TCF3::HLF acute lymphoblastic leukemia: still challenging to cure thirty years later

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TITLE	Two types of genomic rearrangements create alternative *E2A-HLF* fusion proteins in t(17;19)-ALL.
AUTHORS	Hunger SP, Devaraj PE, Foroni L, Secker-Walker LM, Cleary ML.
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While the majority of children, adolescents, and young adults with B-cell acute lymphoblastic leukemia (B-ALL) can be cured by risk-adapted multi-agent chemotherapy regimens optimized during the past 50 years, long-term survival has remained elusive for pediatric patients with the rare (<1% of cases), but to date universally-fatal, t(17;19) subtype harboring *TCF3::HLF* (formerly *E2A-HLF*) fusions first identified and reported in 1991.[1] A landmark

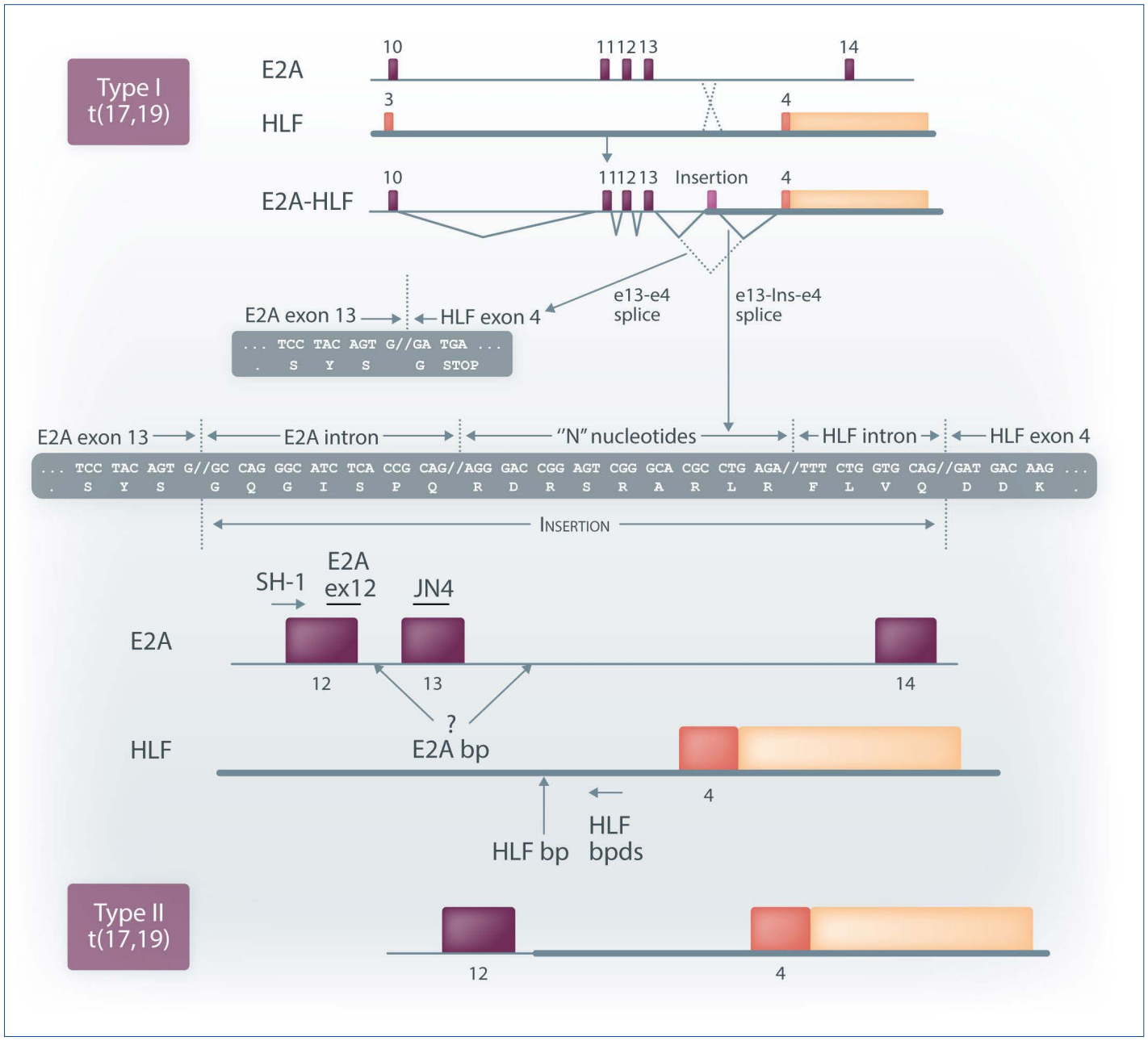

Figure 1. Two genomic rearrangements within t(17;19)(q22;p13) acute lymphoblastic leukemia induce unique clinical phenotypes. Type I rearrangements (upper panel) involving *E2A* (now *TCF3*) exon 13 and *HLF* exon 4 are associated with disseminated intravascular coagulation. Type II rearrangements (lower panel) involving *E2A* exon 12 and *HLF* exon 4 are associated with hypercalcemia. The uncommon *TCF3::HLF* B-ALL subtype occurs almost exclusively in pediatric patients, most commonly in adolescence. (Figure adapted with permission from Hunger *et al.* Blood 1994).[2]

study by Dr Stephen Hunger and colleagues in 1994[2] cloned and further defined the two major *TCF3::HLF* fusion breakpoints that are now known to be associated with highly characteristic clinical presentations in patients with this deadly form of B-ALL (Figure 1). Type 1 rearrangements result in translocation between exon 13 of *TCF3* and exon 4 of *HLF* and are associated with a severe disseminated intravascular coagulation phenotype. Type 2 rearrangements result in translocation between exon 12 of *TCF3* and exon 4 of *HLF* and induce a severe hypercalcemia phenotype. The precise mechanisms of these phenomena remain incompletely elucidated. Such clinical manifestations are extremely unusual in other B-ALL subtypes and provide important early clues regarding potentially worrisome leukemia-associated genetic alterations to be detected via cytomolecular assays. Regardless of the specific t(17;19) breakpoints and distinctive clinical phenotypes, patients with *TCF3::HLF* B-ALL have poor initial responses to chemotherapy and/or experience early relapses (usually within two years of diagnosis) that have been unsalvageable to date with intensive chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT) in first remission.

Chemoresistance in *TCF3::HLF* B-ALL has been attributed in part to upregulation of P-glycoprotein expression and ABC multi-drug resistance transport proteins and to upregulation of RAS, BCL-2, and other pro-survival pathways. Recent preclinical studies based upon gene expression characterization and biochemical high-throughput drug screening of primary *TCF3::HLF* ALL specimens have identified potential Achilles's heels for targeted therapies, including MEK inhibition (also germane given frequent *KRAS* or *NRAS* co-mutations), BH3 family protein inhibition with navitoclax and/or venetoclax, SRC family kinase inhibition with dasatinib, and Aurora kinase inhibition with alisertib.[3] However, such precision medicine approaches have not been widely evaluated in the clinic given the relative rarity of patients with *TCF3::HLF* B-ALL.

As in other relapsed/refractory B-ALL subtypes, there is tremendous interest in learning if paradigm-shifting CD19-targeted or CD22-targeted antibody-based or cellular immunotherapies will ultimately be able to declare victory over the *TCF3::HLF* B-ALL villain. Encouragingly, recent case series have reported successful remission induction in a small number of patients with relapsed/refractory *TCF3::HLF* B-ALL treated with blinatumomab-to-HSCT or CD19 chimeric antigen receptor T cells,[4,5] although most children have experienced subsequent relapse with longer follow-up. Further studies are necessary to determine if these promising immunotherapeutic approaches are truly high-risk genetics-agnostic and can be further optimized for long-term cure of the unique, and quite deadly, *TCF3::HLF* B-ALL subtype.

Disclosure

No conflicts of interest to disclose.

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