Identification of genetic signatures in bone metastasis of breast and prostate cancer

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Introduction

Bone metastases (BM) cause high mortality and are present in 70-90% of advanced breast and prostate cancer patients. Cancer is a complex genetic disease where no single gene has been shown to be solely responsible for the initiation, growth or progression. Therefore, more complete understanding of the multiple genes responsible for disease progression, and more specifically, for the development of BM is needed to support development of novel therapies and diagnostic tools for BM. The aim of this study was to identify genetic signatures specific for BM in solid tumors, more specifically in breast cancer (BC) and prostate cancer (PC).

Materials and Methods

Genetic data was obtained from cBioPortal (Cerami et al., 2012 and Gao et al., 2013). A dataset of 500 metastatic solid tumors 'MET500 cohort' was used based on availability of metastasis-specific biopsy data (Robinson et al., 2017). The biopsies were analyzed by whole-exome and -transcriptome sequencing.

Biopsies from BM were obtained from 44 patients (8%), of which 27 (61.4%) with PC and 8 (18.2%) with BC, and biopsies from other than BM (no-BM) from 456 patients (92%), of which 64 (14%) with PC and 83 (18.2%) from BC (Table 1). The 'BM' and 'no-BM' biopsy groups were compared separately for BC and PC. To confirm cancer type specificity of the findings, the BC and PC BM biopsy data were compared. Only significant findings ($p<0.05$) are reported.

Finally, the impact of identified altered genes on clinical outcome (survival) was analyzed more broadly in BC (13 studies, over 7 000 samples) and PC (19 studies, over 6 000 samples) specific datasets regardless of metastasis status.

Table 1*:* Summary of 'MET500 cohort' containing metastatic biopsy specimens from 500 patients with solid cancers. 91 patients had metastatic breast and 91 metastatic prostate cancer. Totally 44 BM biopsy samples were obtained from the skeleton (including biopsy sites of bone, pelvis, pleura and vertebra) of which 61.4% and 18.2% were in prostate and breast cancer, respectively.

Table 1.	Number of patients	Bone metastasis (BM) biopsy	Other than BM (no-BM) biopsy
Total	500	44 (8%)	456 (92%)
Breast cancer	91 (18.2%)	8 (18.2%)	83 (18.2%)
Prostate cancer	91 (18.2%)	27 (61.4%)	64 (14.0%)

Results

Table 2*:* Altogether 48 genetic alterations including mutations and gene-fusions were identified in the BM biopsy group. From the 48 genes, 8 and 3 corresponded to genetic alterations observed in BC and PC, respectively, when comparing the BM and no-BM biopsy groups. None of these genes overlapped in BC and PC BM biopsy samples. In BC, the identified 8 genes were GPR139, RASIP1, DTHD1, GGT7, LONP2, ATG4B, PI15 and MKRN3. In PC, the 3 genes were RNF139, KRTAP4-7 and ZNF516. Of these, 4 and 1 genes were associated with clinical outcome in BC (Figure 1) and PC (Figure 2). The rest of the alterations had no significant correlation on survival.

Table 2.	Genetic alterations in BM vs no-BM biopsies (all cancers)			Prostate cancer (n, %)		Breast cancer (n, %)	
Gene name	**Cytoband**	**BM (n, %)**	**no-BM (n, %)**	**BM**	**no-BM**	**BM**	**no-BM**
GPR139	16p12.3	3 (7.5%)	1 (0.2%)			3 (37.5%)	0 (0%)
RASIP1	19q13.33	3 (7.5%)	2 (0.4%)			2 (25%)	1 (1.2%)
DTHD1	4p14	4 (10%)	6 (1.3%)			2 (25%)	0 (0%)
GGT7	20q11.22	2 (5%)	1 (0.2%)			2 (25%)	0 (0%)
LONP2	16q12.1	2 (5%)	1 (0.2%)			2 (25%)	0 (0%)
ATG4B	2q37.3	2 (5%)	2 (0.4%)			2 (25%)	0 (0%)
PI15	8q21.13	2 (5%)	2 (0.4%)			2 (25%)	0 (0%)
MKRN3	15q11.2	3 (7.5%)	8 (1.7%)			2 (25%)	1 (1.2%)
RNF139	8q24.13	3 (7.5%)	1 (0.2%)	3 (11.1%)	0 (0%)		
KRTAP4-7	17q21.2	6 (15%)	16 (3.5%)	5 (18.5%)	2 (3.1%)		
ZNF516	18q23	3 (7.5%)	8 (1.7%)	3 (11.1%)	0 (0%)		

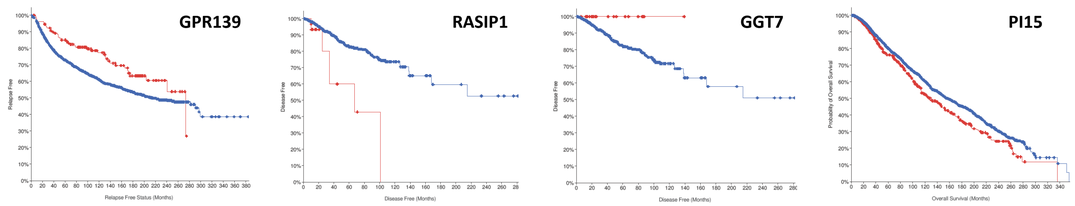

Figure 1*:* In BC patient cohorts, GPR139 was associated with improved relapse-free survival, RASIP1 with decreased disease-free survival, GGT7 with increased disease-free survival, and PI15 with lower overall survival when comparing patients with altered (red line) or unaltered (blue line) genes (13 studies, over 7 000 samples from cBioPortal).

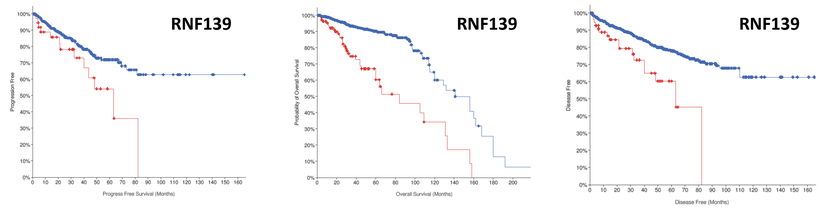

Figure 2*:* In PC patient cohorts, RNF139 was associated with decreased progression free survival, overall survival and disease-free survival when comparing patients with altered (red line) or unaltered (blue line) genes (19 studies, over 6 000 samples from cBioPortal).

In summary, the study identified 4 novel genetic alterations in bone metastasis of breast cancer and 1 novel genetic alteration in bone metastasis of prostate cancer that are associated with clinical outcome. None of these genetic alterations have been linked to bone metastasis earlier.

Conclusions

The study identified novel genetic alterations in BC and PC BM. Based on published studies, none of these genetic alterations have been previously linked to BM even though there are studies indicating that they have a role in cancer.

In general, there is a limited number of BM specific biopsy samples or data associated with them available. This is also the limitation of the cohort used in the study, and the use of larger number of samples is needed to verify the findings.

Future directions include studying the roles of these genetic alterations in metastatic progression and in BM microenvironment by comparing to paired primary tumor or other metastatic location, as well as studying possible influence of preceding treatments.

Some of the identified genetic alterations could potentially be used as diagnostic tools or targeted to provide treatments specifically for patients with currently incurable BM.

References

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Abbreviations:

BM = bone metastasis, GPR139 = G Protein-Coupled Receptor 139, RASIP1 = Ras Interacting Protein 1, DTHD1 = Death Domain Containing 1, GGT7 = Gamma-glutamyltransferase 7, LONP2 = Lon Peptidase 2, Peroxisomal, ATG4B = Autophagy Related 4B Cysteine Peptidase, PI15 = Peptidase Inhibitor 15, MKRN3 = Makorin Ring Finger Protein 3, RNF139 = Ring Finger Protein 139, KRTAP4-7 = Keratin Associated Protein 4-7, ZNF516 = Zinc Finger Protein 516.