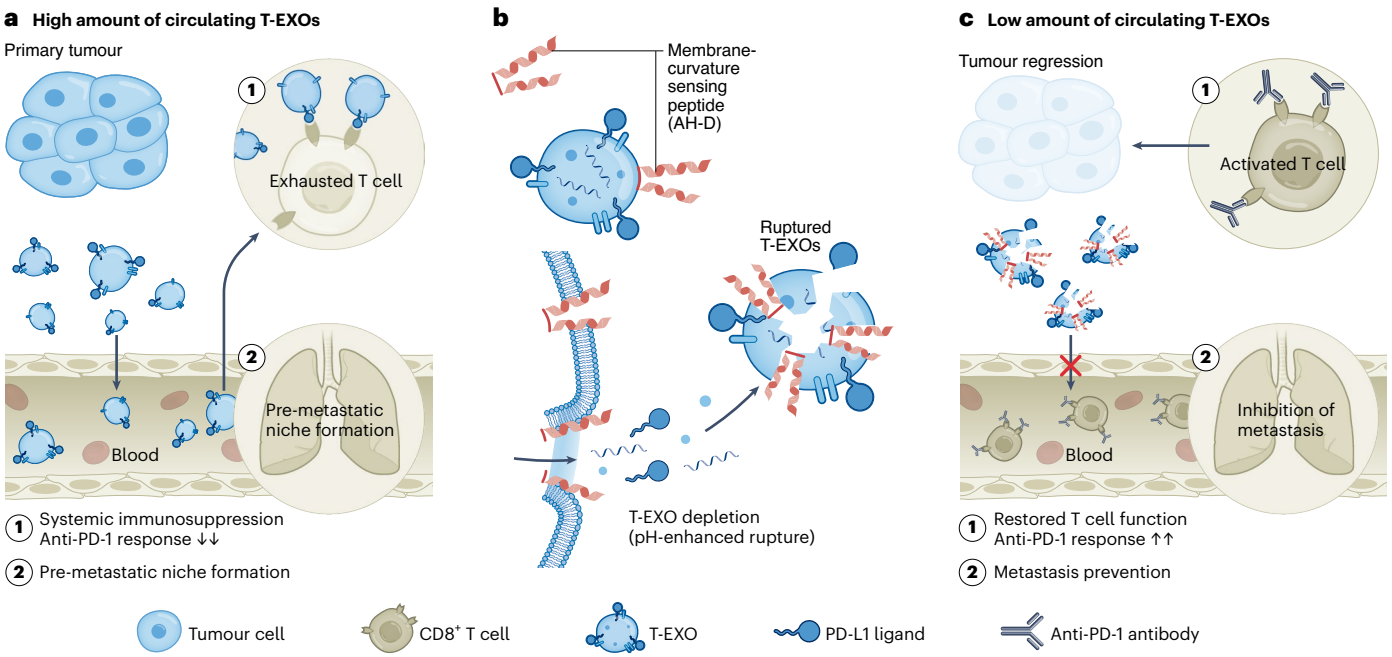

Fig. 1 | Exosome-disrupting peptide for cancer immunotherapy. a, Schematic showing that T-EXOs lead to tumour progression by (1) systemic suppression of T cell functions and (2) formation of a pre-metastatic niche. **b**, The study by Park and colleagues shows that a membrane-curvature sensing antivirus peptide (AH-D peptide) can specifically lyse and deplete T-EXOs in the acidic tumour microenvironment and in blood circulation. **c**, In an in vivo B16F10 melanoma mouse model, AH-D peptide treatment greatly decreases circulating T-EXOs, which (1) restores T cell function and improves anti-PD-1 response and (2) inhibits the formation of metastases in the lung. Figure adapted with permission from ref. 9, Springer Nature Ltd.

and thus could similarly induce off-tumour toxicities. Because of these challenges, the development of a broadly applicable approach that can directly inhibit T-EXOs is an unmet need in the clinic.

Inspired by membrane-curvature-sensing antiviral peptides that disrupt membrane-enveloped viruses in vivo[8], writing in *Nature Materials*, Jae Hyung Park and colleagues report that a 27-mer amphipathic peptide (termed AH-D) can directly disrupt T-EXOs and improve anti-PD-1 therapy (Fig. 1)[9]. The AH-D peptide selectively disrupts highly curved exosome membranes (<300 nm diameter) through a curvature-dependent pore formation and membrane lysis mechanism. The AH-D peptide shows improved T-EXO lysing capacity in the acidic tumour microenvironment (pH 6.5). The substantial disruption of T-EXOs both in the tumour tissue and in circulation prevents T-EXO-mediated $CD8^+$ T cell dysfunction and thus improves the therapeutic outcomes of anti-PD-1 therapy.

In an in vivo B16F10 melanoma mouse model, the authors show that AH-D peptide treatment greatly decreases exosomal PD-L1 levels in plasma, reduces T cell exhaustion, increases $CD8^+$ T cell infiltration and thus enhances anti-PD-1 therapy. Moreover, disruption of circulating T-EXOs also inhibits the formation of a pre-metastatic niche, thereby preventing pulmonary metastasis. These results demonstrate that disrupting T-EXOs using the AH-D peptide is a safe and effective material-based strategy to decrease T-EXO-mediated immune suppression and improve the therapeutic outcome of anti-PD-1 immune checkpoint blockade therapy.

The results of Park and colleagues are of broader interest to the cancer immunotherapy field, as the AH-D peptide can potentially be harnessed synergistically with a variety of cancer immunotherapies beyond anti-PD-1 therapy. For example, CD47 is an immune checkpoint that is also highly expressed on tumour exosomes[10]. Combining the AH-D peptide with anti-CD47 could potentially enhance the antitumour efficacy of anti-CD47 therapy. Park and colleagues show that using the AH-D peptide to disrupt T-EXOs substantially improves melanoma treatment using anti-PD-1. Many other solid tumours, such as pancreatic cancer and colon cancer, also secrete large amounts of exosomes. The AH-D peptide could readily be used with anti-PD-1, anti-CD47 or other immunotherapies for the treatment of these cancers. One of the key advantages of the AH-D peptide described here is that it can selectively disrupt T-EXOs, particularly in the acidic tumour microenvironment. The AH-D peptide can therefore be adapted as a trigger for tumour-microenvironment-responsive drug or gene delivery when using exosomes as carriers. It will be interesting to see how this AH-D peptide compares with previously reported exosome-inhibition strategies in combination with immune checkpoint blockade therapy. Future work should also address whether the AH-D peptide induces a humoral response, which could in principle cause an anti-AH-D antibody response and result in rapid clearance of the peptide. Such a response could be sidestepped by replacing the peptide with lipid nanoparticles carrying messenger RNA encoding the AH-D peptide. While further investigation is required to fully harness the potential of the AH-D peptide for cancer immunotherapy, the combination of the AH-D peptide and immune checkpoint blockade therapy makes a substantial stride forwards in therapeutic efficacy compared with traditional immune checkpoint blockade therapy.

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Competing interests

The authors declare no competing interests.