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RESEARCH ARTICLE

Hypoxia inducible transcription factor (HIF-1) regulates CXCL13 expression: Clinical implications in pediatric non-Hodgkin's lymphoma

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Abstract

Background: Lymphomas are B and/or T cell clonal neoplasms in various states of differentiation, characteristically compromising lymph nodes. They are constituted by B and T lymphocytes that reach the node by chemokine-mediated recruitment including CXCL13. Hypoxia-inducible transcription factor (HIF-1α) plays a role in cellular adaptation to oxygen concentration changes. It also regulates expression of chemokines such as CXCL12, CCL20, and CCL5 as well as some of their receptors such as CCR7 and CXCR4.

Methods: We performed *in silico* analysis of the CXCL13 promoter, pharmacologic modulation of HIF-1α activity and, using reporter plasmids, site-directed mutation and DNA-protein interaction analysis we analyzed the relation between HIF-1α activity and CXCL13 expression. Moreover, we did tissue microarray and immunohistochemistry to see the expression of HIF-1α and CXCL13.

Results: This study detected three possible HIF-1α binding sites suggesting that this chemokine may be regulated by the CXCL13 transcription factor. We showed that CXCL13 expression is directly dependent, whereby an increase in HIF-1α activity increases CXCL13 expression and decreased HIF-1α activity in turn decreases CXCL13 expression. We proved that HIF-1α transcriptionally regulates the expression of CXCL13 in a direct manner. We established that HIF-1α and CXCL13 are greatly overexpressed in the most aggressive pediatric lymphomas.

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Conclusions: For the first time, this study showed that HIF-1α directly regulates transcriptional CXCL13 and that both proteins are overexpressed in the most aggressive forms of pediatric lymphoma. This suggests that they may play a significant role in the pathogenesis of pediatric non-Hodgkin's lymphoma.
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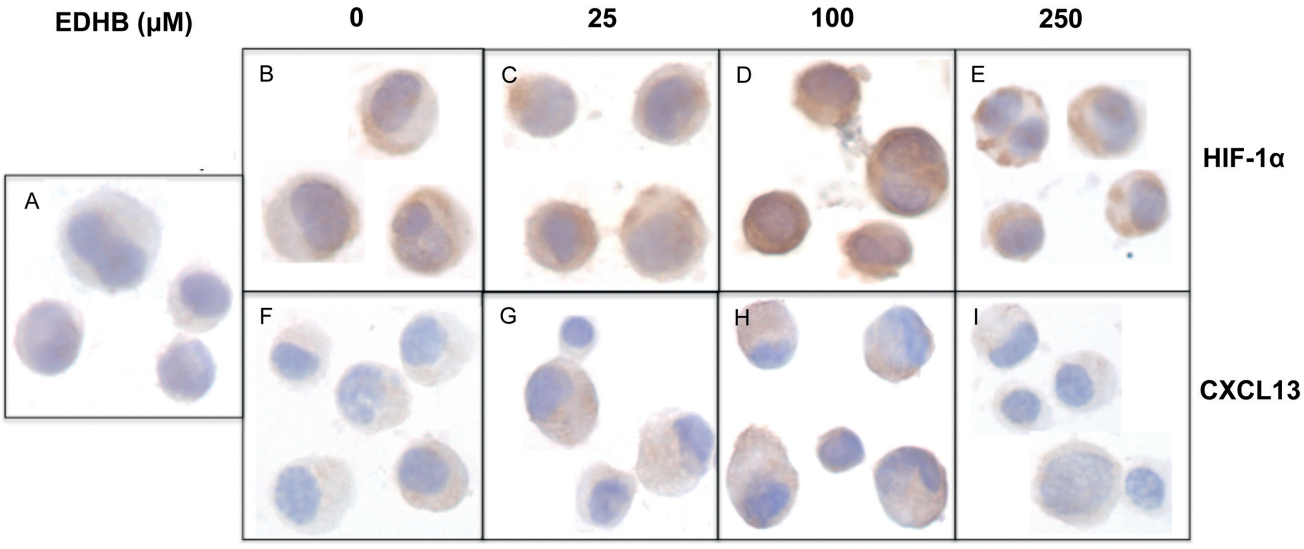
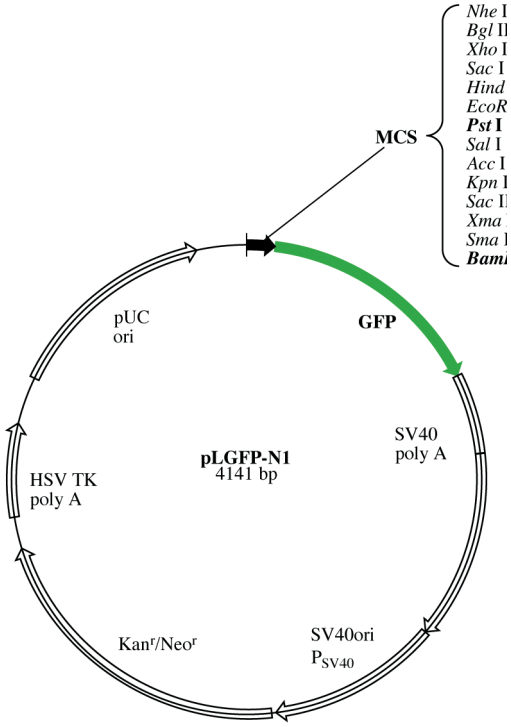
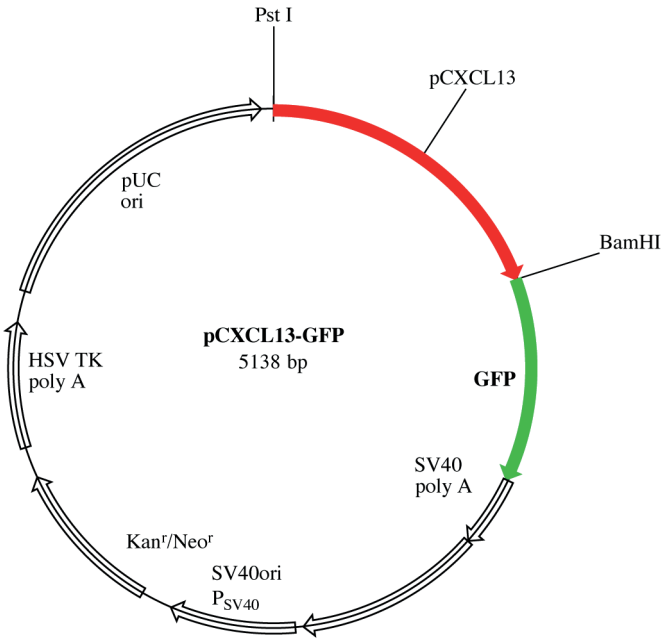
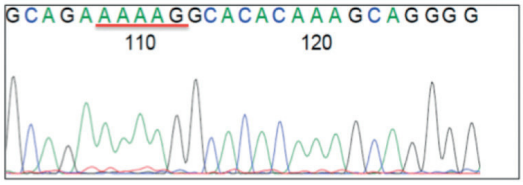
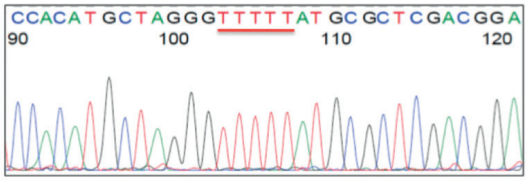
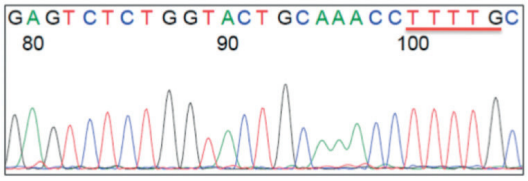
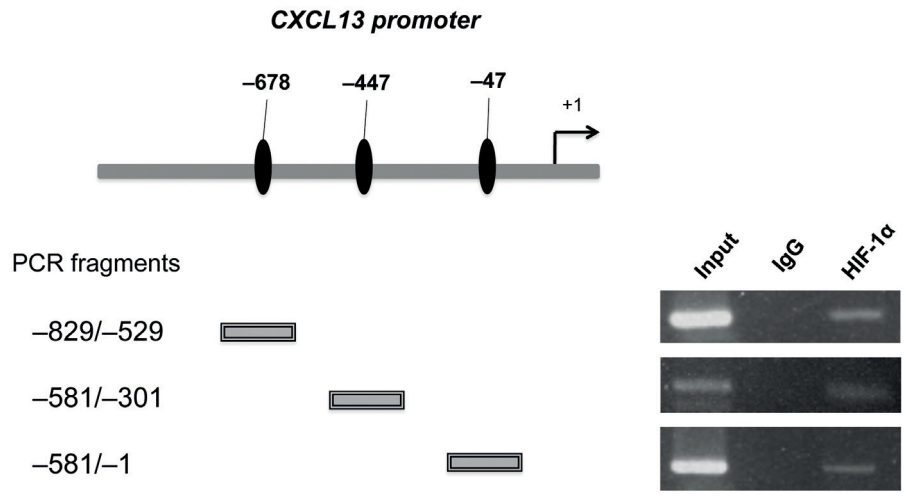
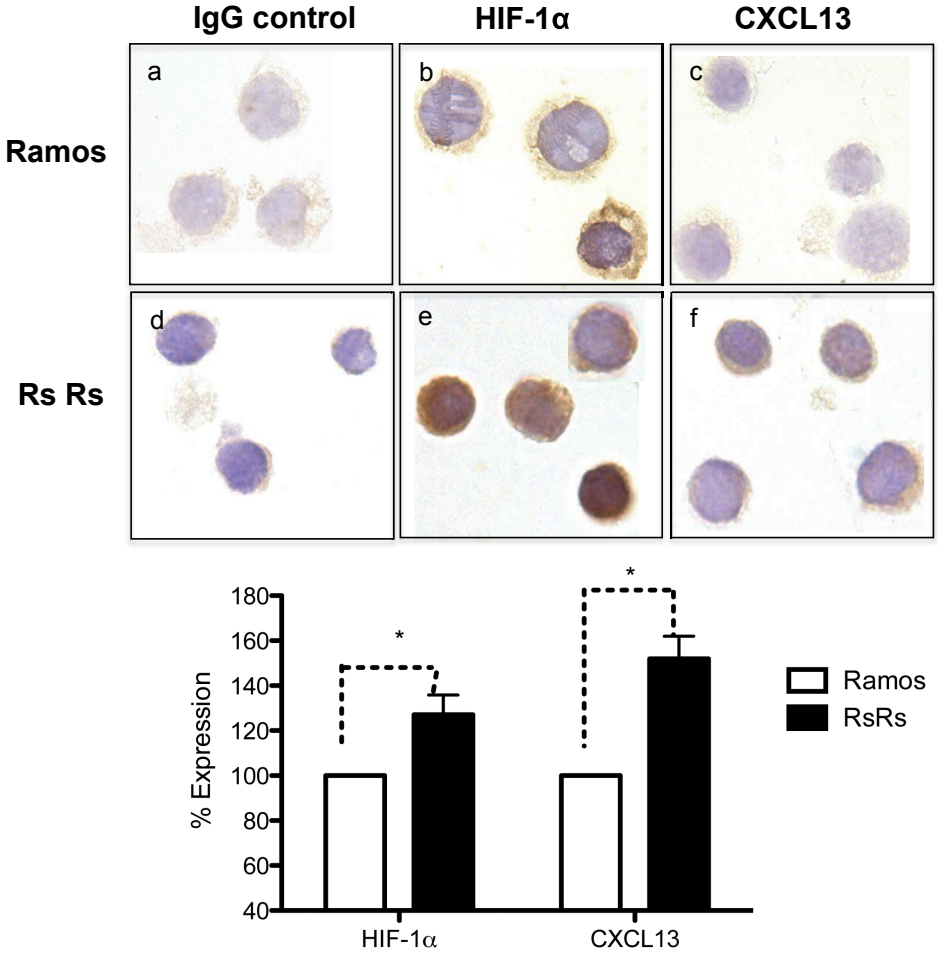

EDHB (μM)
0
25
100
250
A
B
C
D
E
F
G
H
I
HIF-1α
CXCL13

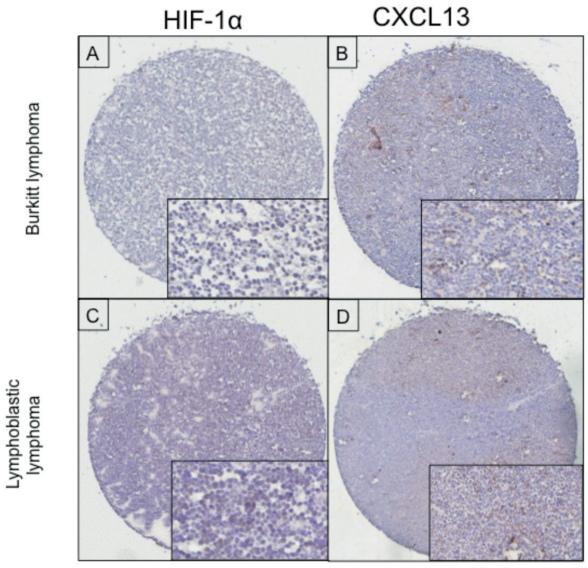

MCS
Nhe I
Bgl II
Xho I
Sac I
Hind
EcoR
Pst I
Sal I
Acc I
Kpn I
Sac II
Xma
Sma
Bam
pUC
ori
GFP
SV40
poly A
pLGFP-N1
4141 bp
HSV TK
poly A
Kanr/Neor
SV40ori
PSV40

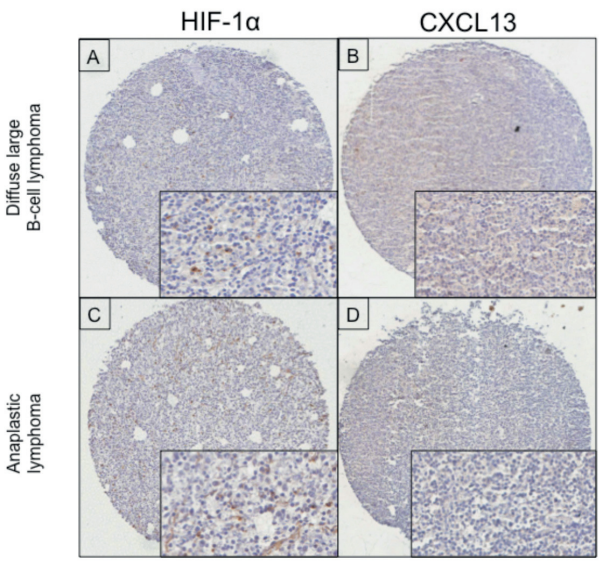

Pst I
pCXCL13
BamHI
pUC
ori
pCXCL13-GFP
5138 bp
HSV TK
poly A
GFP
SV40
poly A
Kanr/Neor
SV40ori
PSV40

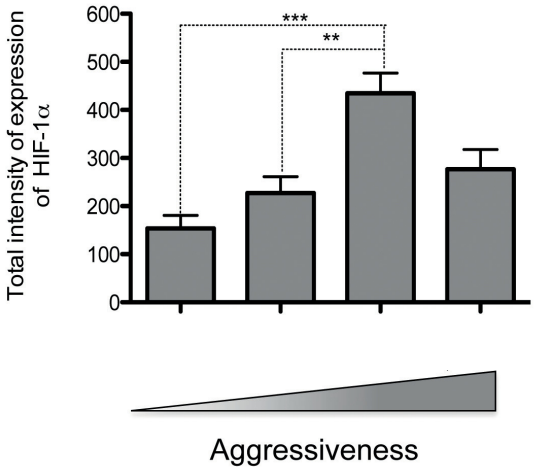
CAGA***CACAG*** GCAC	**AAAAG**	
AGGG***ACGTG*** ATGC	**TTTTT**	
GCAAACC ***CACAG*** *C*	**TTTTG**	

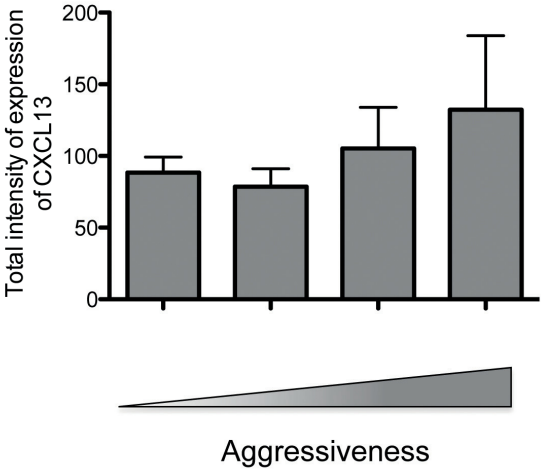

CXCL13 promoter
–678
–447
–47
+1
PCR fragments
–829/–529
–581/–301
–581/–1
Input
IgG
HIF-1α


IgG control
HIF-1α
CXCL13
Ramos
Rs Rs
a
b
c
d
e
f
% Expression
180
160
140
120
100
80
60
40
*
*
HIF-1α
CXCL13
Ramos
RsRs


HIF-1α
CXCL13
A
B
C
D
Burkitt lymphoma
Lymphoblastic lymphoma


HIF-1α
CXCL13
A
B
C
D
Diffuse large B-cell lymphoma
Anaplastic lymphoma


Total intensity of expression of HIF-1α
600
500
400
300
200
100
0
***
**
Aggressiveness


Total intensity of expression of CXCL13
200
150
100
50
0
Aggressiveness