

Therapeutic targeting in lung cancer for the treatment of lymph node metastasis: CENPM.

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The high rate of brain metastasis in patients with non-small cell and small cell lung cancer demands discovery of novel therapeutic targets to treat lymph node metastasis which serves as an intermediate to the CNS (central nervous system) (1-5). We recently utilized whole transcriptome technologies to define the full complement of differentially expressed kinases and phosphatases in HER2+ breast cancer: in the primary tumor, and in metastasis to the CNS (6-8). Here we utilize whole transcriptome technologies (9, 10) to measure total transcription in the lymph node metastases of humans with small cell and non-small cell lung cancer. We describe here a therapeutic target that is up-regulated and differentially expressed in lymph node metastasis in humans with small cell and non-small cell lung cancer, CENPM, as a candidate therapeutic target for the medical management of lymph node metastasis in human lung cancer.

We utilize genomic and transcriptomic technologies to study the genomic sequences (DNA), the transcriptome (RNA), and epigenetic modification (eg., CpG-DNA) of humans with cancer. This includes the primary tumor, the source of the transformation - like mutant variants of p53 - subtypes of the primary tumor, including luminal, basal and HER2+ forms in breast cancer, and adeno and squamous forms of NSCLC in lung cancer, "regional" metastasis to the lymph nodes, metastasis to distant sites, including the lungs, the liver and the brain, and the circulating tumor stem cell. Here we measure total transcription in metastasis to the lymph nodes to discover and describe a therapeutic target identified through rigorous study of the lymph node metastatic transcriptome in small cell and non-small cell lung cancer: a therapeutic target that is up-regulated and metastasis-specific, providing ideal therapeutic index to minimize toxicity and maximize efficacy: CENPM.

Results

Figure 1: CENPM is differentially expressed in lymph node metastasis in humans with lung cancer..

I. Lymph node metastases and primary tumors from humans with non-small cell lung cancer.

n=2 primary tumors from humans with non-small cell lung cancer

n=2 lymph node metastases (tumor) from humans with non-small cell lung cancer

GeneID	p-value	lfcSE	stat	log2FC	baseMean	Gene	Rank	%DE
79019	9.41E-02	0.897	-1.6743866	-1.5012792	205.43	CENPM	1889/20667	90.9

Through quantitative comparison of total transcription in the primary tumors of the lung and in lymph node metastases of humans with non-small cell lung cancer (5), we discovered differential expression of centromere protein M, encoded by *CENPM* in metastasis to the lymph nodes in humans with NSCLC (**Chart 1**). The expression of CENPM changed more than 90% of the human NSCLC lymph node metastatic transcriptome when considering all transcripts whose expression was measured - in this case, 20,667 transcripts ("Rank"). Note the negative fold-change indicating increased quantity of CENPM messenger RNA in NSCLC lymph node metastases, demonstrating up-regulation of CENPM during NSCLC disease progression.

II. Lymph node metastases and primary tumors from humans with small cell lung cancer.

n=2 primary tumors from humans with small cell lung cancer

n=4 lymph node metastases (tumor) from humans with small cell lung cancer

ID	p-value	t	B	logFC	Gene	Rank	%DE
A_24_P399888	5.57E-02	-2.22	-4.26788	-2.59767127	CENPM	6532/58341	88.8

Through measurement of total transcription in the lymph node metastases of humans with small cell lung cancer as compared to primary tumors of the lung, we validated differential expression of CENPM in SCLC lymph node metastasis in humans (**Chart 2**). The expression of CENPM here changed more than nearly 90% of the lymph node metastatic transcriptome when considering all transcripts whose expression was measured - in this case, 58,341 transcripts ("Rank"). Note the negative fold-change indicating increased quantity of CENPM messenger RNA in lymph node metastases, demonstrating up-regulation of CENPM during disease progression and metastasis in humans with lung cancer.

Thus, differential and increased expression of CENPM defines the lymph node metastatic transcriptome in human lung cancer.

Discussion

Adjunctive treatments in medical oncology limit the emergence of resistant tumor clones during treatment with a second agent (whether neoadjuvantive chemotherapy or a targeted therapy like trastuzumab). Inhibitors of CENPM, once evaluated for toxicity and safety, can immediately be tested for efficacy in patients with lymph node metastasis who have failed previous treatment, with the goal of identifying the most effective inhibitors of lymph node metastasis in humans with lung cancer. A multi-kinase approach delivered in conjunction with chemotherapies that target dNTP synthesis, replication of the daughter strand and activity at the spindle at anaphase, and target *CDKN* inactivation and ATP-binding cassette pump expression in resistant cases, is most likely to be most effective in limiting tumor clone resistance (11).

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Methods

We utilized GSE235634 for this tumor transcriptome study, measuring whole transcription in metastasis to the lymph nodes and in primary tumors from humans with lung cancer (along with GSE162102 for target validation) using RNA-sequencing and microarray data (published) and R-based computational methods.