emerging field of targeting epigenetic regulators in cancer, the results presented in these articles highlight the potential of using such therapies, not only in AML, but perhaps in other cancers that are dependent on aberrant epigenetic activity for survival.

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Hijacking T Cell Differentiation: New Insights in TLX Function in T-ALL

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DOI 10.1016/j.ccr.2012.03.026

TLX1 and TLX3 are two closely-related homeobox transcriptional repressors frequently misexpressed and translocated in T cell acute lymphoblastic leukemia (T-ALL). In this issue of *Cancer Cell*, Dadi et al. provide new insights into how these factors are recruited by ETS-1 to the TCRα enhancer and actively repress differentiation.

In the majority of human cancers, tumor cells tend to share aspects of their identity with a corresponding cell of origin, a property that has proved useful for diagnosis in the clinic and provided researchers with a wide range of potential therapeutic targets. In particular, acute lymphoblastic leukemia (ALL) often presents as a snapshot of lymphocyte differentiation, based on surface marker expression and characteristic molecular genetic signatures (Aifantis et al., 2008). A large amount of data over the last decade has underlined the connection between physiological lymphocyte differentiation and the transformation events that lead to ALL. Whole-genome profiling and sequencing studies have suggested that some of the most common mutational targets in ALL are also key regulators of normal differentiation, including *IKZF1* and *PAX5* in B-ALL and *NOTCH1* and *GATA3* in T cell ALL (T-ALL) (Mullighan and Downing, 2009). Such findings have suggested that certain oncogenic lesions have the ability to "freeze" cellular differentiation at distinct stages. Therefore, a thorough understanding of how oncogenes halt developmental processes will provide clues toward the reinforcement of differentiation and, presumably, the desired outcomes of cell cycle exit and/or programmed cell death. In this issue of *Cancer Cell*, Dadi et al. (2012) reveal how two such oncogenes (*TLX1* and *TLX3*) manage to interfere with a critical stage of T cell differentiation, leading to development of a subset of T-ALL.

T cell differentiation and ALL are ideal models to study such oncogenic effects due to our detailed knowledge on the phenotypic and molecular programs of differentiation. T cells mature in the thymus following a highly orchestrated process, controlled by cell intrinsic (transcription factors) and cell extrinsic (antigen, cytokines, and chemokines) factors. Uncommitted, multipotent progenitors enter the thymus through the cortico-medullary junction, sense Notch ligands, and initiate commitment to the T cell lineage. At this point the T cell receptor (TCR) β, γ, and δ loci become accessible and the outcome of rearrangement leads to either the differentiation toward the γδ lineage or (as it happens with the vast majority of T cells) the expression of the pre-TCR, which helps drive cellular proliferation and leads to the $CD4^+8^+$ stage. At this stage, the TCRα locus undergoes recombination which leads to the surface expression of a TCRαβ and subsequent selection events (Sleckman et al., 1998). RAG-mediated rearrangement of the TCRα locus is a process controlled by distinct

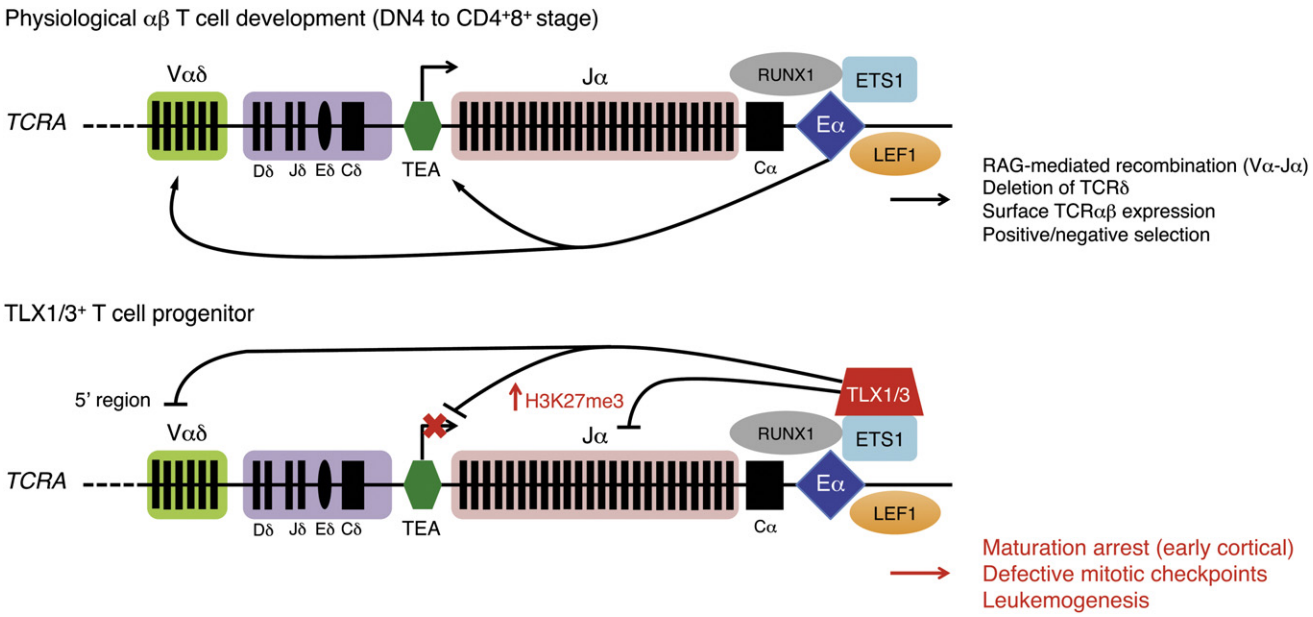

Figure 1. TLX-Mediated Repression of the TCRα Enhancer

Under normal conditions of αβ T cell development (top), transcriptional access to the TCRα locus at the late double-negative (DN) to $CD4^+8^+$ stage is imparted primarily by the function of the Eα enhancer, shown bound by its transcriptional activators ETS-1, RUNX1, and LEF1. The onset of Vα-Jα recombination begins with transcription from the TEA promoter and increased histone acetylation throughout the Jα region. In a subset of T cell leukemias where *TLX1* or *TLX3* are misexpressed (bottom), Dadi et al. (2012) found that ETS-1 can recruit TLX1/3 to Eα and that this correlates with an enrichment of repressive histone modifications and lack of *TCRA* gene expression, ultimately leading to an arrest in differentiation.

cis-regulatory regions, most notably the Eα enhancer, and a large number of factors regulating chromatin accessibility, locus contraction and gene transcription (Schatz and Swanson, 2011). Interestingly, topology is essential for normal maturation, suggesting an intimate relationship between developing progenitors and thymic microenvironments. Human and mouse T cell differentiation follow similar rules with very small differences, underlining the evolutionary conservation of such a critical process. Human T-ALL cases can be roughly separated into three categories, reminiscent of physiological developmental stages: (1) immature, early T-ALL, expressing markers and genes characteristic for pre-committed progenitors; (2) early cortical, αβ-committed thymocytes, harboring TCRβ rearrangements and (in most cases) expressing a pre-TCR; and (3) late, TCR-expressing leukemia, with full rearrangement of the TCRα locus.

In concordance with previous studies, Dadi et al. (2012) found that TLX1 and TLX3 are overexpressed in a significant fraction of T-ALL, and their expression defines a molecular signature characteristic of early cortical thymocytes. *TLX1* is overexpressed in 5%–10% of pediatric and up to 30% of adult T-ALL as a consequence of chromosomal translocations. Similarly, *TLX3* is overexpressed as a result of t(5;14)(q35;q32) in approximately 25% of pediatric and 5%–10% of adult T-ALL cases. *TLX1*, which is not expressed during physiological T cell differentiation, was first implicated in T-ALL from a t(10;14) translocation by Hatano et al. (1991). As a result of this translocation, TLX1 is ectopically expressed in thymocytes driven by cis-regulatory elements of the TCRα/δ locus. The targeting of antigen receptor loci by translocations is a frequent event in ALL, most likely caused by the function of RAG nucleases and the accessible state of the chromatin during specific differentiation stages. TLX1/3 overexpression defines a distinct subgroup of T-ALL, one that predicts an overall favorable prognosis, bears characteristic molecular and cellular phenotypes, and is enriched in *NUP12-ABL1* fusions or mutations in *WT1*, *PHF6*, and *RUNX1* (Van Vlierberghe et al., 2010). Transgenic expression of *TLX1* in the thymus of mice eventually leads to T cell neoplasms (De Keersmaecker et al., 2010). Interestingly, these $TLX1^+$ tumors are prone to aneuploidy and show marked defects in the activation of normal mitotic checkpoints, possibly due to deregulated expression of *Chek1*. Further analysis revealed that ectopic *TLX1* expression alone is likely insufficient to induce T cell leukemia but leads to aberrant T cell differentiation and sets the stage for secondary transformation events. Indeed, genetic lesions in loci encoding known regulators of lymphocytic transformation were identified, including mutations in *Notch1*, *Pten*, *Tp53* and, most notably, *Bcl11B*, a factor controlling early T cell progenitor differentiation in the thymus (Gutierrez et al., 2011). Altogether, these data suggested that TLX1 might act first and foremost as an antagonist of physiological T cell development. However, the mechanism by which TLX1/3 could exert this effect remained elusive.

Intriguingly, Dadi et al. (2012) found that $TLX1/3^+$ leukemias were significantly less likely to have TCRα rearrangements. Accordingly, increased levels of the repressive histone mark H3K27me3 was observed across the TCRα locus in these leukemias, suggesting that the unrearranged TCRα segments were epigenetically silenced in the presence of TLX1/3. However, their most critical finding is that the TLX factors could directly interfere with Eα function through

interaction with ETS1, a critical component of the complex that binds and activates Eα (Figure 1). To test the biological significance of this interaction on the enhancer element, the authors silenced TLX1/3 in human T-ALL cell lines and observed increases in differentiation and cell death, suggesting abortive differentiation and induction of apoptosis. Ectopic expression of rearranged TCRα caused identical effects. These findings therefore connect proper TCR rearrangement and expression to tumor differentiation state.

Altogether, the work of Dadi et al. (2012) presents a novel mechanism of differentiation arrest orchestrated by the TLX oncogenes in the induction and maintenance of T-ALL. To this end, it will be important to determine whether additional transcriptional targets that are potentially perturbed by TLX1/3 are also important for progression of the disease. This is an important question as the differentiation defects seen in *TLX1* transgenic mice are distinct from those caused by paucity of TCRα rearrangement in human leukemia. One such example could be the downregulation *BCL11B*, a target of TLX1 that is essential for T cell commitment. Further investigation on the potential synergistic role other factors play in the TCR recombination (Polycomb complex, the CTCF insulator protein, and others) and on the mechanisms leading to sustained expression of the TLX proteins will shed light on the intricacies of this leukemia. Ultimately, the most intriguing implication of this study is whether there are means of regulating TLX function using targeted therapies to enforce differentiation of TLX1/3$^+$ T-ALL. A similar approach of "differentiation therapy" has been extremely effective in the treatment of acute promyelocytic leukemia with all-trans retinoic acid (Kogan and Bishop, 1999). Given that their expression is normally restricted to embryonic development, TLX1/3 could prove to be ideal targets in the treatment of large fraction T cell leukemias with limited potential for adverse side effects.

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Personalized Medicine: Patient-Predictive Panel Power

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Two recent papers published in *Nature* demonstrate the power of systematic high-throughput pharmacologic profiling of very large, diverse, molecularly-characterized human cancer cell line panels to reveal linkages between genetic profile and targeted-drug sensitivity. Known oncogene addictions are confirmed while surprising complexities and biomarker relationships with clinical potential are revealed.

The need to identify predictive biomarkers of tumor response has intensified with the era of molecularly-targeted therapies that exploit addictions and vulnerabilities in tumors with identifiable molecular traits, in contrast to the one-size-fits-all approach that dominated cytotoxic chemotherapy (Yap and Workman, 2012). Two recent *Nature* articles describe a systematic large-scale approach to this challenge by high-throughput profiling many targeted agents against hundreds of clinically-relevant human cancer cells lines with detailed genetic annotation (Garnett et al., 2012; Barretina et al., 2012).

There are three important general take-home messages from these two studies. (1) The articles provide the most extensive