Healthcare, Drug development

Enhancing antibody-dependent cellular phagocytosis by Re-education of tumor-associated macrophages with resiquimod-encapsulated liposomes

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Abstract

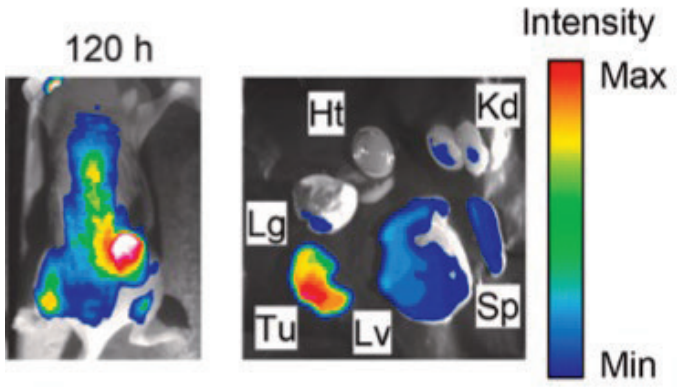
We developed the tumor-associated macrophage (TAM)-targeting liposomes encapsulating the TLR7/8 agonist resiquimod (R848). The R848-liposomes can convert the phenotype of macrophages from tumor-supportive M2 type to tumor-suppressive M1 type and the resulting macrophages can efficiently engulf the targeting tumor cells in an antibody-dependent manner (antibody-dependent cellular phagocytosis, ADCP). In vivo, R848-liposomes were accumulated into the tumor tissue of xenograft mice, and the combination with therapeutic antibody resulted in the shrink of the tumor. We confirmed the reduction of tumor burden was associated with the phenotypic change of TAMs in the tumor tissue.

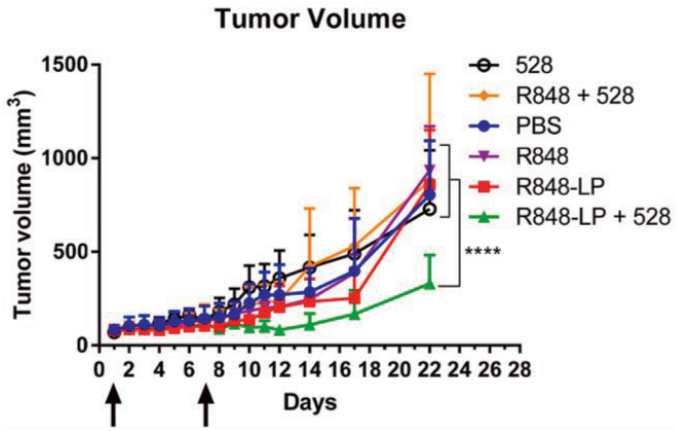
Background & Results

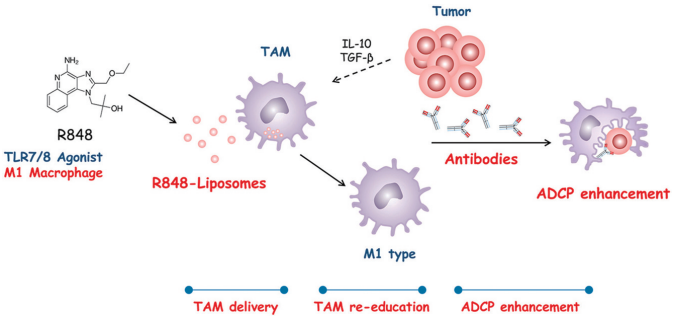
Macrophages are important therapeutic targets in cancer because the tumor-associated macrophages (TAMs) assist the tumor cells for their growth, evasion from immunity, and metastasis. The phenotype of TAMs is classified into two types: tumor-suppressive M1 type and tumor-supportive M2 type. In many cancers, M2-TAMs are the major fraction of TAMs and these TAMs may support the progression of the tumor. Therefore, the conversion of M2-TAMs into M1 type would build the anti-tumor microenvironment and improve the anti-cancer therapeutics, especially the antibody therapeutics via the antibody-dependent cellular phagocytosis (ADCP). Resiquimod (R848), an antagonist for TLR7/8, is known to induce the M1 phenotype in macrophages. We tried to deliver the R848 into TAMs in vivo and evaluated whether the treatment with R848-encapsulating liposomes can improve the therapeutic effect of antibodies in the mice xenograft model. We demonstrated that R848-liposomes can induce the M1 phenotype in the mouse-derived macrophages and enhance the ADCP against multiple cancer cell lines. After the intravenous injection, the R848-liposomes could accumulate in the transplanted tumors in the mice. The combination of R848-liposomes and antibody therapeutics (anti-EGFR antibody, clone 528) significantly suppressed the tumor growth in the tumor-bearing mice.

Significance of the research and Future perspective

We demonstrated the TAM-targeting delivery of R848 using liposomes could convert the TAMs from M2 to M1 phenotype and improve the therapeutic effect of antibody therapeutics via the ADCP.







Patent
Treatise Li, H; Somiya, M; Kuroda, S. Enhancing Antibody-dependent Cellular Phagocytosis by Re-education of Tumor-associated Macrophages with Resiquimod-encapsulated Liposomes. Biomaterials. 2021 Jan; 268:120601. doi: 10.1016/j.biomaterials.2020.120601.
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