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by Panagiotis Ntziachristos

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Sunburned blasts: ultraviolet imprints on aneuploid pediatric leukemia

Panagiotis Ntziachristos[1,2,3,#]

1 Leukemia Therapy Resistance Lab, Department of Biomolecular Medicine, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium

2 Cancer Research Institute Ghent (CRIG), Ghent University, Ghent, Belgium

3 Center for Medical Genetics Ghent (CMGG), Ghent University, Ghent, Belgium

correspondence should be addressed to:

Panagiotis Ntziachristos, pntziachr@gmail.com, Panagiotis.Ntziachristos@ugent.be

Department of Biomolecular Medicine, Faculty of Medicine and Health Sciences, Ghent University; Cancer Research Institute Ghent; Center for Medical Genetics Ghent

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In this issue of *Haematologica*, Suurenbroek and colleagues address one of the most counterintuitive observations to have emerged from whole-genome sequencing of pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL): the recurrent presence of single-base substitution signature 7a (SBS7a), a canonical fingerprint of ultraviolet (UV) light-induced pyrimidine-dimer formation, in a defined subset of aneuploid cases(1). SBS7a was originally defined in cutaneous and other sun-exposed malignancies, where cytosine-to-thymine (C>T) transitions at dipyrimidine sites and the diagnostic CC>TT double substitutions record the transcription-strand bias of nucleotide-excision repair (NER)(2,3). Its appearance in a bone-marrow disease has remained a mechanistic puzzle since its initial description in high-hyperdiploid, intrachromosomal amplification of chromosome 21 (iAMP21), and low-hypodiploid pediatric BCP-ALL(4,5).

Suurenbroek and colleagues attempted to investigate the etiology, timing, and anatomical context through the combined analysis of a 191-case BCP-ALL whole-genome cohort, a 1,033-case pediatric pan-cancer cohort, cross-cancer comparisons with 273 adult skin cancers and 7 pediatric cutaneous anaplastic large-cell lymphomas (ALCL), and single-cell whole-genome sequencing in two informative cases. The study has important emerging findings:

a) SBS7a in pediatric malignancy is restricted to aneuploid BCP-ALL and to tumors with documented cutaneous localization. Past research has associated SBS7a with high-hyperdiploid, iAMP21, and low-hypodiploid BCP-ALL (4,5), but without reference to a broader pediatric denominator. By showing, across 1,033 pediatric tumors, that SBS7a is essentially absent from solid and neurological pediatric cancers, and within the hematological compartment is confined to BCP-ALL and cutaneous ALCL, the authors narrow the space of SBS7a in childhood cancer to lymphoid lineages compatible with transient cutaneous residency.

b) The mutational portrait of SBS7a-positive BCP-ALL is quantitatively indistinguishable from that of *bona fide* UV-driven tumors. Previous characterizations of SBS7a in skin cancer(2,3) had established its diagnostic features but were not directly benchmarked against BCP-ALL. Here, the CC>TT burden, transcriptional strand asymmetry, and dinucleotide-context preferences of SBS7a-positive BCP-ALL superimpose on those of cutaneous tumors. This weakens the case for a phenocopy arising from an unrelated process.

c) SBS7a accumulation in BCP-ALL is not explained by an intrinsic DNA-repair defect. Germline NER deficiencies, such as those underlying xeroderma pigmentosum, produce UV-like signatures(2), and it was legitimate to suspect that BCP-ALL might harbor somatic NER lesions. By screening NER pathway genes and examining pathway-level expression and transcriptional strand bias, the authors formally exclude this alternative. This finding further enhances the case for a genuine UV exposure event rather than a replication-repair defect.

d) SBS7a mutations accumulate early in the clonal tree and cease to be deposited once bone-marrow colonization is complete (see **Figure**). Previous analyses of clonal dynamics in BCP-ALL(6) and in relapsed ALL(7) had shown that therapy-induced mutational signatures accrue between diagnosis and relapse, whereas endogenously acquired signatures (SBS1, SBS5) are typically present at diagnosis; SBS7a had never been placed in such a temporal framework. Using bimodal allele-frequency analyses, longitudinal diagnosis-to-relapse pairs, and single-cell whole-genome sequencing lineage trees, the authors show that SBS7a is deposited before bone-marrow engraftment, and relapse-specific SBS7a mutations are in fact minor-clonal at diagnosis rather than newly acquired in the marrow. This reframes SBS7a as a pre-leukemic, extramedullary mutational process and nominates the skin as a mutagenic niche for aneuploid B-lymphoid progenitors (see Figure). Prenatal first hits in fetal-liver lymphoid progenitors are documented for several BCP-ALL subtypes (8), but a postnatal, environmentally induced extramedullary mutagenic niche has not previously been proposed.

e) Ten pathogenic driver mutations, including lesions in *CREBBP* and *NR3C1*, are attributable to SBS7a. Both genes are established contributors to glucocorticoid resistance and relapse in BCP-ALL(7), and somatic *CREBBP* variants have been shown to be positively selected under therapy pressure(7). The observation that a subset of these drivers can be generated by UV-induced mutagenesis prior to bone marrow engraftment is new. The cohort size with 43 SBS7a-positive cases analyzed in depth is insufficient for formal prognostic inference, and further functional evidence that SBS7a-derived *CREBBP* or *NR3C1* variants drive therapy resistance is needed.

A few limitations suggest further future research attempts: The link between UV light and SBS7a in BCP-ALL remains correlative; irradiation studies in subtype-matched progenitor systems might be required to fully exclude alternative dipyrimidine-damaging insults such as reactive oxygen species, psoralens, alkylating adducts, or endogenous photosensitisers, even though their

canonical signatures are reportedly distinct(2,9). Additionally, no clinical, imaging, or histopathological evidence is provided for transient cutaneous residency of the (pre)leukemic clone, leaving the anatomical center of the model inferential; targeted re-analysis of leukemia-cutis cases would be a tractable intermediate step, and prospective dermatologic surveillance would directly test the current correlative case. Furthermore, the molecular determinants of subtype specificity remain unresolved: a cell migration-relevant gene signature emerged from a post-hoc over-representation analysis is currently speculative; functional skin-homing assays and humanized xenografts capable of capturing pre-diagnostic extramedullary phases are warranted(10). Single-cell whole-genome sequencing covered only 26 cells from two patients, which limits the statistical power to detect ongoing low-frequency SBS7a mutagenesis in the marrow; the cessation of medullary deposition is a working model rather than a demonstrated absence, particularly because relapse-specific SBS7a mutations were not fully reconciled with this claim and skin re-exposure during remission cannot be excluded. Finally, European-ancestry overrepresentation precludes a properly powered test of the melanin/UV-penetration mechanism invoked as a plausibility argument. Future studies, including broader ancestral representation and populations with higher skin pigmentation, will be needed to test the proposed melanin/UV-penetration mechanism.

In summary, Suurenbroek and colleagues establish that UV-induced mutagenesis contributes to the early clonal evolution of a defined subset of pediatric BCP-ALL, occurs in an extramedullary context before bone-marrow engraftment, and can generate pathogenic driver mutations with potential relevance for therapy response. The pan-cancer restriction of SBS7a to cutaneously competent lymphoid lineages, the identity of its mutational portrait with UV-driven tumors, and the temporal anatomy of its acquisition are conceptual advances offered by the study. The principal weaknesses are the absence of formal causal proof of UV exposure, the inferential rather than observational status of the cutaneous-residency model, and a clinical-impact claim that remains, on present numbers, hypothesis-generating. The skin is not a classical niche for pediatric lymphoid progenitors, but it may function as one.

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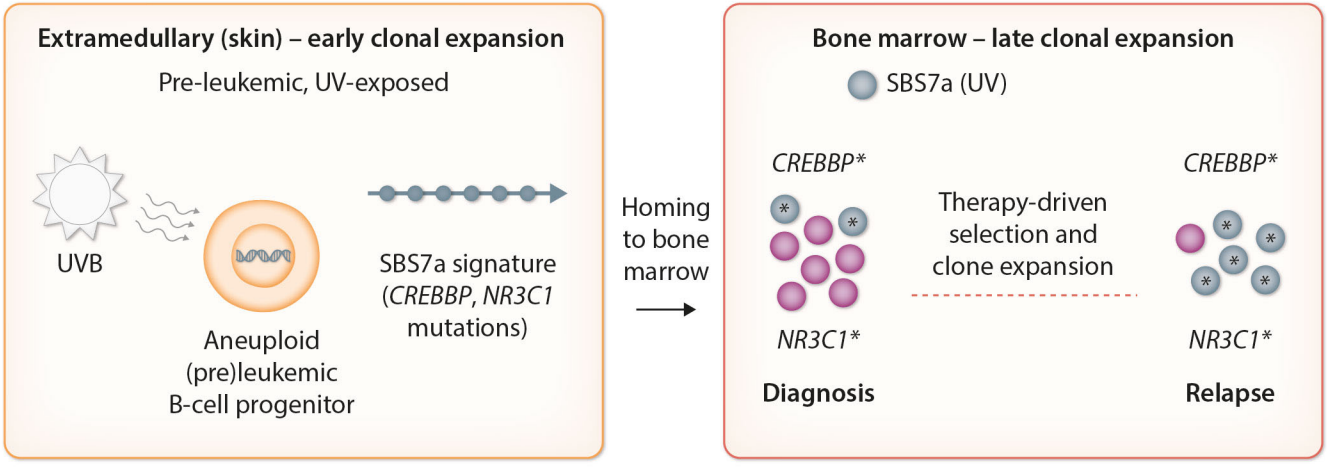
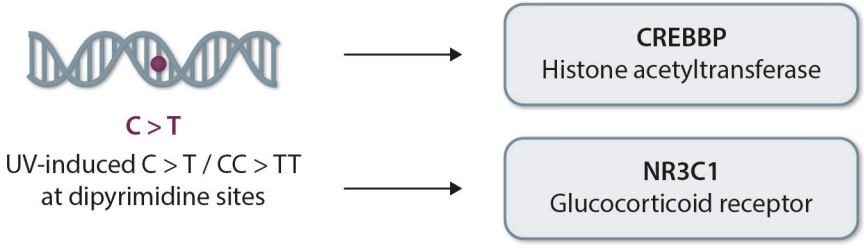
Figure Legend. Proposed model arising from Suurenbroek et al. (A) Temporal clonal phylogeny of SBS7a-positive aneuploid BCP-ALL. Aneuploid (pre)leukemic B-cell progenitors transiently reside in sun-exposed extramedullary sites where UV-induced pyrimidine dimers generate SBS7a mutations (C>T and CC>TT at dipyrimidine sites) along the trunk of the clonal tree. After homing to the bone marrow, the clones expand. (B) The *CREBBP* and *NR3C1 loci* are affected by SBS7a mutations. Open questions are summarized at the bottom of the figure.

A. Temporal clonal phylogeny of SBS7a-positive aneuploid BCP-ALL



B. SBS7a-derived driver mutations and potential clinical relevance



Open questions

1. **Subtype specificity**
   aneuploid karyotypes vs. translocation-driven subtypes
2. **Causal proof of UV exposure**
   controlled irradiation of subtype-matched progenitors; skin-homing and xenograft models
3. **Clinical weight of SBS7a-derived drivers**
   functional impact of CREBBP / NR3C1 variants; prospective validation in larger cohorts
4. **Population diversity in future cohorts**
   broader inclusion of patients