CApSiZing T-cell acute lymphoblastic leukemia

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In this issue of Hematologica, Cardoso *et al.* identify *CASZ1* as a novel player in T-cell acute lymphoblastic leukemia (T-ALL), an aggressive hematological malignancy with a high risk of relapse and associated long-term complications.[1] Thus, discovering new factors involved in the development of leukemia will enhance our basic understanding of the pathophysiology of this disease and may lead to the identification of novel therapeutic targets for T-ALL treatment. In this context, it is noteworthy that *CASZ1* is particularly enriched in patients expressing elevated levels of *TAL1*, a well described major oncogene in T-ALL.[2]

CASZ1, the mammalian homolog of the Drosophila zinc finger transcription factor Castor, is known for its critical role in vascular and neural development.[3,4] *CASZ1* consists of two alternatively spliced isoforms (*CASZ1a* and *CASZ1b*) which, however, seem to play similar roles. Interestingly, embryonic deletion of *Casz1* leads to abnormal heart development and lethality in mice.[5] Moreover, the potential role of *CASZ1* in cancer is complex. Caren *et al.* first showed that the loss of several genes in the chromosome region 1p36, particularly *CASZ1* and *PIK3CD*, is associated with the development of neuroblastoma.[6] This initial discovery sparked a cascade of investigations into the diverse roles of *CASZ1* across various cancer types and physiological processes. Beyond its tumor suppressor role in neuroblastoma, where *CASZ1* low expression also significantly correlates with poor clinical outcomes,[7] it has been shown that overexpression of *CASZ1* is associated with metastasis in ovarian cancer,[8] highlighting its potential tissue-specific role in cancer development.

In the present study, the authors start dissecting the role of *CASZ1* in T-ALL by examining its interplay with key oncogenes and T-ALL-specific mutations. Taking advantage of the BloodSpot database, they found that the *CASZ1b* isoform (which shows higher evolutionarily conservation than *CASZ1a*), was significantly upregulated in T-ALL cell lines and patient samples. Interestingly, *CASZ1b* upregulation was especially marked in cases with high *TAL1* expression, suggesting that *TAL1* might regulate *CASZ1b*. Indeed, *TAL1* overexpression or knockdown in different human T-ALL cell lines led to upregulation or downregulation of *CASZ1b*, respectively. Moreover, the authors found that TAL1 directly binds to the *CASZ1b* promoter, further reinforcing the positive correlation between *TAL1* and *CASZ1* in T-ALL. Still, *CASZ1* was generally overexpressed in T-ALL compared to normal T cells, suggesting that additional mechanisms might be involved in the regulation of *CASZ1* in TAL1-negative T-ALL cases and, more broadly, supporting a relevant role for *CASZ1* in T-ALL overall. Next, the authors demonstrate that *CASZ1* overexpression is sufficient to confer interleukin (IL)-3-independent growth in the otherwise IL-3-dependent Ba/F3 murine pro-B cell line, suggesting a pro-oncogenic role for *CASZ1*. In order to dissect the underlying mechanism, the authors performed gene expression profiling analyses in this setting and found that *CASZ1* correlated with overexpression of the PI3K-AKT-mTOR signaling axis, which is well known to play a critical role in T-ALL.[9] Notably, pharmacological inhibition of the PI3K/mTOR pathway rescued the oncogenic effects driven by *CASZ1* in Ba/F3 cells, both *in vitro* and *in vivo*. Similarly, *CASZ1* also positively correlates with the PI3K-AKT pathway in T-ALL cells, underscoring the central role of the PI3K/AKT/mTOR pathway downstream of *CASZ1*. Still, how might *CASZ1* contribute to regulating the PI3K-AKT pathway remains a key lingering question.

Building upon these findings, the authors next used a zebrafish model of NOTCH1-induced T-ALL to demonstrate that *CASZ1* not only accelerated thymic hyperplasia but also actively promoted the development of NOTCH1-induced leukemia *in vivo*. Next, the authors performed a variety of experiments in human T-ALL cell lines *in vitro* in order to investigate the functional relevance of *CASZ1*. Under normal conditions, overexpressing *CASZ1* had no impact on the viability or proliferation of human T-ALL cells. However, under stress conditions such as serum starvation, *CASZ1* overexpression displayed a prosurvival role. Moreover, *CASZ1* also conferred resistance to a variety of chemotherapeutic drugs commonly used in T-ALL treatment, such as daunorubicin, dexamethasone or L-asparaginase, suggesting a broader protective role from different types of cellular stress. Finally,

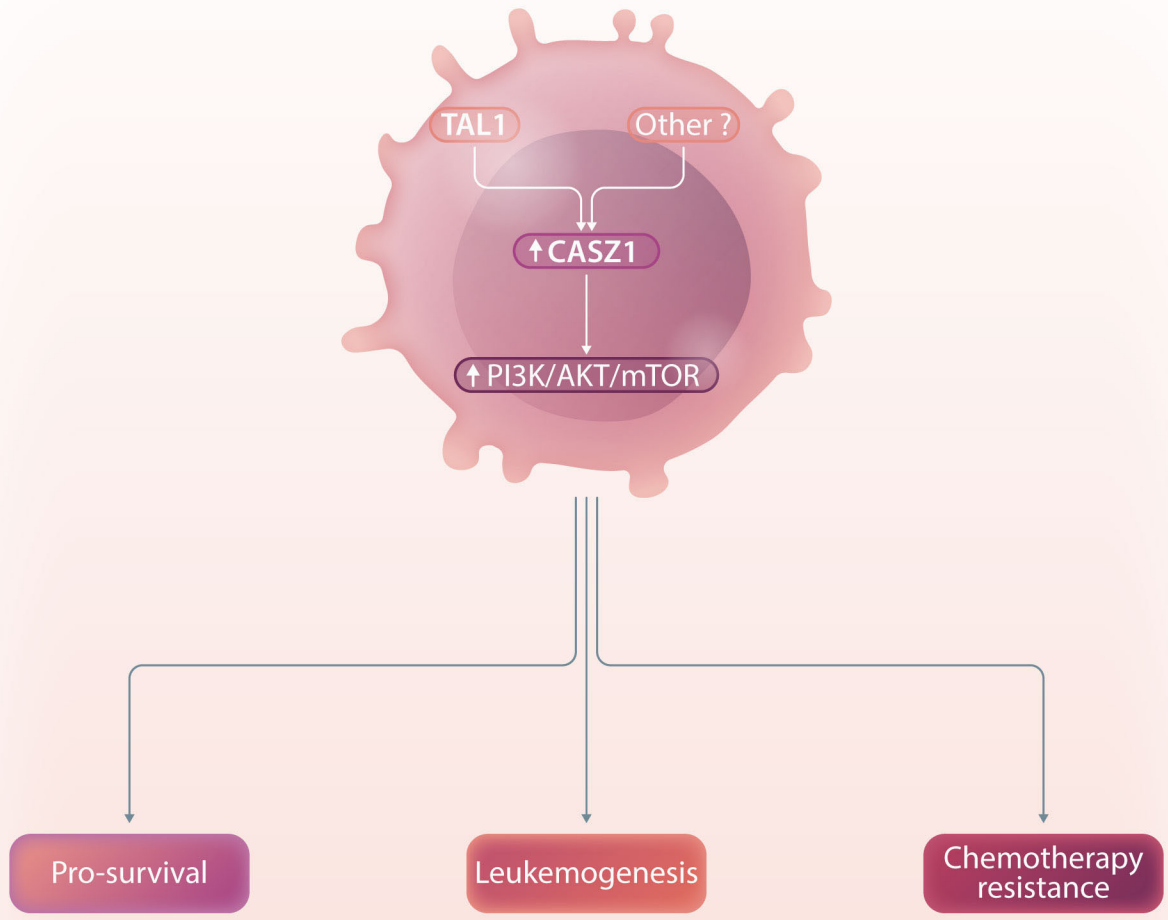

Figure 1. CASZ1 effects in T-cell acute lymphoblastic leukemia.

although *CASZ1* levels did not stand out as an independent prognostic factor in newly diagnosed cases of T-ALL, high levels of *CASZ1* were associated with poorer prognosis in patients with relapsed T-ALL.

Overall, this report uncovers a previously unknown oncogenic role for *CASZ1* in T-ALL, which might be of particular relevance in the response to common anti-leukemic drug treatments and in the progression of (heavily pretreated) relapsed T-ALL cases. Thus, further studies are warranted to investigate the potential role of CASZ1 as a novel therapeutic target in T-ALL treatment.

Disclosures

No conflicts of interest to disclose.

Contributions

KM and DH contributed equally.

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