The Reptation Mechanism in Tumor Imaging

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Introduction
An extended worm-chain polymer undergoes reptation in self-diffusion. Reptation is movement along a tube that follows the contour path of the polymer (2,3). Likewise, in a small force field, a reptating polymer will move around obstacles and through a fibrous matrix. This is the principle by which DNA is separated according to length in gel electrophoresis (4). Such a mechanism may be operative in the uptake of reptating polymers by tumors through the action of convection and the porous nature of the tumor endothelium and the adjacent extracellular matrix (5).

The optimum exploitation of this mechanism may allow significantly higher enhancement of tumors than has been seen with small molecular weight contrast agents or with globular protein contrast agents.

Theoretical
From fundamental principles, De Gennes (2) derived the form of the friction coefficient for reptation to be $f = N^2$, where $N$ is the number of monomers in the polymer chain. If such a polymer has an exponentially decaying blood circulation with a lifetime of $\tau$, then it follows directly that the uptake into the tumor will be proportional to

$$C_{\text{tumor}}(T) = \frac{\tau}{N^2},$$

where $C_{\text{tumor}}(T)$ is the concentration of the polymer in the tumor at a time $T > \tau$. The longer the polymer circulates in the blood the more opportunity it has to enter the tumor. However, if the polymer is made longer and longer, the increasing friction coefficient retards its movement into the tumor by the factor $N^2$. Since the circulation time of polymer agents such as Gd-DTPA-polylsine is as short as 15 minutes for $N=60$ and increases to 14 hours for $N=830$, we expect there to be a maximum in the uptake of agent into tumors as a function of $N$ in accordance with eqn. 1. If such a maximum occurs, then the process of reptation will be shown to be important in the uptake of polymer agents into tumors.

Methods

Contrast Agents. Various polylsine chains (Sigma Aldrich) were substituted with DTPA at very high levels through a modified mixed anhydride method. The highly substituted polymers contained from 5% to 10% free lysines by the TNBS assay. The high DTPA substitution causes the polymer to assume an extended worm-chain configuration as previously observed (5).

Animal model. Female Fisher 144 rats (average 160 grams) were implanted with rat mammary adenocarcinoma cells (ATTC 13762) by subcutaneous injection. The tumors grew to 33 cm size in 11 days, at which points the experiments commenced. All procedures followed an approved animal use protocol (Albany Medical College Institutional Animal Care and Use Committee).

Imaging. A GE CSI scanner was used for imaging at 2T with a 32 cm bore. A birdcage quadrature coil was used for transmission and receiving. T1 weighted images were obtained (TR 250ms, TE 18 ms, NEX 16). Rats were imaged prior to injection of contrast agent. Injection was through the tail vain at 0.025 mmole Gd/kg, or 4 pmole Gd for 160 gram rats. The rats were then imaged immediately after injection, and then at 24 hrs.

Results
The observed tumor enhancements as a function of chain length are shown in Fig. 1. There is a maximum in tumor enhancement at $N \approx 450$. The solid line is the theoretical prediction with use of a free parameter — the enhancement value at a particular chain length as a scaling reference. In the curve shown, the reference value used was that for $N = 613$, the best determined value (n=9, 90%+/- 20%). The blood circulation decay rates where determined from measurements of blood levels at various times after injection, (time constant of 15 minutes for the short chain and 14 hours for the longer chains). Finally, a correction for biphasic behavior of blood circulation for the longer chains was incorporated in the full treatment, of which eqn. 1 is a simplified version.

![Figure 1. Tumor enhancement as a function of chain length](image_url)

References