Novel insights on TLX1 function in T-ALL pave the way towards differentiation therapy

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The mutational landscape of T-cell acute lymphoblastic leukemias (T-ALL) has been intensively studied over the past decades and we now have an extensive list of genetic defects that can occur in these tumors.[1] Central to T-ALL pathogenesis is the NOTCH1 signaling cascade which is hyperactivated in more than 50% of T-ALLs.[2,3] In addition, T-ALL cells are characterized by chromosomal rearrangements that juxtapose transcription factor genes such as TLX1 (also called HOX11), TLX3 (also called HOX11L2) or TAL1 to strong promotor and enhancer elements, resulting in overexpression of these oncogenic transcription factors.

These rearrangements and resulting transcription factor overexpression in T-ALL have been known for many years. However, first insights into the oncogenic mechanism of TLX1 in T-ALL have only recently been obtained. The Ferrando group showed that mice with T-cell specific TLX1 expression develop T-cell neoplasms that show a distinct gene expression signature characterized by down-regulated transcripts and that are shared with human TLX positive tumors.[4,5] Furthermore, they observed that TLX1 tumor cells show defective activation of the mitotic checkpoint due to downregulation of mitotic checkpoint genes in TLX1 pre-leukemic cells. These observations can be linked to the aneuploidy that is seen in TLX1 positive mouse and human tumors.[4]

Now a study by Dadi *et al.* also provides clues on how TLX1 hijacks T-cell differentiation and mediates the characteristic early cortical maturation block in TLX$^+$ T-ALL patients.[6] They show that the TCRα locus in TLX$^+$ T-ALLs is characterized by the repressive H3K37me3 histone modification and that TLX1 inhibits TCRα rearrangement by binding the ETS1 transcription factor and repressing TCRα enhancer activity. As a consequence, T cells with an unsuccessful rearranged TCRα locus cannot continue their development and are blocked at this stage of differentiation. Interestingly, RUNX1/AML1 and LEF1, two transcription factors for which recently inactivating mutations in T-ALL were described,[7,5] bind the TCRα enhancer locus together with ETS1 and TLX1 to initiate TCRα rearrangement. Furthermore, RUNX1 and LEF1 were identified as master regulators acting downstream of TLX1 and TLX3 and these factors are down-regulated by TLX proteins in T-ALL.[5] These results make it tempting to speculate that inactivation or downregulation of RUNX1 and LEF1 is an alternative and/or co-operating mechanism in T-ALL to impair TCRα rearrangement.

These novel insights into the action mechanism of TLX factors in T-ALL open up new opportunities for therapeutic design in TLX$^+$ T-ALL. Dadi and colleagues nicely show that downregulation of TLX proteins in TLX+ T-ALL cell lines abolishes the cellular differentiation blockage and induces cell death; effects that could also be obtained by overexpression of TCRαβ protein in TLX$^+$ cells.[6] Although there is still a long way to go before suitable small molecule drugs are identified, these results pave the way for 'differentiation treatment' in TLX$^+$ T-ALL. Such treatment could abrogate the TLX mediated inhibition of TCRα rearrangement and could prove to be very effective, similar to the all-trans retinoic acid based differentiation treatment in acute promyelocytic leukemia.[8]

References

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