The Molecular Mechanisms of CD19-Negative Relapse in B-Cell Lymphoma after CAR T-Cell Immunotherapy

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To Cite This Article: Zhihong Wu, Weihong Chen. The Molecular Mechanisms of CD19-Negative Relapse in B-Cell Lymphoma after CAR T-Cell Immunotherapy. Am J Biomed Sci & Res. 2021 - 14(2). AJBSR.MS.ID.001965. DOI: 10.34297/AJBSR.2021.14.001965.

Received: September 06, 2021; Published: September 13, 2021

Abstract

The chimeric antigen receptor T cell (CAR T-cell) immunotherapy is the most antitumor ability in relapse/refractory (R/R) hematological malignancies but it still shows a high relapse rate. A few studies have been found that the molecular mechanisms of CD19-negative relapse after CAR T-cell therapy are the CD19 loss or down-regulation in lymphoma, including lineage switching, CD19 gene mutation, selective shearing, and subcloning of CD19-negative cell. The gene rearrangement, fusion genes and IL-6 may be to influence the therapeutic effect of CAR T-cell immunotherapy. The gene mutations of APX5, IKAROS, EBF1, GNA13, SOCS1, TNFALP3, XPO1, FLT3 etc. have been currently found after CAR T-cell therapy relapse. The review reports the molecular mechanisms of CD19-negative relapse in B-cell lymphoma after CAR T-cell immunotherapy.

Keywords: CD19-negative relapse, B-cell lymphoma, CAR T-cell immunotherapy, Molecular mechanisms

Introduction

CAR T-cell immunotherapy is a great advance in the treatment of hematologic malignancies. Some researches find that the complete remission rate about 70%-90% for relapsed/refractory B-cell acute lymphocytic leukemia [1]. However, a study has also found that rate of lymphoma is about 30-50% after CAR T-cell treatment. We have reported that there are two main causes for CD19-positive and CD19-negative relapse after CAR T-cell immunotherapy [2-4]. CD19-positive relapse is mainly due to low efficiency and persistence, senescence of CAR T-cell in vivo. And there are also some confounding factors such as: different co-stimulatory, the market methods, various categories and dosage of CAR T-cell, tumor heterogeneity and so on [2,3]. Moreover, the main mechanisms of CD19-negative relapse after CAR T-cell therapy may be the presence of the loss or down-regulation of CD19 expression, the effects of other molecular and still unclear genetic mutations, and the indirect effects of other cytokines.

Directly Related Molecular Mechanisms

The CD19 loss may be due to mutation of CD19 gene or selective shearing and subcloning of CD19-negative cells.

The lineage switch is the interconversion of the B-lymphocyte lineage with the myeloid cell lineage. In recurrent cases, deletion or down-regulation of PAX5, IKAROS and EBF1 was found [6,7]. PAX5, located on chromosome 9, is a member of the coding paired-frame (PAX) family of transcription factors. It encodes 50-kD B-cell specific activator protein (BSAP), which is expressed in pre-B and mature B cells [8]. IKAROS, located at chromosome 7, encodes product is a zinc finger structure-containing transcription factor that plays a critical regulatory role in early lymphocyte
αXPO1, located on chromosome 2, corresponds to a monitoring
innate and acquired immune responses, hormone regulation, and
involved in a variety of acute and chronic inflammatory responses,
suppressor of cytokine signaling (SOCS) protein family. SOCS1 is
to a monitoring region of CDS. It is an important member of the
maturation [14]. SOCS1, located on chromosome 17, corresponds
region of Exon1-4. It encodes the G
revealed mutations of GNA13, SOCS1, XPO1T and TNFALP3 in ctDNA.
monitoring results of circulating tumor DNA (ctDNA) in the patients
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Mutations in ctDNA
The patients of relapse lymphoma have been found some
mutated genes after CAR T-cell treatment. In one study, continuous
monitoring results of circulating tumor DNA (ctDNA) in the patients
revealed mutations of GNA13, SOCS1, XPO1T and TNFALP3 in ctDNA.
GNA13, located on chromosome 17, corresponds to a monitoring
region of Exon1-4. It encodes the Ga13 protein, which acts to regulate
cell morphology, contraction, migration and differentiation and
maturation [14]. SOCS1, located on chromosome 17, corresponds to
a monitoring region of CDS. It is an important member of the
suppressor of cytokine signaling (SOCS) protein family. SOCS1 is
involved in a variety of acute and chronic inflammatory responses,
innate and acquired immune responses, hormone regulation, and
the generation and development of many tumors in the body [15].
XPO1, located on chromosome 2, corresponds to a monitoring
region of Exon15-17 It is an important member of the importinβ
family of nuclear export protein receptors, mainly responsible for
the nuclear export of some tumor suppressor proteins and growth
regulator proteins [16]. TNFALP3 corresponds to a monitoring
region of CDS. There are few relevant studies about TNFALP3. The
mutations of GNA13, SOCS1, XPO1T and TNFALP3 in ctDNA would
exist associated with prognosis after CAR T-cell treatment [17].

Gene rearrangement and Fusion Genes
Rearrangement of 11q23 occurs to patients with MLL-r. The
most common of which is MLL-AF4. At present, fusion gene of
ZNF384 in 12q13, as well as internal repeat crosstalk of the FLT3
gene, are also found in patients of relapse with lineage switch.
FLT3, located on chromosome 13, encodes a class III receptor
tyrosine kinase that regulates hematopoiesis. Activated receptor
kinase phosphorylation activates multiple signaling pathways,
including apoptosis, proliferation and differentiation of myeloid
hematopoietic cells [18]. The gene rearrangement or fusion genes
cause relapse of MLL remains to be investigated after CAR T-cell
immunotherapy [5,19,20].

Indirectly Related Molecular Mechanisms
The IL-6 gene, encoded a cytokine that functions as inflammation
and B-cell maturation, is located on chromosome 7. In a study,
MLL patients with t (4,11) rearrangements who were treated
with CAR T-cells developed cytokine release syndrome (CRS) [21].
The patients that occurred CRS developed myeloid relapse while
the other patients that were in remission didn't occur CRS. It has
also been shown that IL-6 can drive myeloid differentiation of
lymphocytes or cloning of myeloid cells. The results show that IL-6
contributes to myeloid transformation in mixed leukemias [6].

Conclusion
The current research on CD19-negative relapse is thought to
be the loss of CD19 after CAR T-cell immunotherapy. The
lineage switching, CD19 gene mutation, selective shearing, and
subcloning of CD19- negative are thought to result in the loss of
CD19. Moreover, the IL-6, mutated and fused genes have also been
discovered. Further studies are needed for its relapse mechanism.

Future Perspectives
CD19 is the most common target in CAR T-cell immunotherapy.
CD22 is a target for salvage therapy after Anti-CD 19 CAR T-cell
treatment [22]. The bispecific anti-CD20 and anti-CD19 CAR T-cells
are also available to treat lymphoma [23]. The loss of surface
antigens may lead to relapse. Therefore, research in the molecular
field may be the way forward for CAR T-cell immunotherapy.
Financial Support and Sponsorship

1. The relapse mechanism of genetic mutation for the relapsed/refractory lymphoma after CAR T-cell therapy has been approved by Shenzhen Science and Technology Innovation Committee. Award Number: JCYJ20180228163509339. Grant Recipient: Weihong Chen.

2. CAR T-38 cell therapy for disease progression/relapse multiple myeloma has been approved by Shenzhen municipal Health Commission. Award Number: 201606021. Grant Recipient: Weihong Chen.

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