Tumor endothelial leakiness: endothelial pore size distribution determined by permeability measurements with contrast agents of differing hydrodynamic radius.

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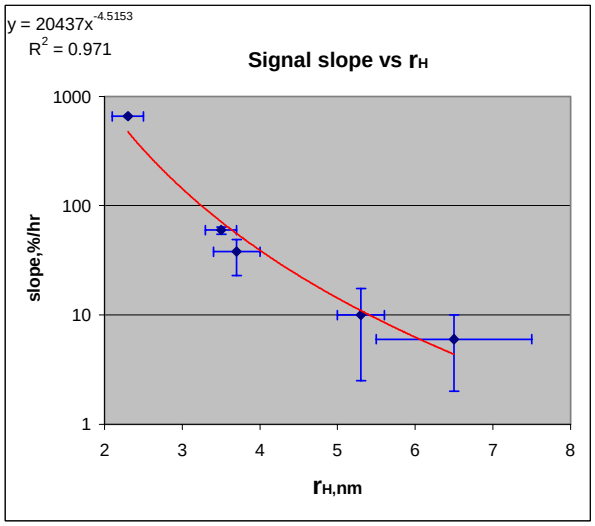
Introduction: Endothelial leakiness is one of principle parameters describing effects of angiogenesis in growing tumors. The use of labeled molecules and fluorescence is one way to approach characterizing this leakiness. But it has long been recognized that dynamic measurements of contrast agent uptake by MRI yields information on tumor permeability and has been used to stage disease. The MR methods generally do not reveal much uptake as the agent size gets large (they are directed, rather, at endothelial targets[1])—this, in apparent disagreement with the fluorescence observations, which report that extravasation occurs for objects as large as 200nm to 1 μm in subcutaneous tumors[2]. Clearly a quantitative understanding of endothelial pore size distribution would resolve this disagreement and may also lead to more intuition on differences between tumor types or between benign and malignant lesions.

Materials and Methods: We use globular and coiled agents of various hydrodynamic sizes as probes of permeability in a rat mammary tumor model (Mat B III). For a given agent, the permeability, or the rate constant k_1 for transfer from blood to tumor, depends on two key factors:

$$k_1 \propto \frac{N_p}{f} \text{ , where } \qquad N_p = \int_{\infty}^{R_H} \eta_p(r)dr$$

N_p is the pore density allowing passage of the test agent, and f is the friction coefficient of the agent in molecular transport processes such as diffusion. N_p is the integral of the pore distribution from very large values to the hydrodynamic size of the test agent. We determined the signal uptake slopes for agents of hydrodynamic sizes (by dynamic light scattering) from 3.5 (albumin) to 7nm (IgG) in radius (1.5T GE Scanner, T_1 weighted spin echo, (9/250). We further extrapolate from our albumin data to those reported in the literature for albumin and Gadomer 17 for a similar rat mammary tumor model to check for behavior to yet smaller sizes (down to ~ 2nm radius) and to check for consistency[2].

Results and Discussion: As can be seen from Figure 1, the slope uptake as a function of r_H is very steep and follows a power law of $r^{-\beta}$, where the exponent β is 4.5. The slope power law gives directly the pore distribution power law as a result of integration and then the division by f which scales as r_H. This distribution is valid down to ~ 2nm radius size and is expected to continue to hold for globular agents larger than 7nm radius. This latter assumption is based on the well-behaved power law dependence over the tested range. Yet, on the small size end of the pore distribution, some limiting maximum number of pores will certainly apply and we do not expect to connect to very small agents such as Gd-DTPA (0.35nm radius)—the projected slopes are beyond the reported observations for such agents. Large objects such as liposomes of >100nm range will not extravasate under the simple pore transport mechanism considered here. In such cases, alternative routes of transport such as endocytosis must be invoked.



References:

1) Anderson SA et al., MRM 2000; 44:433-439.
2) Hobbs SK et al., PNAS 1998; 95:4607-4612.
3) Demsar F et al., Electro Magnetobiology 1998 ; 17:283-297.