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COMMENTARY

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The role of small Extracellular Vesicles (sEVs) and Rab27a in nanoparticle metastasis and tumor targeting

Jiahua Si,[1,2] Xinming Su,[1,2] Zhuoyan Jin,[1] Hanqi Lou,[1] and Shiwei Duan[1,*]

[1]Department of Clinical Medicine, School of Medicine, Hangzhou City University, Hangzhou 310000, China

[2]These authors contributed equally

*Correspondence: duansw@hzcu.edu.cn

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In recent years, Nanoparticles (NPs) have garnered significant attention in cancer treatment. In 2024, Professor Zhiyong Qian's team published groundbreaking research in Nature Materials, introducing novel nanomaterials for tumor therapy. This study has opened new avenues for future clinical applications, particularly in nanomaterial-based drug delivery systems, which have become a major research focus. However, only approximately 0.7% of NPs successfully reach tumor sites, and the precise mechanisms by which tumor-suppressing NPs function remain unclear. Consequently, progress in optimizing NPs for tumor targeting has been limited. There is an urgent need to elucidate the mechanisms by which NPs inhibit cancer cells.

Previous studies have demonstrated that the tumor microenvironment (TME) not only promotes tumor growth but also impairs cellular immunity and reduces NP sensitivity.[1] Small extracellular vesicles (sEVs), key components of the TME, have been recently identified as inhibitors of NP transport.[2] However, the exact mechanism by which sEVs prevent NP accumulation in tumors remains unclear. To investigate this, Ningqiang Gong and his team examined the impact of high concentrations of sEVs secreted by cancer cells on NP efficacy.

Building on prior research, the team uncovered a unique regulatory mechanism in which tumors secrete sEVs to engulf lipid nanoparticles (LNPs) and transfer them to Kupffer cells in the liver. This phenomenon was observed exclusively in tumor-bearing mice, with no comparable effect in normal mice. In subsequent experiments, the researchers used LNPs co-encapsulating small interfering RNA (siRNA) targeting Rab27a (siRab27a) and mRNA encoding the stimulator of interferon genes (mSTING) to bypass the tumor's defense mechanism, significantly enhancing the tumor-killing efficacy of NPs.

Previous studies had established Rab27a as a key oncogene that inhibits cellular immunity by promoting sEV production.[3] To validate Rab27a's role in NP resistance, the researchers employed clustered regularly interspaced short palindromic repeats (CRISPR) technology to generate Rab27a knockout (KO) nude mice. As shown in Figure 1A, comparison of LNP distribution in KO and wild-type (WT) mice revealed increased LNP accumulation in the tumors of Rab27a KO mice, while LNP levels in the liver were markedly reduced. Flow cytometry analysis confirmed that in WT mice, LNPs primarily accumulated in Kupffer cells, with minimal distribution in other liver or immune cells. These findings demonstrated that Rab27a-mediated sEV secretion facilitates LNP transport to the liver, where they are subsequently phagocytosed by Kupffer cells. In contrast, LNPs remained localized at the injection site in normal mice, reinforcing the pivotal role of sEVs in tumor defense mechanisms.

Further investigation into the pathways involved in NP resistance revealed that Kupffer cells exhibited selective phagocytosis of sEVs, albeit with relatively low overall phagocytic activity. This led the authors to hypothesize that interactions between sEVs and LNPs, as well as between sEVs and Kupffer cells, contributed to this process. Transmission electron microscopy (TEM) and pull-down experiments confirmed that van der Waals forces played a crucial role in these interactions. The researchers further hypothesized that this phagocytosis depended on adhesion factors on receptor surfaces. KO of intercellular adhesion molecule 1 (ICAM-1) on sEVs significantly inhibited LNP uptake by Kupffer cells. Additionally, Kupffer cells exhibited markedly higher expression of CD11b and CD18 —subunits of the ICAM-1 receptor macrophage-1 antigen (Mac-1)—than other liver cells, explaining their preferential phagocytosis of LNP-bound sEVs. These findings align with research by Professor Gang Wang, published in Nature. Moreover, the authors observed reduced expression of SIRPα (a surface receptor) in

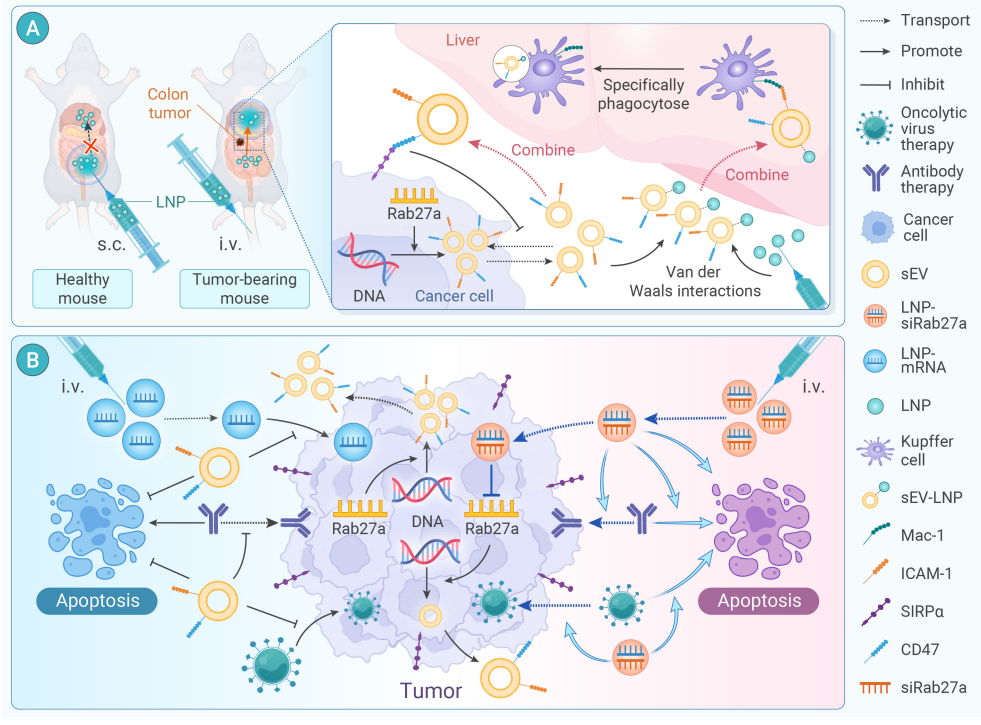

Figure 1. Unraveling the role of sEVs in tumor defense mechanisms and its implications for nanoparticle-based cancer therapies (A) Differential behavior of lipid nanoparticles (LNPs) in normal and tumor-bearing mice. In normal mice, subcutaneously injected LNPs remain localized at the injection site without metastasis. In contrast, in tumor-bearing mice, LNPs metastasize to the liver after subcutaneous injection. This behavior is attributed to Rab27a in cancer cells, which promotes the production of sEVs. Cancer cells use SIRPα on their surface to bind CD47 on sEVs, preventing the sEVs from metastasizing freely. However, the large quantities of sEVs produced bind to LNPs via van der Waals forces, facilitating their transport to the liver. In the liver, Kupffer cells recognize ICAM-1 on the surface of sEVs through their surface adhesion factor Mac-1, enabling specific phagocytosis of sEV-LNP complexes by Kupffer cells. (B) Tumor-produced sEVs as a defense mechanism. Tumors actively produce sEVs, with Rab27a playing a key role in enhancing sEV production. These sEVs can bind to LNPs, viruses, and antibodies, thereby blocking their entry into cancer cells and inhibiting their tumor-killing effects. However, LNPs loaded with siRab27a can successfully penetrate cancer cells and suppress Rab27a expression. This inhibition reduces sEV production, consequently diminishing the sEV-mediated blockade of LNPs, viruses, and antibodies. As a result, the tumor-killing efficacy of these therapeutic agents is significantly enhanced.

Kupffer cells compared to other Mac-1-expressing cells, further elucidating the liver-specific accumulation of LNPs.

The team then explored the role of SIRPα in tumor defense mechanisms. In tumor cells, SIRPα was highly expressed on the cell surface, where it interacted with CD47 on sEVs to prevent LNP uptake by cancer cells. KO of CD47 on sEVs confirmed that this interaction inhibited tumor cell uptake of LNPs. Notably, while SIRPα expression was significantly lower in normal cells than in tumor tissues, it remained higher than in liver Kupffer cells. This pattern explained why sEVs undergo liver-specific metastasis and are engulfed by Kupffer cells upon binding to LNPs. As shown in Figure 1B, the authors leveraged these findings to enhance LNP-based tumor treatments, integrating their approach with existing clinical therapies. They found that siRab27a-loaded LNPs significantly promoted NP accumulation in tumors. Furthermore, co-delivery of siRab27a with the anti-tumor gene mRNA PTEN (mPTEN) and the immunotherapy target STING further enhanced tumor-killing efficacy while minimizing systemic toxicity in tumor-bearing mice.

The findings suggest that tumors not only inhibit NP entry via sEV secretion but also extend this defense mechanism to other clinical cancer therapies, including oncolytic virus and antibody-based treatments.

Despite these advances, several key questions remain unresolved. Prior studies have shown that Rab27a promotes sEV production in HeLa cells and is closely associated with Slp4 and Slac2b expression.[3] However, the role of this regulatory pathway in other cancer types remains unverified. The precise mechanisms underlying Rab27a's interactions with Slp4 and Slac2b are unclear, raising the possibility that multiple proteins contribute to Rab27a-induced sEV production. Identifying these proteins could facilitate the development of NP-based strategies to block Rab27a activity, thereby inhibiting sEV production and improving tumor targeting.

Additionally, while siRNA-based therapies hold promise, concerns remain regarding off-target effects, which may pose risks to patients.[4] The use of targeted therapeutics could mitigate these risks. Although direct experimental evidence linking the CD47-SIRPα pathway to sEV-mediated NP resistance is lacking, numerous CD47-SIRPα-targeting drugs have demonstrated clinical efficacy. The authors propose that combining these novel NPs with immunotherapy could enhance tumor suppression.

The study also identified a novel link between Rab27a expression and growth hormone-releasing hormone, which promotes sEV production and suppresses hepatocyte proliferation.[5] These findings suggest that bioinformatics approaches could be leveraged to identify upstream regulators of Rab27a, presenting additional therapeutic targets for modulating tumor immune responses and enhancing treatment efficacy. Notably, LNPs bind to tumor-derived sEVs —absent in normal cells —via van der Waals forces, directly inhibiting their transport into tumors. CD47 on sEVs recognizes SIRPα on cancer cells, further blocking LNP uptake. Additionally, ICAM-1 on sEVs specifically interacts with Mac-1 on Kupffer cells, promoting liver metastasis of sEV-bound LNPs and subsequent phagocytosis by Kupffer cells. However, whether other nanomaterials form similarly strong van der Waals interactions with sEVs remains unknown.

In conclusion, this study advances our understanding of sEVs as key mediators of tumor defense mechanisms. By elucidating the inhibitory role of the TME in NP delivery, the authors challenge the conventional view of sEVs as mere waste carriers and signaling mediators. Their findings address fundamental challenges in NP-based cancer therapies and provide a foundation for enhancing their clinical efficacy. This research paves the way for future innovations in cancer treatment, offering hope for improved patient outcomes and higher cure rates.

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AUTHOR CONTRIBUTIONS

JS, XS, ZJ, and HL collected and analyzed the literature, drafted the figures and wrote the paper; SD conceived and gave the final approval of the submitted version. All authors have read and agreed to the published version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.