Tumor-draining lymph node lingers between protumor and antitumor immunity

Bei Li, Chu-Xia Deng, Yunlu Dai**

Cancer Centre and Institute of Translational Medicine, MoE Frontiers Science Center for Precision Oncology, University of Macau, Macau SAR 999078, China.
*E-mail: yldai@um.edu.mo *(Y. D.);* cxdeng@um.edu.mo *(C. D.);* beili@um.edu.mo *(B. L.)*

The tumor-draining lymph node (TDLN) can be early engaged by the peripheral tumor to promote metastatic progression. Representatively, in addition to increasing the expression of programmed death-ligand 1 (PD-L1), tumor cells secrete exosomal PD-L1 to infiltrate TDLN and immunosuppress T cells activity[1]. This preemptive action associates with a large percentage of clinical failures in immune checkpoint blockade (ICB) therapy. The strategy to downregulate the secretion of these exosomes may alleviate the TDLN exhaustion through restoring and proliferating functional T cells and aid ICB therapy. Therefore, we develop an assembly of exosome inhibitor (GW4869) and ferroptosis inducer (Fe^{3+}) via amphiphilic hyaluronic acid. Cooperation between the two active components in the constructed nanounit induces an anti-tumor immunoresponse to B16F10 melanoma cells and stimulates cytotoxic T lymphocytes and immunological memory. The nanounit enhances the response to PD-L1 checkpoint blockade[2].

However, the immunological role of the TDLN does not end in protumor metastasis. Increasing evidence has shed a light on the significance of TDLN in antitumor immunity. Inspired by clinical updates that suggest conserving TDLNs of breast cancer patients during surgery[3], we develop a bioresponsive flex-patch to fuel TDLN for precise immunoadjuvant therapy. This flex-patch can self-assemble synergistic anti-tumor components and spatiotemporally release them into TDLN, after an in-situ implantation on postsurgical tumor area (Figure 1). Functional agents are personally screened according to tumor heterogeneity, and can promote the activation and cytotoxic killing capacity of tumor-specific $CD8^+$ T cells in TDLN. This adjuvant treatment protects postsurgical patients from tumor relapse.

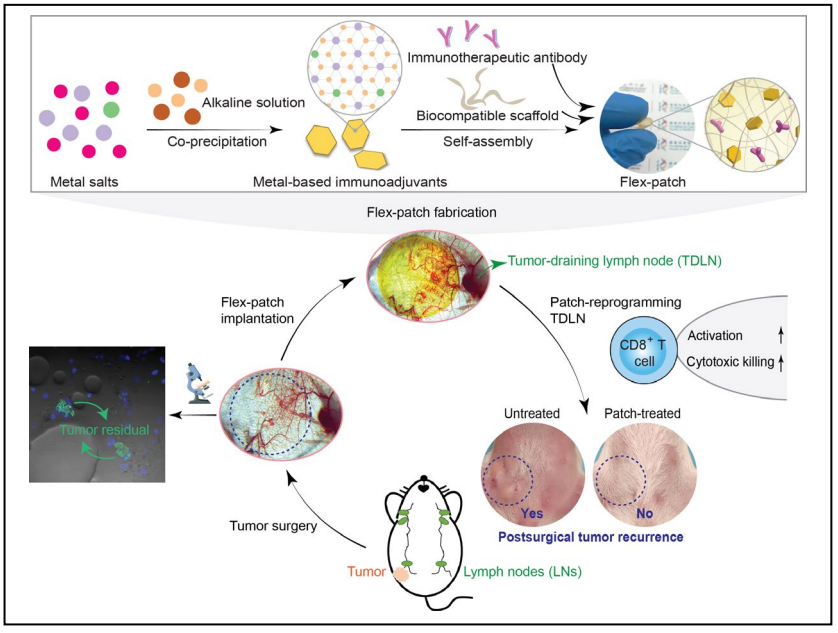

Figure 1: Schematic illustration of the flex-patch fabrication and its postsurgical immunoadjuvant performance

References

[1] Poggio, M. *Cell* **2019**, *177*, 414-427.
[2] Wang, G. *Nature Communications* **2021**, *12*, 5733.
[3] Galimberti, V. *Lancet Oncology* **2018**, *19*, 1385-1393.