Aggressive Metabolic Phenotype in Breast Cancer Investigated by 7T Phosphorus Spectroscopy In Vivo

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Introduction

Preclinical data suggests that there is a metabolic phenotype corresponding to basal-type tumours—the typically more aggressive type of breast cancer [1]. However, the metabolic phenotype associated with basal/aggressive tumours is as of yet unvalidated in vivo, and there is no consensus as to whether the phenotype observed in NMR experiments is due to the preclinical models exhibiting the phenotype are not representative of the tumour micro-environment in humans, specifically high acidity causing the phosphoethanolamine (PE) to dominate as compared to phosphocholine (PC) [2]. Here we investigate whether the metabolic phenotype we have occasionally observed in vivo (PE>PC) in breast cancer tumours correlates with tumour aggressiveness as predicted by preclinical literature.

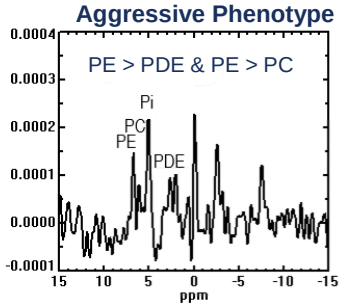
Methods

We created new metabolic phenotype groups to account for the PE>PC phenotype and prevent miss categorization: 1) Phosphoethanolamine (PE) > Phosphomonoesters (PME), 2) PE = PDE, 3) PE>PDE & PE ≤1.1*PC, and 4) corresponding to the aggressive phenotype in preclinical data (PE>PDE and PE≥1.1*PC peak). We conducted a blind ranking of the first 15 patient from the Patient Risk Based on Functional MRI (PROFILE) breast cancer study (see [3] for details). Mitotic count (number of cells dividing per sq mm in histology) was used to inform tumour aggressiveness. Assuming an exponential growth model for tumours, the natural log of the mitotic count for each tumour was plotted versus the non-invasive 31P ordinal groups, The r value metric was evaluated for correlation strength (weak correlation r < 0.3; correlation 0.3 < r < 0.7; strong correlation r > 0.7), for the new groups and for groupings that do not differentiate between PE and PC.

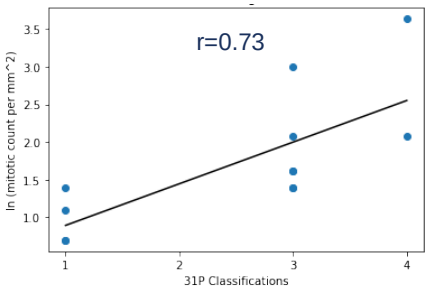
Results

The metabolic phenotype under investigation (group 4, example spectra below) has the highest mean mitotic count of all the groups. The mitotic count of each member of the group is higher than the mean for the previous group. Plotting the natural log of the mitotic count vs. the ordinal groupings of the 31P in vivo data yields an r value of 0.73 for this dataset.

Aggressive Phenotype



31P vs. Histology



Ordinal Group Statistics

Category	Mean mitotic count	n
1: PE < PDE	2.75	4
2: PE = PDE		0
3: PE > PDE, PE<1.1*PC	7.67	6
4: PE > PDE, PE>(1.09*PC)	23	2

Discussion & Conclusion

Metabolic phenotype is downstream of gene expression and influenced by the environment, making it an invaluable preclinical target for personalized medicine [4]. Here we were able to identify an aggressive tumor type known in preclinical data hitherto unidentified in vivo due to the enhanced spatio/temporal and spectral resolution at 7T allowing the PE and PC peaks to be resolved. The r-value for the same dataset grouped without differentiating between PC and PE gave an r = 0.3. However, it has been shown that the PC peak is not always visible in 7T data [5]. The exponential growth model does not apply to large tumors due to the restricted access to the microvasculature [6], and tumors exhibit a slow in growth rate as tumours exceed 1 cm in diameter [7]. In line with such a growth model, the tumour with the highest mitotic count in category 4 has a diameter less than 1 cm (0.9 cm) and the category 4 tumour with the lower mitotic count has a diameter of greater than 1 cm (1.7 cm).

The data provides evidence (based on r value) to support the hypotheses that the in vivo 31P spectroscopy dataset evaluated has a strong correlation with histological measures of tumour aggressiveness, and that the metabolic phenotype under investigation (category 4) relates to high mitotic counts.

Reference

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4. **Griffin, J.L. and J.P. Shockcor, *Metabolic profiles of cancer cells.* Nat Rev Cancer, 2004. 4(7): p. 551-61.**