Targeting intracellular drugs to macrophages using esterase-sensitive motif (ESM) technology; application to anti-cancer agents

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Abstract

Tumor-associated macrophages (TAMs) are now thought to have the potential to facilitate, rather than restrict, the development of human cancer. The availability of agents that reliably alter the function of TAMs would be of considerable therapeutic benefit. We present a novel esterase-sensitive motif (ESM) technology that allows targeted delivery of chemotherapeutic agents to monocytes/macrophages.

Introduction

Many chemotherapeutic agents, such as HDAC inhibitors, are cell-selective in vitro and in vivo. However, the pharmacokinetics of these drugs typically result in extensive leakage to non-target tissues, with consequent toxicity. A novel approach is required to overcome this problem. Our work indicates that the esterase technology can be used to deliver drugs specifically to monocytes/macrophages.

ESM technology

• ESM technology offers broad specificity - it is active in most human tissue.

Using ESM technology to target monocytes and macrophages

• ESM technology is based on amino acid ester hydrolysis by HCEs.

ESM technology: macrophage-targeting

• ESM technology is used in a variety of ways to target macrophages.

Compound 1: an HDAC inhibitor enter

• Compound 1 is a chemical log HLogP 0.3.

Macrophage-selective HDAC inhibitors: hydrolysis is necessary for cellular potency

• Hydrolysis of Compound 1 is necessary for cellular potency.

Summary and Conclusions

• ESM technology allows the precision delivery of macrophage-targeted agents, from diverse chemical classes.

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• Select agents can be potent inhibitors in whole blood and human whole blood cell populations.