Quantitative cell signalling activity profiling of solid tumors to support personalized treatment in the FINPROVE basket trial; presentation of skin tumor data

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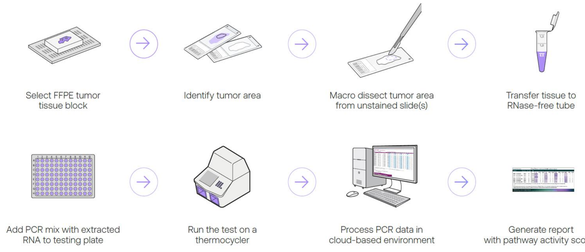
Background:

Genomic profiling is commonly used to characterize tumors, but clinical treatment successes are limited: For many tumors no druggable targets are found and not all genetic variations have clear biological and clinical implications. A new way of looking for druggable targets is to measure the activity of Signal Transduction Pathways (STP). These STP are a series of molecular events that transmit signals from the exterior of a cell to its interior and play an important role in tumor progression.

By measuring STP activities, the tumor driving pathway can be quantified, resulting in unique tumor profiling (using healthy tissue as reference) and, in an individual patient, give guidance for personalized treatment. Recently, we have demonstrated this for breast and ovarian tumors, leading to clear actionable results. Here the results of STP profiling of skin tumors are presented.

This approach of STP profiling will be used in the FINPROVE study (NCT05159245) to determine potential additional druggable targets and can be compared to genomic profiling in several solid tumor types.

Methods:



Using the mRNA-based OncoSIGNal pathway activity profiling PCR test (InnoSIGN), STP activities of 7 pathways (Hh, MAPK, PI3K, TGFβ, Notch, AR and ER) were quantified and expressed on a scale from 0-100 for 25 tissue samples from healthy skin (HS), 35 primary melanoma (PM), 39 metastatic melanoma (MM) and 18 basal cell carcinoma (BCC) Only samples with ≥ 50% epithelial cell content were included. High pathway activity in a tumor sample was concluded when its score was higher than the 95th percentile of reference skin STP activity. p-values are measured using the Wilcoxon test.

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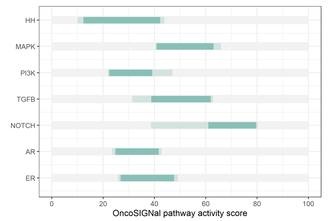
Results:

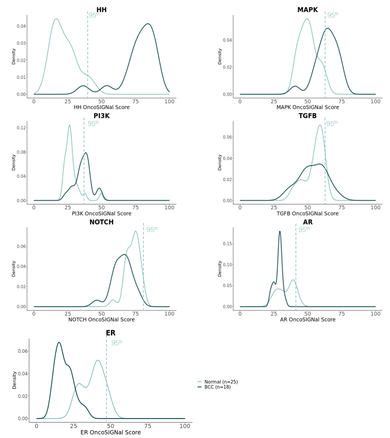
Reference range for normal pathway activity based on healthy skin



	Hh	MAPK	PI3K	TGFβ	Notch	AR	ER
95th	39.3	61.6	36.9	62.0	79.7	41.8	47.8
99th	43.0	63.1	46.7	62.9	80.3	42.8	49.2

Normal skin pathway activity ranges depicted in the green highlighted area (solid green 95th percentile, light green 99th percentile).

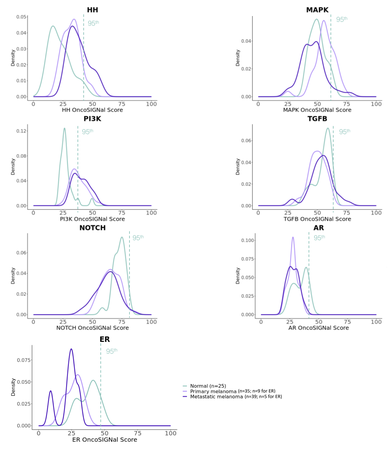
BCC has different pathway profile compared to healthy skin



STP	Median STP activity HS n=25	BCC n=18	p-value
Hh	20.4	81.3	2.3 E-11
MAPK	49.1	64.7	1.3 E-06
PI3K	26.6	36.8	1.6 E-05
TGFβ	57.5	53.6	0.71
Notch	74.2	65.9	0.0004
AR	37.3	29.2	0.0024
ER	39.7	16.6	8.9 E-10

Hh, MAPK and PI3K activity are all significantly increased in BCC, with most profound difference in Hh activity

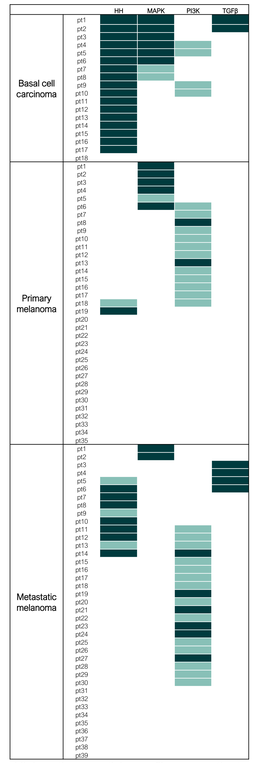
Primary and metastatic melanoma have different pathway profiles compared to healthy skin



STP	Median STP activity HS n=25	PM n=35	p-value	Median STP activity MM n=39	p-value
Hh	20.4	33.2	6.0 E-05	36.7	8.6 E-09
MAPK	49.1	56.2	0.0009	45.9	0.048
PI3K	26.6	36.8	1.4 E-07	40.4	4.3E-11
TGFβ	57.5	50.8	0.0085	54.3	0.34
Notch	74.2	65.9	2.6 E-05	63.8	3.8 E-06
AR	37.3	27.7	0.0005	27.5	0.0002
ER	39.7	27.3	0.001	24.7	0.0006

Hh and PI3K activity are both significantly increased in primary and metastatic melanoma.
MAPK activity is only increased in primary melanoma as compared to healthy skin tissue

High STP profiling of BCC, primary and metastatic melanoma, each showing different actionable targets



High pathway activity profiles per patient: light green > 95th percentile, dark green > 99th percentile of normal range of skin tissue

High MAPK, Hh, TGFβ and PI3K pathway activity per patient is shown for: BCC (top panel), primary melanoma (middle panel) and metastatic (bottom panel) melanoma.

Between three tumor groups, different pathway activity profiles.

	Hh	MAPK	PI3K	TGFβ
BCC (n=18)	94%	44%	22%	11%
Primary melanoma (n=35)	6%	17%	37%	0%
Metastatic melanoma (n=39)	26%	5%	51%	10%

Also within groups, there are differences in profiling per patient.

Actionable STP determined in:

94% of BCC patients; mostly Hh and MAPK

54% of primary melanoma patients; mostly MAPK and PI3K

77% of metastatic melanoma patients; mostly Hh, TGFβ and PI3K

Note: Notch, AR and ER are not shown since these pathways hardly show high activity compared to activity in healthy skin.

Conclusions:

1. BCC, primary and metastatic melanoma have different pathway activity profiles as compared to healthy skin tissue
2. Different actionable high STP activity can be determined in BCC, metastatic and primary melanoma
3. Pathway activity profiling may enhance personalized therapy

The OncoSIGNal test will be employed in the FINPROVE trial to identify patient specific actionable targets in several tumor types using tissue specific normal range references.