Autocatalytic Drug Delivery Vehicles based on Targeting Extracellular DNA

Niren Murthy
Georgia Institute of Technology. Department of Biomedical Engineering, Atlanta Georgia 30332-0535

Statement of Purpose:

Cancer is one of the leading causes of death in the world and new strategies for treating it are greatly needed. Chemotherapy has tremendous potential for improving the treatment of cancer but has had limited clinical success because of its high toxicity. Targeting chemotherapy to tumors has the potential to improve its efficacy; however this has been challenging because tumor receptors are generally expressed at concentrations too low for cell killing by chemotherapy. There is therefore great interest in developing new strategies for targeting therapeutics to tumors.

In this report we present a new drug targeting system, termed H-gemcitabine, which can upregulate the tumor receptor it targets and has autocatalytic drug targeting properties. H-gemcitabine (**1**) is composed of the DNA binding agent Hoechst conjugated to gemcitabine (see Figure 1). The autocatalytic drug targeting mechanism of H-gemcitabine is shown in Figure 1b. H-gemcitabine initially targets tumors by binding extracellular DNA (E-DNA) via its Hoechst moiety, which is overproduced in tumors due to their necrotic core. After localizing in tumors H-gemcitabine releases free gemcitabine, which diffuses into neighboring tumor cells and kills them, which triggers the release of more E-DNA. Therefore on subsequent rounds of therapy increased levels of H-gemcitabine are targeted to the tumor, due to the cell killing from the previous rounds of H-gemcitabine therapy. We show here that H-gemcitabine has autocatalytic drug targeting properties in tumor spheroids, and is significantly more effective than free gemcitabine at treating xenografted tumors in nude mice. We anticipate numerous applications of H-gemcitabine, given its unique autocatalytic drug targeting ability.

Results and Discussion

In this presentation we will present the results of our in vivo investigations with H-gemcitabine. These results are summarized below. HT29 tumor cells were implanted subcutaneously into nude mice and they were treated with one, two, three, or four consecutive doses of either H-gemcitabine or free gemcitabine (10 mg/kg gemcitabine equivalents), and the tumor size and E-DNA level in the tumors were measured. Our data demonstrates that H-gemcitabine is significantly more effective than free gemcitabine at treating colon tumors. For example, during the 15 day treatment time course, H-gemcitabine was approximately 10 times more effective at suppressing tumor growth than free gemcitabine. In particular, H-gemcitabine treated tumors grew by 45% versus a 434% increase in tumor size for gemcitabine treated mice. H-gemcitabine's ability to kill tumor cells also resulted in an increase in tumor E-DNA. For example, tumors treated with one dose of H-gemcitabine show only a 20% increase in E-DNA, whereas those treated with four doses show a 210% increase.

In summary, we demonstrate that H-gemcitabine is an autocatalytic drug delivery vehicle. H-gemcitabine targets E-DNA in tumors and also upregulates E-DNA by killing tumor cells. We anticipate numerous applications of H-gemcitabine given the widespread presence of E-DNA in tumors and the great need for effective tumor drug targeting strategies.

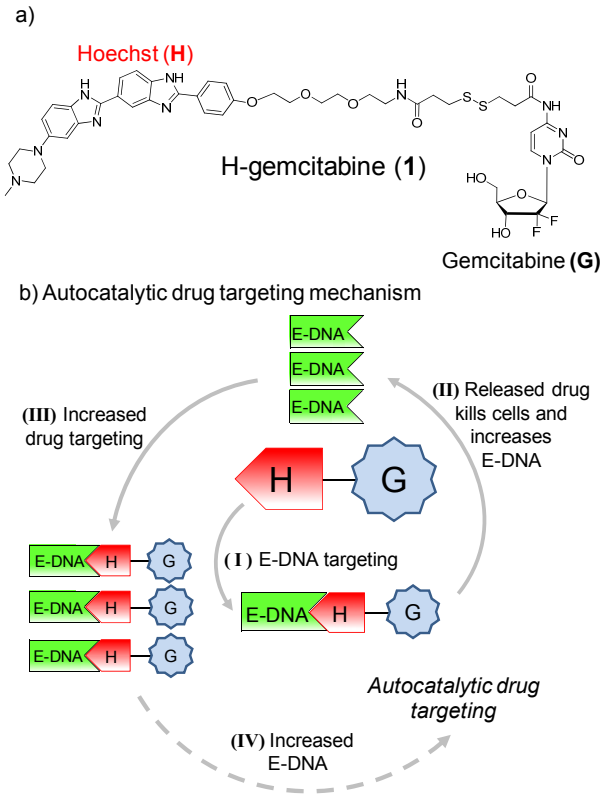

Figure 1. H-gemcitabine is an autocatalytic drug delivery vehicle. a) Chemical structure of H-gemcitabine. b) H-gemcitabine's autocatalytic drug targeting cycle. (I) H-gemcitabine initially targets tumors by binding E-DNA. (II) Gemcitabine is released from H-gemcitabine and kills tumor cells, causing the release of more E-DNA. (III) and (IV) A higher level of H-gemcitabine is targeted to the tumor on subsequent rounds of chemotherapy because of the increased E-DNA from earlier rounds of H-gemcitabine cell killing.

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