Expression of anaesthetic and analgesic drug target genes in breast tumours is associated with disease metastasis, but not local recurrence.

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Why we did it?

- Breast cancer leading cause of cancer death in women, mainly due to metastasis.¹
- Anaesthetic & Analgesic technique at the time of surgery may influence the development of metastasis.^{2,3}
- Could this effect be modulated (in part) at the Anaesthetic/Analgesic drug-receptor level?

Aims of study

- Compile a list of the major receptor targets for common Anaesthetic and Analgesic drugs.
- Identify the specific proteins in each receptor that binds the Anaesthetic/Analgesic, then a list of the genes that encode for each protein.
- Use the BreastMark Database to screen our list of genes for outcomes (specifically metastasis) after breast cancer surgery.

Choosing the List of Gene targets

- Literature search to identify specific binding sites of common Anaesthetic & Analgesic drugs.
- 23 Gene Targets were chosen:

GABA_A Receptor Subunit:

- Alpha 1-3, Alpha 5
- Beta 1-3
- Gamma 1-3

Glycine Receptor Subunits:

- Alpha 1
- Beta

Transporters:

- NA channel transporter
- 5HT channel transporter

NMDA receptor Subunits:

- GRIN1
- GRIN2A-C
- GRIN3A
- GRINa

Opioid Receptors:

- Mu Opioid Receptor
- Delta Opioid Receptor
- Kappa Opioid Receptor

The BreastMark Database

- Validated, online database with gene expression data from multiple, previously published gene studies.
- Links the genetic expression of receptors in breast cancer tissue to clinical outcomes after breast cancer surgery.

Results

- 9 of the 23 targets genes were associated with metastasis ($p=0.049$).
- After Benjamini & Hochberg method to correct for multiple testing, 5 of the 23 targets were associated with metastasis ($p=0.075$).

Table 1: The 5 statistically significant target genes.

Receptor Groups	Receptor	Hazard Ratio	P-Value
NMDA Receptors	Grin3a	0.586 (0.435-0.789)	0.0004
	Grina	1.353 (1.118-1.638)	0.0018
NA Channel Transporter	SLC6A2	1.254 (1.067-1.473)	0.006
Glycine Receptor	GLRB	0.6916 (0.5875-0.814)	$8.389e^{-06}$
GABA _A Receptor Subunits	GABA _A Gamma1	0.641 (0.457-0.9005)	0.009709

Graphs 1 & 2: The Kaplan-Meier Curves of Glycine Beta Subunit & NMDA GRINa Subunit; 2 of the statistically significant target genes.

Conclusion

- There is an association between the genetic expression of certain Anaesthetic & Analgesic target receptors in breast cancer tissue and altered rate of metastasis after breast cancer surgery.
- As a group, Anaesthetic & Analgesic drug receptor targets may be enriched with prognostic markers.
- Important areas for future research have been identified.

References

1. Lu J, Steeg PS, Price JE, et al. Cancer Res. 2009 69: 4951-4953. 2. Snyder GL, Greenberg S. Br J Anaesth 2010;105:106-15. 3. Heaney A, Buggy DJ. Br J Anaesth 2012; 109(Suppl. 1):i17-28.