Reviewer's report

Title: Interstitial fluid pressure, vascularity and metastasis in ectopic, orthotopic and spontaneous tumours.

Version: 2 Date: 2 July 2007

Reviewer: Kristian Pietras

Reviewer's report:

General

Lunt et al. present a series of experiments investigating the impact of various physiological and phenotypical parameters on tumor interstitial fluid pressure (IFP) for a range of different experimental cancers, including syngeneic, xenografted and spontaneous tumors. While site of implantation/appearance and tumor size were the main determinants of IFP, few other correlations could be made with regard to prediction of IFP based on tumor hypoxia, proliferation, vessel density or overall perfusion. Moreover, tumor IFP was not found to be a useful marker in general for metastatic spread or for post-transplantation values of IFP. The studies are in general well-performed, albeit mainly correlative in nature.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The most interesting sets of experiments presented are the attempts to correlate tumor IFP with growth and phenotypic characteristics, such as proliferation, hypoxia and vascular density (Fig. 5). However, the authors have chosen to compare the various characteristics in tumors grown at different sites, intramuscularly (high IFP) or orthotopically (low IFP). As the authors point out in the discussion (p16-17), the large difference in absolute values of tumor IFP between the different sites is most likely due to the mechanical properties of the implantation site. Thus, a more relevant comparison would be to correlate the phenotypic characteristics with the IFP of tumors from the same implantation site.

2. The finding that donor IFP did not predict for IFP after transplantation of tumors into a recipient mouse is interesting and reflects an apparent and significant degree of stochastic determination of the tumor IFP. However, the interpretation of the data presented in Fig. 2c is confounded by the inclusion of transplantations of donor tumors grown intramuscularly to an orthotopic site in the recipient mouse. Since the authors already demonstrated that tumors at these sites display disparate IFP values, the comparison is flawed. Instead, the data from orthotopic-to-orthotopic site transplantations should be extended to allow stand-alone conclusions.

3. In the attempt to correlate tumor IFP with metastatic incidence, the authors
compare groups of tumors with high IFP (above median) or low IFP (below median) (Fig. 4a-e), but find no correlations. It may be that the division of groups based on above or below median tumor IFP is too coarse. The authors should present a similar analysis based on more divergent groups, e.g. lower vs upper quartile.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. On p18, the authors have stated that “…heterogeneity in tumour IFP values is probably largely attributable to differences in vascular resistance and permeability…”. While differences in vascular resistance and permeability are possible, and maybe even likely, explanations for heterogenous tumor IFP values, the authors do not address this possibility experimentally, and thus the statement is pure speculation. The authors should substantiate the statement with experimental data, or rephrase.

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Discretionary Revisions (which the author can choose to ignore)

1. The authors discuss “angiogenic and vascular normalisation properties” (p18) as a possible cause for the observed variability in tumor IFP. In line with this, and with the studies on vascular density and perfusion, the authors should present correlations between pericyte coverage (i.e. degree of vascular “normality”) and tumor IFP.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.