Peptide ligand mediated drug delivery to TAMs

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ABSTRACT SUMMARY

The microenvironment of solid tumors is characterized by a reactive stroma with an abundance of inflammatory mediators and leukocytes. Tumor associated macrophages (TAMs) were found to play critical roles during the growth and metastasis of malignant tumors. We report in this paper an attempt to deliver drugs into TAMs using a peptide ligand conjugated liposome formulation. It can be used to modulate the TAM phenotype for therapeutic benefits.

INTRODUCTION

Myeloid-derived suppressor cells (MDSCs) belong to myeloid lineage and represent a group of relatively immature cells at different stages of differentiation, which were consisted of tumor-associated macrophages (TAMs), tie-2 expressing monocytes (TEMs), tumor associated neutrophils, etc. During the development of tumor, these cells were recruited to the tumor microenvironment and promoted tumor growth by stimulating tumor angiogenesis, suppressing tumor immunity, and promoting metastasis1.

Macrophages constitute an extremely heterogeneous population. They originate from blood monocytes, which differentiate into distinct macrophage types, schematically identified as M1 (or classically activated) and M2 (or alternatively activated)2. It is now generally accepted that TAM have an M2 phenotype and have functions such as promoting tumor cell survival, proliferation, and metastasis3.

Recent studies have shown that all-trans retinoic acid (ATRA) had a potent activity in eliminating MDSCs in cancer patients and in tumor-bearing mice4. ATRA may interact with these cells to induce differentiation into mature myeloid cells. In this study we propose to design an ATRA containing liposome and target its delivery towards TAMs and examine the therapeutic effects in cancer.

EXPERIMENTAL METHODS

DSPE-PEG2000-Maleimide PH1 and PH2 peptide (control peptide) were synthetized as previous describe5.

Peptide liposomes were prepared using a film dispersion method followed by membrane extrusion as our previous report5.

RESULTS AND DISCUSSION

Single cell suspension of tumor was analyzed by FACS. TAMs were CD11b+Gr1lowF4/80+ (Figure 1). The fluorescence liposome bindings with TAMs were also analyzed using FACS in vitro. The results suggested that the binding capacity of PH1 liposomes with TAMs was stronger than that of PH2 liposome (Figure 2).

Figure 1. The characterization of tumor associated macrophages in 4T1 mice.

Figure 2. The binding of PH1 liposome and PH2 liposome with TAMs in vitro.
PH1 liposome was intravenous injected to tumor-bearing mice at the dose of 250μl, 5mg/ml. Tumor TAMs were isolated and analyzed by FACS after six hours. It shows that most cells which have been bound to PH1 liposomes in vivo were TAMs (Figure 3).

CONCLUSION
TAMs with expression of CD11b^Gr1_lows^F4/80^ were isolated from the mice tumor and characterized. PH1 liposome has been prepared which may target to TAMs effectively. It may be used to deliver ATRA to TAMs and modulate the TAM phenotype for therapeutic benefits.

REFERENCES

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