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COMMENTARY

Digging into the HLA pockets: A new association with acute leukaemias

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Summary

Acute leukaemias represent a highly heterogeneous group of clonal proliferations of myeloid or lymphoid blasts. In the last decade, the contribution of immunogenetics to cancer biology has elicited a renewed interest in the structures of immune adaptive responses, due to the growing body of evidence concerning their involvement into disease pathogenesis and treatment. The report by Boukouaci and colleagues suggests new associations between patterns of distribution of specific human leukocyte antigen motifs and leukaemogenesis.

Commentary on Boukouaci Wahid et al. Comparative analysis of the variability of the HLA peptide-binding pockets in patients with acute leukemias" Br J Haematol 2023;200:203-215.

KEYWORDS
HLA, immunogenetics, leukaemia

EDITORIAL

Acute leukaemias represent a highly heterogeneous group of clonal proliferations of myeloid (AML) or lymphoid (ALL) blasts. Recent advances in genomic medicine illuminated the pathogenesis of these diseases, unveiling a plethora of molecular alterations that underpin the observed variety of clinical presentations.[1] The identification of such aberrations is consequential for the assessment of patients' prognosis and establishment of appropriate treatments. This notwithstanding, long-term outcomes are still dismal and depend on a multitude of factors conditional to both patients' and disease-related features. In particular, relapse remains the most common cause of treatment failure and, especially in the higher-risk setting, allogeneic haematopoietic stem cell transplant (HSCT) plays a paramount role in disease eradication.

The fine control of the mechanisms underlying the immune synapse (e.g., the interface between antigen-presenting or target cells and lymphocytes via human leukocyte antigen [HLA]-peptide-T cell receptor interactions) guarantees the main functions of the human immune system, such as defence against pathogens, tolerance towards autoantigens and tumour surveillance. Therefore, the impairment of such mechanisms underpins disease susceptibility, as exemplified by the observed associations of autoimmune, infectious and neoplastic disorders with specific-risk allele genotypic configurations.[2,3]

In the last decade, the contribution of the immune system to cancer biology has elicited a renewed interest in the structure of adaptive responses due to the growing body of evidence concerning their involvement into disease pathogenesis and treatment. This is particularly true in acute leukaemias. Indeed, historical research had already highlighted a potential association between several HLA haplotypes and childhood leukaemia,[4] while a recent genome-wide association study[5] has identified HLA-DQA2 (rs3997854) as a

disease susceptibility locus for cytogenetically normal AML. Furthermore, approaches leveraging anti-tumour immune effectors, such as bi-specific T-cell engagers (BiTE) and cellular therapies (chimeric antigen receptor, [CAR]-T), are revolutionizing the current therapeutic arsenal of acute leukaemia, particularly ALL.

In this issue, Boukouaci et al.[6] took advantage of the Eurocord/European Blood and Marrow Transplant (EBMT) registry to explore the patterns of distribution of specific HLA motifs in a retrospective cohort of 849 patients with ALL (n = 426) and AML (n = 423) who had undergone HSCT from umbilical cord blood between 2001 and 2018. The authors found that a specific motif in P4 of the HLA DRB1*16:01/02/03/05 alleles (RFDRAY) was associated with acute leukaemias of lymphoid lineage (Figure 1). Furthermore, other specific motifs unique to ALL as compared to AML were the YYVSY in P9 of the HLA DQB1*05:02/04/05 alleles along with the serine 57 in the P9

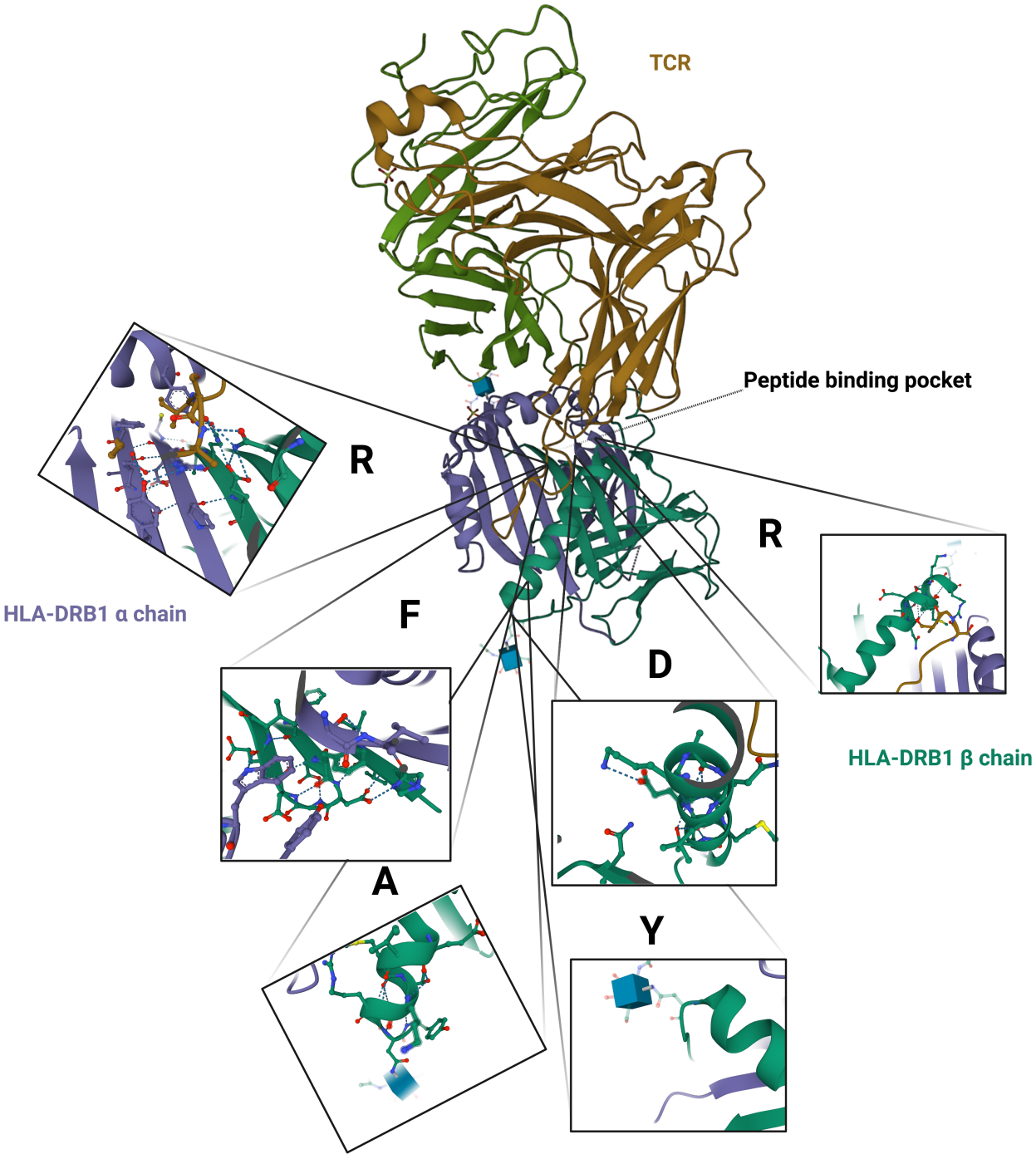

FIGURE 1 Three-dimensional crystallographic structure of DRB1-TCR complex. The illustration highlights the residuals found enriched in HLA-DRB1 binding pockets of acute lymphoblastic leukaemia patients. These amino acids correspond to the positions: 13, 26, 70, 71, 74, and 78 for P4 pocket. These structures were extracted from the Protein Databank (PDB, ref PDB: 10.2210/pdb2WBJ/pdb). [Colour figure can be viewed at wileyonlinelibrary.com]

of HLA DQB1*05:02. Despite the absence of healthy controls, the study confirms a specific HLA signature unique to ALL when compared to AML. It is also important to note that the median age of the ALL patients in the studied population, selected from the Eurocord/EBMT registry, was 7 years (range 0.6–46 years). While representing a limitation of the study and highlighting the need for confirmation on larger cohorts, this observation raises questions regarding potential, yet not fully elucidated, immune disturbances (e.g. of antigen processing mechanisms) which might contribute to early-in-life leukaemogenesis. Perhaps, still unclear viral triggers and subsequent ineffective antigenic clearance, driven by such HLA configurations, may underpin the ontogenesis of ALL in this setting.

Importantly, only motifs belonging to class II HLA (DQB1, DRB1) pockets were characteristically associated with ALL in this study.[6] Analogies to previous reports on specific class II HLA alleles and human pathology of an autoimmune nature and cancer are obvious and warrant further studies. A recent work on HLA evolutionary divergence (HED), a new metric that can be considered as an indirect measure of the breadth of the human immunopeptidome, found that lower class II HED imprinted a higher risk of leukaemic progression in patients with acquired aplastic anaemia.[7] Therefore, one could speculate that specific HLA class II configurations may hamper the mechanisms of immune recognition and antigenic clearance, or instead participate in oncogenic peptide presentations (tumour-associated antigens), thereby enhancing the process of leukaemogenesis, immune evasion and immune resistance.[8] This mechanism may be at play in the fraction of acute leukaemias relapsing post-HSCT, where it is impossible to pinpoint the exact drivers of disease relapse (such as recapitulation of diagnostic molecular markers or clonal evolution and acquisition of new aberrations).[9] Furthermore, if confirmed by future studies, the better characterization of the role of HLA class II (e.g. specific peptide binding pockets motifs, HED) may also have consequences on donor choice for transplant purposes. Perhaps, the quintessential relationship between acute leukaemias, immune system and HLA is exemplified by the mechanism of HLA loss as a means of immune escape post-HSCT.[10]

Furthering our understanding of immune biology of acute leukaemias is a fundamental step towards the precise characterization of immunogenetic predisposition and disease susceptibility, a task still far from being completed. However, given the results achieved in solid tumours and the current possibilities of modern medicine, clarifying the contribution of the immune system and the various actors at play (e.g. HLA) driving leukaemogenesis will enable in the future more personalized and patient-tailored immunotherapeutic strategies.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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