The proto-oncogene TCL1A deregulates cell cycle and genomic stability in CLL

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BACKGROUND

T-cell leukemia/lymphoma 1A (TCL1A) is a lymphoid proto-oncogene whose aberrant up-regulation and prognostic impact has been reported for a variety of mature T- and B-cell leukemias. We previously demonstrated TCL1A to be overexpressed in the majority of cases of CLL, where it acts as a sensitizer in B-cell receptor signaling and as a predictor of inferior therapy response (*Herling et al. Blood 2009*). At the molecular level, TCL1A was shown to physically interact with the kinases AKT and ATM, both molecules that govern cell survival and the DNA damage responses (*Gaudio et al. Blood 2012*). However, the spectrum of molecular and cell-biological consequences of TCL1A dysregulation is not fully represented by its currently recognized effectors.

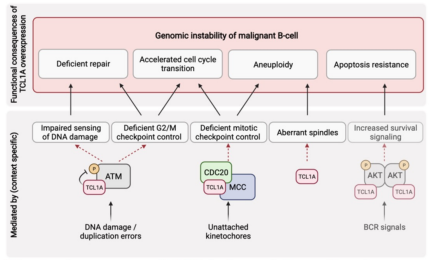
In proteomic screens of TCL1A-bound molecules in CLL cells and B-cell-lymphoma lines, we identified regulators of cell cycle and DNA repair pathways as novel TCL1A interactors, particularly enriched under induced DNA damage and mitosis. These data emphasize the need of further experiments that would comprehensively address the molecular mechanism of TCL1A and its interactors.

SUMMARY

TCL1A perturbs cell cycle and genome stability

1. TCL1A accelerates cell cycle transit and drives genome instability in B-cells
2. TCL1A directly engages CDC20 via defined motifs and impairs the interaction with its negative regulators
3. Low CDC20 in CLL correlates with genome instability and aggressive disease

Concept of TCL1A-driven genomic instability in malignant B cells



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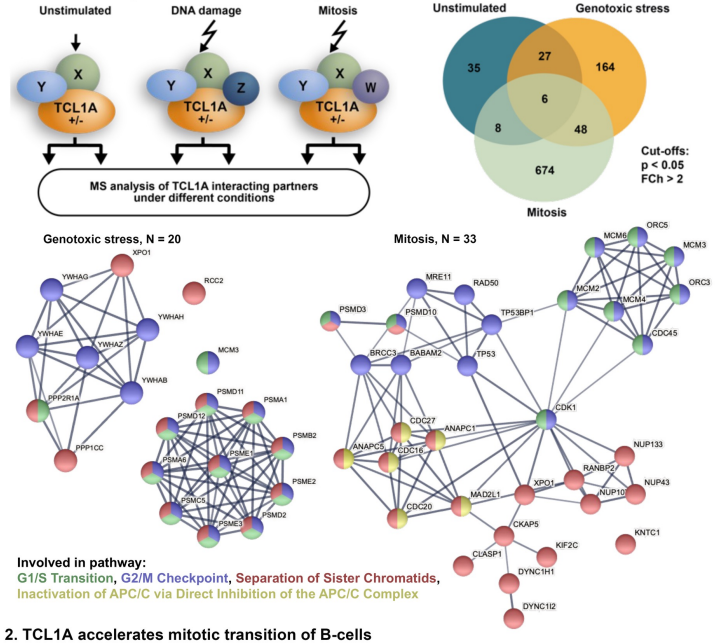
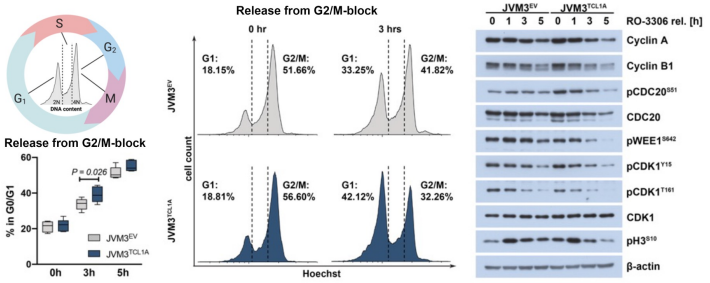
Blood. 2023 Mar 23;141(12):1425-1441.

RESULTS

1. MS based analysis of TCL1A interacting partners identifies mitotic checkpoint regulators

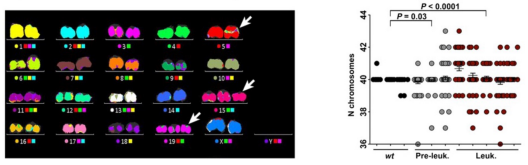


2. TCL1A accelerates mitotic transition of B-cells

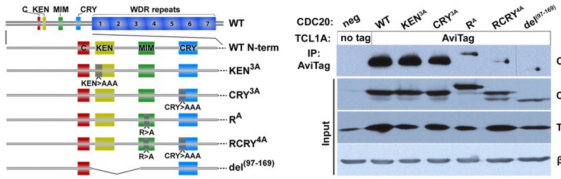


3. TCL1A overexpression leads to aneuploidy

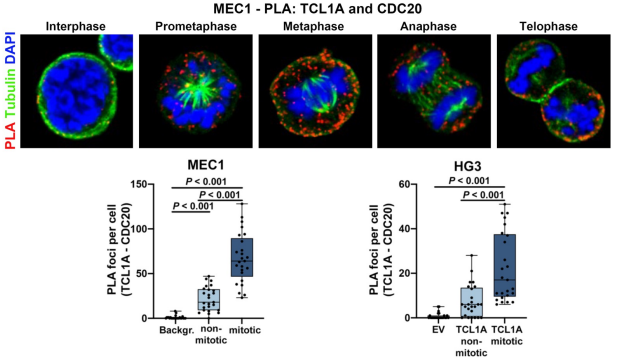
Representative SKY of a B-cell from an *Eμ-TCL1A* mouse



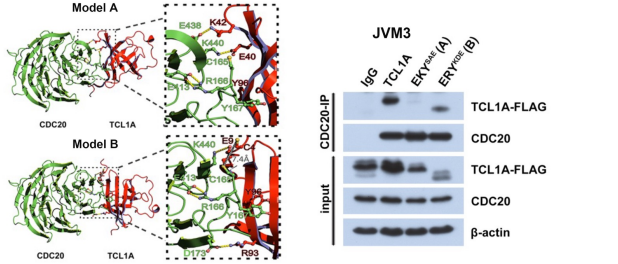
4. The CRY and MIM motif in CDC20 are involved in the interaction with TCL1A



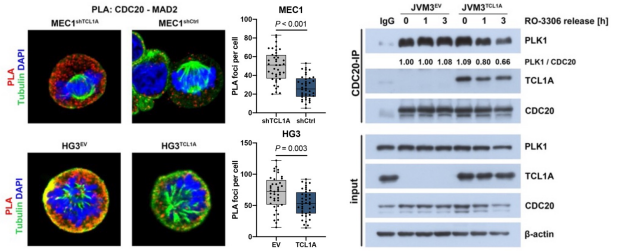
5. TCL1A and CDC20 interact during mitosis in the cytoplasm and at the spindles



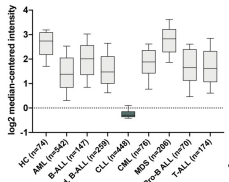
6. Defined amino acids of TCL1A are involved in its interaction with CDC20



7. TCL1A impairs CDC20's interaction with its negative regulators MAD2 and PLK1

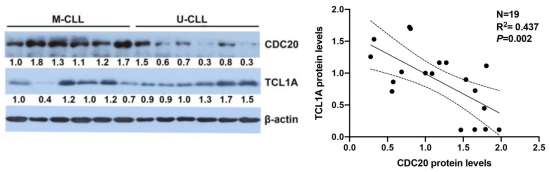


8. CDC20 is specifically downregulated in CLL

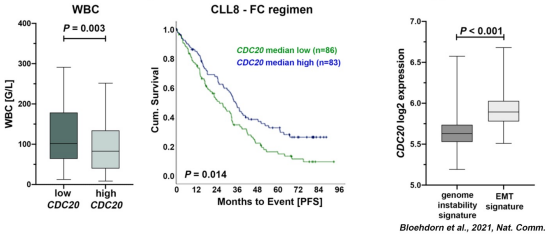


oncomine.org; Haferlach et al., J. Clin. Oncol. 2010

9. TCL1A and CDC20 expression show an inverse correlation in CLL



10. Lower *CDC20* expression correlates with features of aggressive CLL



Bloehdorn et al., 2021, Nat. Comm.

11. CDC20 ablation accelerates leukemic outgrowth in mice