The role of the Chemokine-like MARVEL trans membrane-type proteins

CMTM6-8 in survival of B cell precursor Acute Lymphoblastic Leukaemia

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Aims

1. To write a critical review of the current literature concerning the CMTM6-8 gene cluster and formulate a testable research hypothesis.
2. To analyse Single Nucleotide Polymorphism (SNP) data available at the leukemia research genotypic group (LRGC) for presence of focal deletions in CMTM6-8 and BLNK genes.
3. To analyse relevant gene expression data available from the internet database Gene Expression Omnibus (GEO).
4. To discuss whether the CMTM6-8 genes and associated downstream signalling pathways have potential as therapeutic targets in B cell precursor acute lymphoblastic leukaemia (B-ALL).

Hypothesis

• Loss of CMTM6 expression may provide a survival advantage for leukemic cells in patients or a hostile xenoterm environment.

Introduction

ALL is the most common cancer in children, accounting for around 25% of all childhood cancers in those less than 15 years of age. This type of cancer can be rapidly fatal; early diagnosis and treatment is therefore essential.

Although up to 90% of children with ALL can now be cured, a significant number of patients do not respond to treatment and ultimately relapse with poor prognosis. The loss of CMTM6-8 genes are generally uncloned and have intermediate prognosis.

Developing novel therapies as well as identifying genetic markers of relapse is essential for improving treatment outcome in B-ALL.

Expression Microarray Data:

Expression data from normal cells during B cell development showed that BLNK and CMTM8 have a regulated gene expression during their transition from common lymphoid progenitors to pre-B cell (GSM 299955).

Expression data available at the online microarray platform r2. One data set, published by Caroll et al. (2014) consisted of bone marrow samples obtained from 98 pre-B ALL patients; whereas another published by Murphy et al. (2016) contained 200 bone marrow samples from both T and B ALL patients.

Microarray expression data uploaded from published papers onto GEO were also investigated.

Discussion

Evidence from SNP data suggests that the CMTM6-8 focal deletion was not initially present but instead arose in one of the secondary xenografts. However, I am unable to unequivocally determine at what point the CMTM focal deletion occurred. Furthermore, I found that the immunogenetically normal patient has a very similar focal deletion of CMTM7 and -8 as well as a TEL-AML patient with a BLNK focal deletion.

Methylation and expression data in normal B cells suggests that BLNK and CMTM8-8 have important roles during B cell development. Data analysed from normal B cells and Carroll cohort suggest that CMTM7 and -8 have a role in normal B cell development.

The clinical relevance of chromosomal and genomic abnormalities in B cell ALL development was assessed in a human B cell precursor acute lymphoblastic leukaemia study.

Conclusions

• Loss of CMTM-6 expression may provide a survival advantage for leukemic cells in a hostile xenoterm environment.
• Low CMTM-8 expression may be possible markers of early relapse in certain subgroups of B-ALL patients, although multivariate analysis is required to prove this.
• Preliminary data shows potential for CMTM-6 and -8 to be used as novel therapeutic targets.

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References


