

ABCA3 functions in multi-drug resistance in human cancer during metastasis to the lungs.

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We describe here a function for the ATP-binding cassette gene *ABCA3* in multi-drug resistance in human cancer (1-3), supported by evidence by demonstrating its transcriptional up-regulation with significance at the transcriptome level in metastasis to distant organ sites in human breast cancer (4, 5), and by separate evidence demonstrating that ATP-binding cassette genes function in multi-drug resistance: in resistance to a platinum agent, in resistance to doxorubicin, and in resistance to paclitaxel (2).

1 **Results**

2 **Figure 1:** ABCA3 is differentially expressed in the lung metastases of humans with breast cancer.

3 I. Metastasis to the lung in humans with breast cancer.

4 *n*=6 primary tumor of the breast (human)

5 *n*=2 metastasis to the lung (human)

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GeneID	p-value	lfcSE	stat	log2FC	baseMean	Gene	Rank	%DE
21	2.58E-01	0.691	-1.130612	-0.7808975	2217.54	ABCA3	9074/22997	60.5

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8 Through quantitative comparison of total transcription in the primary tumors in humans with breast
9 cancer and metastasis to the lung, we discovered differential expression of ATP binding cassette
10 subfamily A member 3, encoded by *ABCA3* in metastasis to the lung in breast cancer (**Chart 1**). The
11 expression of *ABCA3* changed more than 60% of the human breast cancer transcriptome when
12 considering all transcripts whose expression was measured - in this case, 22,997 transcripts ("Rank").
Note the negative fold-change indicating increased quantity of *ABCA3* messenger RNA in breast cancer
lung metastasis, demonstrating up-regulation of *ABCA3* during disease progression and metastasis.

13 **Discussion**

14 We described here transcriptional induction of a gene with functions in multi-drug resistance, in
15 lung metastasis in human breast cancer. Novel approaches to challenging metastasis and resistance will
16 utilize chemotherapy in conjunction with i) kinase and phosphatase inhibitors targeted to tissue and tumor
17 type whose functions overlap with that of growth factor and growth factor receptor inhibitors, ii) inhibitors of
18 the ATP-binding cassette family (multi-drug resistance pumps), and iii) CDK4/6 inhibitors, which function
19 as senescence-inducing agents.

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Methods

We measured total transcription in primary tumors and metastasis to distant organ sites including the bones, the brain, the liver and the lungs using microarray and RNA-sequencing datasets (GSEXXXXX and GSEXXXXX) and R-based computational software for exact quantitative determination of multi-drug resistant pump transcriptional induction at the transcriptome level.