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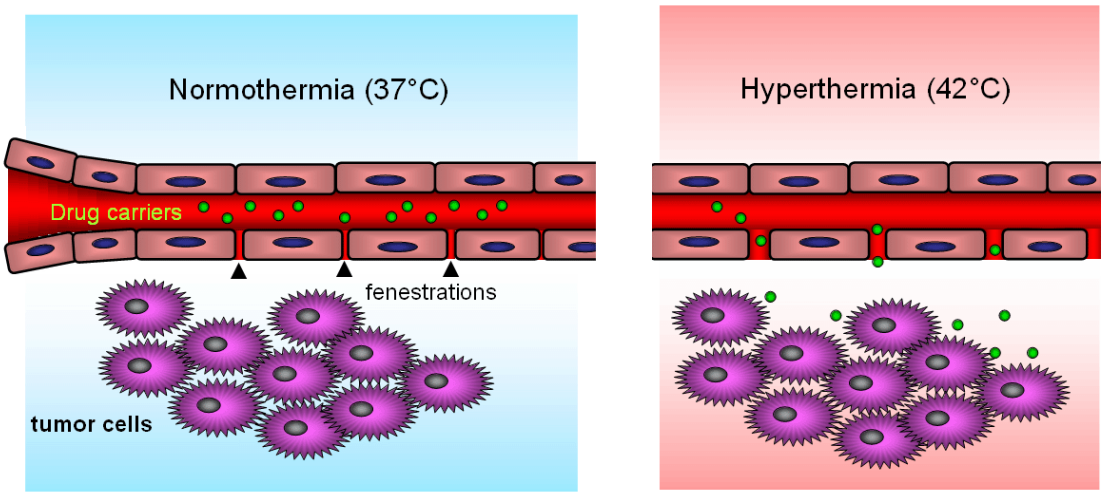
Tumor targeting with hyperthermia inducible gene carriers

Introduction

Targeting of macromolecular drug or gene carriers to tumors can be achieved by several strategies. Drug formulations exceeding a certain molecular weight and circulating in the blood stream after systemic injection will passively accumulated due to incomplete vascular lining of tumor blood vessels and incomplete lymphatic drainage. This so called 'enhanced permeability and retention' effect (EPR-effect) allows for example the accumulation of anticancer drug loaded circulating liposomes. Attaching cell binding ligands to such carriers enables specific internalization by target cells (active targeting).

Besides the well known concepts of passive and active targeting an external physical stimulus, like magnetic force, ultrasound or heat can further enhance tumor deposition when using suitable carrier system, which can respond to such stimuli.

Locoregional hyperthermia is an established treatment regime for solid tumors which, besides other effects, can enhance drug deposition within a locally heated tumor due to increased local blood flow and increased pore sizes of blood vessels. Additionally, thermosensitive drug or gene carriers can be applied which are activated locally in the tumor at elevated temperatures.



Thermosensitive gene carrier systems

We have recently developed a polymeric gene delivery system based on polyethylenimine which forms soluble polyplexes at 37°C, whereas after heating to 42°C particles irreversibly aggregate. The aggregation effect led to elevated transgene expression levels on cultured tumor cells ex vivo.

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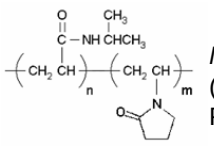
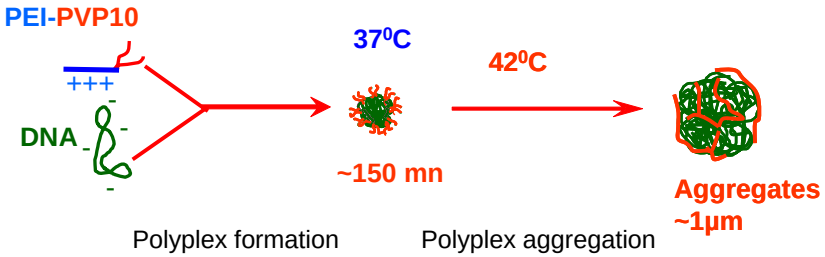
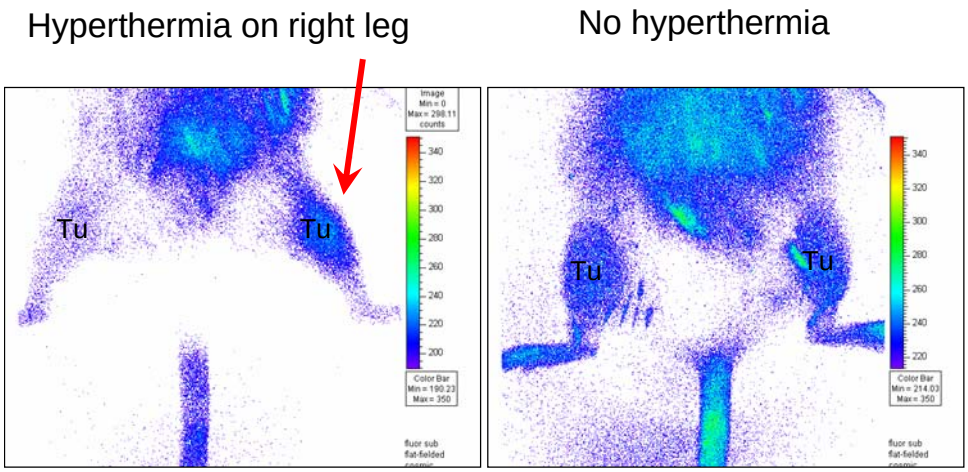


N,*N*-isopropylacrylamide / 1-vinyl-2- Pyrrolidinone co-polymer (**PVP-10**):
Phase transition temperature >40° C: hydrophilic ➔ hydrophobic



A. Zintchenko et al, *Bioconjugate Chemistry,* 2006

We have applied the concept of locoregional mild hyperthermia to enhance accumulation of such thermosensitive gene carriers in subcutaneous tumors (Schwerdt et al, Human Gene Therapy, 2008). Mice bearing two subcutaneous tumors were anaesthetized and one tumor selectively heated to 42°C. After systemic injection of thermosensitive polyplexes selective accumulation of polyplexes and transgene expression occurred only in the hyperthermia treated tumor. Non-thermosensitive polyplexes were not influenced by hyperthermia at all.



Conclusions

Locoregional hyperthermia can selectively direct thermosensitive gene carriers to malignant tissue opening the possibility for site directed tumor treatment.

References:

Temperature dependent gene expression induced by PNIPAM-based copolymers: potential of hyperthermia in gene transfer. Zintchenko A, Ogris M, Wagner E. Bioconjug Chem. 2006; 17: 766-72.

Hyperthermia induced targeting of thermosensitive gene carriers to tumors. Schwerdt A, Zintchenko A, Concia M, Roesen N, Fisher KD, Lindner LH, Issels RD, Wagner E, Ogris M. Hum Gene Ther. 2008; 19: 1283-1292.

MR characterization of mild hyperthermia-induced gadodiamide release from thermosensitive liposomes in solid tumors. Peller M, Schwerdt A, Hossann M, Reinl HM, Wang T, Sourbron S, Ogris M, Lindner LH. Invest Radiol. 2008; 43: 877-92.