Molecular Characterization of the Ras-MAPK pathway in Metastatic Breast Cancer

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Background

- Ras-MAPK pathway is a known driver of tumorigenesis and therapeutic target in a variety of cancers
- However, molecular alterations in the Ras-MAPK are rare in breast cancer (BC) and their clinical implications remain unclear
- As mutational status does not accurately correlate with transcriptional activity, a MAPK pathway activity score (MPAS) based on aggregate gene expression of 10 transcriptional targets, is indicative of MAPK pathway activation. In vitro, MPAS predicts sensitivity to MEK and BRAF inhibition.
- Our goal was to characterize the molecular landscape and clinicopathologic characteristics of breast cancers with Ras-MAPK pathway aberrations.

Methods

- A total of 6,464 BC samples underwent comprehensive molecular profiling at Caris Life Sciences.
- Analyses included next generation sequencing of DNA (592 Gene Panel, NextSeq, and whole exome sequencing, NovaSEQ), RNA (NovaSeq, whole transcriptome sequencing, WTS) and IHC.
- MPAS and immune cell fraction (ICF, Quantiseq) were assessed by mRNA analysis.
- The aberrations with highest MPAS scores were defined as Genomic MAPK Activated Tumors (GMAT) and clinicopathologic findings were compared to wild type (WT).

Results

- The predominant alteration of RAS genes was mutation followed by amplification and no fusions were detected (Table 1).
- The highest MPAS scores were found in KRAS mutants (mut), HRAS mut (Q61, G1213), BRAF V600 (class 1) mut and NRAS Q61 mut (Figure 1) and therefore used to define Genomic MAPK Activated Tumors (GMAT).
- GMAT compared to wild type (WT) had significantly higher PD-L1 expression, TMB and MSI/dMMR. GMAT had less B cells (3.4% vs 4.4%), more M1 Macrophages (4.4% vs 3.4%) and neutrophils (5.5% vs 2.7%) regardless of HR status but less NK cells (2.3% vs 3.0%), MSDCs (0.9% vs 3.0%) only in HR- tumors with respect to WT (Figure 2A and 2B).

Conclusions

RAS, BRAF and MEK1 mutations in BC are associated with high MAPK pathway activation and may benefit from MEKi or BRAFi.

GMAT showed higher immune markers than WT and may warrant further investigation for **combinations targeting the RAS-MAPK pathway and immune checkpoint inhibitors.**

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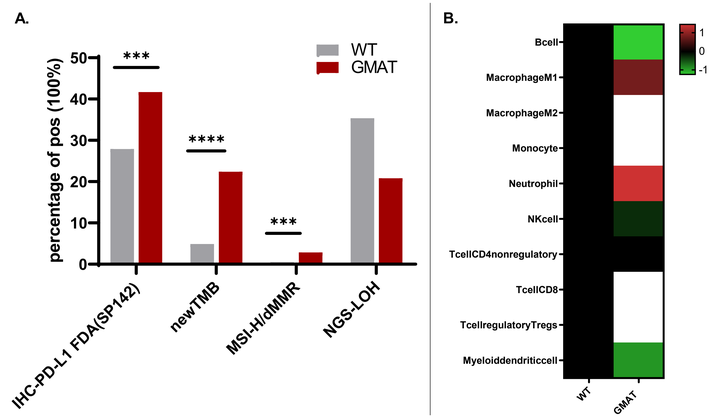

Figure 2A. Immune markers and TMB in GMAT vs WT
Figure 2B. Immune cell profiling in GMAT vs WT

	KRAS				NRAS				MEK1		HRAS				BRAF					WT
	Q61	G1213	other	CNV	Q61	G1213	other	CNV	Mut	CNV	Q61	G1213	other	CNV	class1	class2	class3	Other	CNV	
N (%)	6 (0.10)	71 (1.15)	16 (0.26)	47 (0.78)	3 (0.05)	5 (0.08)	8 (0.13)	–	3 (0.05)	8 (0.13)	10 (0.16)	18 (0.29)	25 (0.40)	–	13 (0.21)	6 (0.10)	9 (0.15)	4 (0.06)	4 (0.06)	4173
MPAS	2.16	1.31	0.99	0.52	3.56	0.65	-0.65		1.21	0.52	3.52	1.55	-0.18		2.49	-0.66	0.04	-0.44	-0.44	-0.1
p	<0.0001			0.39	0.1				0.74		<0.0001				<0.0001					

Table 1. Identifying alterations in Ras-MAPK genes

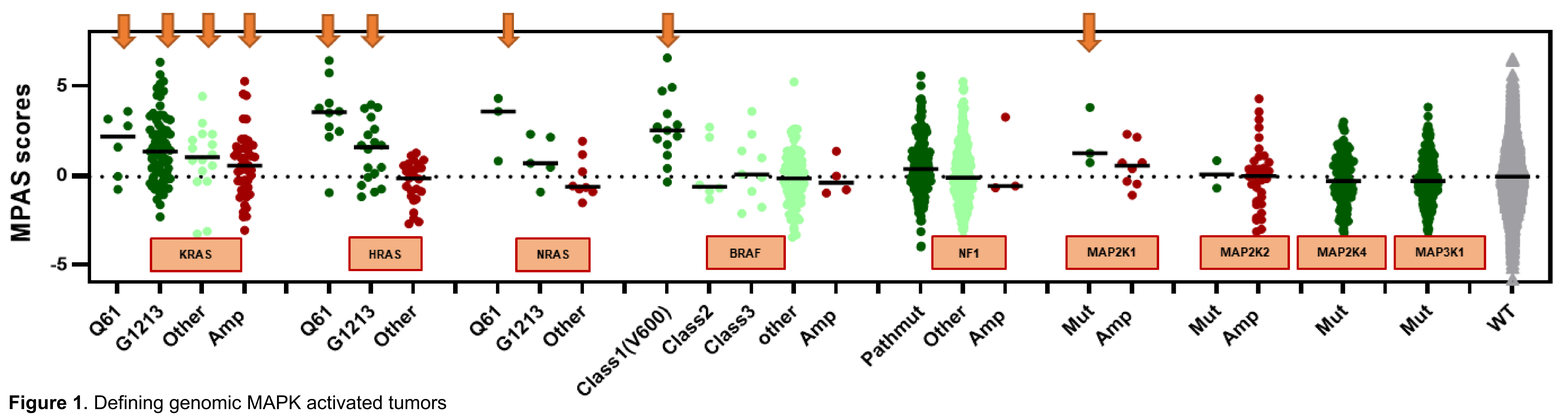

Figure 1. Defining genomic MAPK activated tumors