The neurotrophic tyrosine kinase receptor NTRK2 is over-expressed in a hepatosplenic T-cell lymphoma cell line.

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Hepatosplenic T-cell lymphoma is a rare peripheral T-cell lymphoma with a median survival of less than one year (1). I used differential gene expression profiling to compare the transcriptomes of 63 hematopoietic cancer cell lines to gain insights into the major differences of the HSTCL transcriptome when compared to other malignancies of the blood. I found that the neurotrophic tyrosine kinase receptor type 2 (NTRK2) was significantly and specifically over-expressed in the HSTCL cell line DERL-2. Kinase inhibition has previously proved clinically efficacious in cancer (2,3,4) and unique expression of NTRK2 in HSTCL cells suggests that NTRK2 inhibition may be a viable therapeutic option in HSTCL.

Keywords: HSTCL, hepatosplenic T-cell lymphoma, DERL-2, NTRK2, neurotrophic tyrosine kinase receptor type 2, differential gene expression profiling

Introduction

Hepatosplenic T-cell lymphoma (HSTCL) is a rare peripheral T-cell lymphoma with a median survival of less than one year (1). Here, I performed a comparative gene expression analysis of 63 cancer cell lines of the blood to determine the key transcriptional differences of one of only two HSTCL cell lines, DERL-2 (5). Global gene expression profiling revealed that the neurotrophic tyrosine kinase receptor type 2, NTRK2, was one of the most differentially expressed genes when comparing the transcriptomes of this panel of hematopoietic cancer cell lines. HSTCL cancer cells expressed high levels of NTRK2 and unique expression of NTRK2 by DERL-2 suggests targeting of NTRK2 may be a therapeutic option in HSTCL.

Methods

Differential gene expression profiling to identify the top two hundred and fifty most differentially expressed transcripts in a given comparison was performed using GEO2R. Dataset GSE57083 from the Astra Zeneca cell line library was utilized. “Benjamini and Hochberg” p-value adjustment was used with “auto-detect” log transformation and NCBI generated category of platform annotation. The name of each cell line is included in Table 1. The statistical significance of the difference between mean RNA expression values of each group was calculated by Ordinary one-way ANOVA with Dunnett’s multiple comparisons test (PRISM 8.1.2).

Results

I compared the global gene expression profiles of 63 cell lines using transcriptome data from the Astra Zeneca cell line library to identify differentially expressed genes in hepatosplenic T-cell lymphoma using the DERL-2 cell line. Differential gene expression analysis identifies transcripts whose expression is most significantly different between a given set of comparisons. DERL-2 is one of only two HSTCL cell lines (5), so systems analysis of the DERL2 cell line is critical to understanding the fundamental biology of hepatosplenic T-cell lymphoma.

I found that the gene encoding the type 2 neurotrophic tyrosine kinase receptor, NTRK2, was among the most differentially expressed genes when comparing the transcriptomes of these 63 hematopoietic cancer cell lines (Table 1). The expression of NTRK2 was highest in HSTCL when compared to any other cancer type (Figure 1; $p < 0.0001$ for all comparisons), and DERL-2 expressed NTRK2 at higher levels than any other cancer cell line studied here (Figure 2).

Discussion

Hepatosplenic T-cell lymphoma is an aggressive and rare peripheral T-cell lymphoma with a median survival of less than one year. Development of more effective treatment protocols demands deeper understanding into the manner by which cancer cells sustain their survival. Transcriptional profiling by differential gene expression analysis can provide key insights to the most significant differences in the way a cancer expresses its genes, and importantly, in an unbiased fashion.

Comparative transcriptome analysis of a panel of 63 hematopoietic cancer cell lines revealed that the NTRK2 was one of the most differentially expressed genes among the global gene expression profiles of this panel of cancers. Critically, the HSTCL cell line DERL-2 expressed NTRK2 at higher levels than any other cancer cell line studied.

Kinase inhibition in cancer has previously proved efficacious (2,3,4). Entrectinib is an inhibitor of all TRK types, and has been tested for efficacy and safety in a variety of cancers in two phase I trials, ALKA-372-001 and STARTRK-1. Entrectinib has received approval for the treatment of TRK-fusion positive solid tumors in Japan (7) and on August 15, 2019, entrectinib received FDA approval for the treatment of ROS-positive non-small cell lung cancer and NTRK-driven solid tumors in the United States (8). The data here suggest that NTRK2 inhibition in HSTCL by entrectinib or other pharmacological methods may represent a potential viable option for therapeutic intervention in patients with HSTCL.

References

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Figure 1: NTRK2 is differentially expressed in the hepatosplenic T-cell lymphoma cell line DERL-2 and at higher levels than a panel of 62 hematopoietic cancer cell line.

The expression value of the NTRK2 message from 63 cancer cell lines is shown. The bar represents the mean RNA expression value. AML: $n=17$, CML: $n=4$, DLBCL: $n=15$, B-NHL: $n=5$, Burkitt's Lymphoma: $n=2$, TCL: $n=1$, B-CLL: $n=4$, Myeloma: $n=10$, HSTCL: $n=1$, Sezary Syndrome: $n=1$, B-ALL: $n=1$, ALL=2.

NTRK2

Figure 2: Expression of NTRK2 in 63 hematopoietic cell lines.

The expression value of the NTRK2 message in 63 cancer cell lines is shown.

Cancer Type	Sample	Title	Value	Cell Line Name
AML	GSM1374458	CTV-1 ghp221105	3.0464	CTV1
AML	GSM1374527	EA10068_111346	2.90087	HEL9217
AML	GSM1374536	HL 60 ghp221105	3.37097	HL-60
AML	GSM1374591	EA10068_111342	3.12439	KASUMI3
AML	GSM1374597	KG-1 ghp231105	3.28392	KG-1
AML	GSM1374598	KG-1a ghp231105	3.17806	KG-1a
AML	GSM1374683	ML-2 ghp231105	3.30363	ML-2
AML	GSM1374689	MOLM13	3.5335	MOLM13
AML	GSM1374694	MV-4-11 ghp231105	3.19819	MV411
AML	GSM1374782	OCI-AML5 ghp280606	3.13571	OCI-AML5
AML	GSM1374792	EA10068_111343	3.33657	OCIM2
AML	GSM1374868	EA10068_111345	3.1124	SET2
AML	GSM1374880	SKM-1 ghp231105	3.06392	SKM-1
AML	GSM1374961	TF-1 ghp231105	3.19882	TF-1
AML	GSM1374962	THP-1 ghp231105	3.30766	THP-1
AML	GSM1374976	EA10068_111344	3.1325	UKE1
AML	GSM1374979	EA10068_111341	2.9506	UT7
CML	GSM1374474	EA10068_111347	2.87609	EM2
CML	GSM1374583	K562 ghp231105	3.55309	K562
CML	GSM1374606	KU812 ghp231105	3.23596	KU812
CML	GSM1374669	EA10068_111348	2.90655	MEG01

Table 1: Identifying information for cell lines used in this study.

DLBCL	<u>GSM1374481</u>	EA10068_203557_HG- U133_PLUS_2_FARAGE	3.11429	FARAGE
DLBCL	<u>GSM1374489</u>	EA10068_203542_HG- U133_PLUS_2_HBL1	3.10561	HBL1
DLBCL	<u>GSM1374539</u>	EA10068_203543_HG- U133_PLUS_2_HLY-1	3.22759	HLY-1
DLBCL	<u>GSM1374775</u>	EA10068_203561_HG- U133_PLUS_2_NU-DHL-1	3.06887	NU-DHL-1
DLBCL	<u>GSM1374845</u>	EA10068_203554_HG- U133_PLUS_2_RC-K8	3.21515	RC-K8
DLBCL	<u>GSM1374849</u>	EA10068_203546_HG- U133_PLUS_2_RI-1	3.08234	RI-1
DLBCL	<u>GSM1374904</u>	EA10068_203559_HG- U133_PLUS_2_SUDHL10	2.94403	SUDHL10
DLBCL	<u>GSM1374905</u>	EA10068_203547_HG- U133_PLUS_2_SUDHL2	2.97478	SUDHL2
DLBCL	<u>GSM1374909</u>	EA10068_203555_HG- U133_PLUS_2_SUDHL8	3.34985	SUDHL8
DLBCL	<u>GSM1374963</u>	EA10068_203548_HG- U133_PLUS_2_TMD8	3.01681	TMD8
DLBCL	<u>GSM1374971</u>	EA10068_203549_HG- U133_PLUS_2_U2932	3.03093	U2932
DLBCL	<u>GSM1374972</u>	EA10068_203550_HG- U133_PLUS_2_U-2940	2.95636	U-2940
DLBCL	<u>GSM1374973</u>	EA10068_203562_HG- U133_PLUS_2_U-698-M	3.07306	U698M
DLBCL	<u>GSM1374989</u>	EA10068_203552_HG- U133_PLUS_2_WILL-1	2.99173	WILL-1
DLBCL	<u>GSM1374990</u>	EA10068_203553_HG- U133_PLUS_2_WILL-2	3.02423	WILL-2

B-NHL	<u>GSM1374467</u>	DOHH-2 ghp221105	3.29358	DOHH2
B-NHL	<u>GSM1374558</u>	HT ghp280606	3.60902	HT
B-NHL	<u>GSM1374577</u>	JEKO ghp280606	3.256	JEKO
B-NHL	<u>GSM1374585</u>	Karpas1106 ghp280606	4.52692	Karpas1106
B-NHL	<u>GSM1374861</u>	SC1 ghp280606	3.13603	SC1
Sezary Syndrome	<u>GSM1374569</u>	HUT78	3.70076	HUT78
Lymphoma (Burkitt's)	<u>GSM1374841</u>	Raji ghp231105	3.38518	Raji
Lymphoma (Burkitt's)	<u>GSM1374844</u>	Ramos ghp231105	3.71115	Ramos
TCL	<u>GSM1374580</u>	Jurkat ghp280606	3.70616	Jurkat
B-CLL	<u>GSM1374392</u>	AMO1 ghp280606	3.57681	AMO1
B-CLL	<u>GSM1374393</u>	ARH77 ghp280606	3.06466	ARH77
B-CLL	<u>GSM1374572</u>	IM9 ghp280606	3.62142	IM9
B-CLL	<u>GSM1374579</u>	JJN3 ghp280606	3.43826	JJN3
Myeloma	<u>GSM1374589</u>	Karpas620 ghp280606	3.15973	Karpas620
Myeloma	<u>GSM1374601</u>	KMS12BM ghp280606	3.54134	KMS12BM
Myeloma	<u>GSM1374615</u>	L363 ghp280606	6.51	L363
Myeloma	<u>GSM1374631</u>	LP1 ghp280606	3.27702	LP1
Myeloma	<u>GSM1374691</u>	MOLP8 ghp280606	3.61766	MOLP8
Myeloma	<u>GSM1374767</u>	NCLH929 ghp280606	3.6946	NCLH929
Myeloma	<u>GSM1374799</u>	OPM-2 ghp280606	3.70945	OPM-2
Myeloma	<u>GSM1374855</u>	RPMI8226 ghp280606	3.2933	RPMI8226
Myeloma	<u>GSM1374882</u>	SKMM2 ghp150606	3.1351	SKMM2
Myeloma	<u>GSM1374970</u>	U266B1 ghp150606	3.77695	U266B1
HSTCL	<u>GSM1374460</u>	Bx030_020 HG2	10.8256	DERL2
B-ALL	<u>GSM1374587</u>	KARPAS-231 ghp231105	3.29733	KARPAS231
ALL	<u>GSM1374445</u>	CCRFCEM	3.3986	CCRFCEM
ALL	<u>GSM1374856</u>	EA10068_111349	3.11377	RS411