

CRISPR/Cas9-mediated knockout reveals important role of CD30 in classical Hodgkin lymphoma cell lines

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Introduction

The malignant Hodgkin- and Reed-Sternberg (HRS) cells of classical Hodgkin lymphoma (cHL) highly express the TNF-receptor superfamily member CD30 on their cell surface, which is routinely used for diagnosis of cHL and is becoming the focus of targeted therapy, as cHL shows impressive response to drug-conjugated CD30-specific antibodies. However, the role of CD30 in the pathogenesis of cHL is not well understood and controversially discussed.

Methods

Thus, we established a CRISPR/Cas9 system in cHL cell lines, as well as two other CD30-positive lymphoma entities - anaplastic large cell lymphoma (ALCL) and primary mediastinal B cell lymphoma (PMBL). Efficient knockout (KO) of CD30 was confirmed by detection of homozygous CD30 mutations as well as downregulation of CD30 protein.

Results

Characterization of CD30-depleted HRS cells identified a growth disadvantage under competitive growth conditions and CD30-KO-cultures showed increased cell death which was at least partly mediated by increased apoptosis in several cHL, ALCL and PMBL cell lines. Influences on the activity of the main signaling pathways driving cHL lymphomagenesis were detected, i.e. downregulation of NF- κ B signalling in HDLM-2 (cHL) as determined by RNA-sequencing and confirmed by reduced levels of pIKK. Furthermore, RNA-sequencing data suggest contribution of CD30 signalling to the high MYC signature as a common feature of all cHL cell lines tested.

Conclusion

These results point to an important role of CD30 expression by HRS cells for the pathobiology of cHL.