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EDITORIAL
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T-CELL RECEPTOR CONSTANT BETA CHAIN ISOFORMS – NEW PARADIGM IN THE DIAGNOSIS OF T-CELL NEOPLASMS

IZOFORME KONSTANTE BETA LANCA T-ĆELIJSKOG RECEPTORA – NOVA PARADIGMA U DIJAGNOZI T-ĆELIJSKIH NEOPLAZMI

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The adaptive immune system has evolved to recognize as many foreign antigens as possible [1]. The diversity of antigen recognition abilities by B and T-cells is achieved through combinatorial diversity and “imprecision” diversity. The former is the result of functional antigen-recognizing receptors (immunoglobulin receptor (Ig) and T-cell receptor (TCR)) being modular molecules. There are many variable segments with high sequence variability (V-regions of heavy and light chains of immunoglobulin receptor and alpha-through-delta chains of TCR) and few constant segments (C-regions, in translated protein close to/embedded in the membrane of B and T-lymphocytes). RAG-mediated DNA recombination during the development of B and T-cells in the bone marrow and thymus, respectively, combines variable and constant regions (as well as diversity-D and junction-J segments) into recombined DNA ready for transcription and translation of the message into a functional surface receptor protein [2, 3].

B and T-cell clones are cells with identical recombined antigen receptor. Clones may transiently emerge in reactive conditions such as infections or autoimmune processes. However, the term “clone” is most often used to describe abnormal neoplastic proliferations of cells with identical antigen receptor, presumed to originate from a single cell. In clinical laboratories, testing for B and T-cell clonality is routinely performed for diagnosing lymphoproliferative disorders. While new methods of antigen receptor sequencing by NGS offer the most direct evidence of clonality, most clinical laboratories use PCR method, where polyclonal populations exhibit a vaguely Gaussian distribution of PCR product lengths, while (mono)clonal population is represented by a single prominent PCR product peak [4, 5].

Immunophenotyping has been long used as a surrogate for clonality in B-cell neoplasms, enabled by mutually exclusive use of kappa and lambda light chains in B-cells, and availability of antibodies that recognize constant regions of kappa and lambda chains. Normal polyclonal B-cells are a mixture of kappa and lambda-expressing cells, usually in a 2:1 ratio as kappa locus rearranges first during the B-cell development. In contrast, B-cell clones are typically restricted to one of the two light chains.

Immunophenotyping of T-cells to prove clonality has been significantly more difficult. Flow cytometry immunophenotyping of V-beta chain usage is labor-intensive and complicated for analysis, thus rarely implemented in clinical practice [6]. Instead, phenotypic T-cell aberrancies, such as the loss of pan-T-cell antigens (CD2, CD5, CD7) or markedly skewed CD4:CD8 ratios, have been used as soft indicators of potential clonality. This all changed in 2017 when a British group published a paper describing characterization and use of an antibody directed toward constant region-1 (CR-1) of the TCR-beta chain, one of the two mutually exclusive isoforms (TRBC-1 and TRBC-2) [7]. Anti-TRBC-1 antibody was originally produced and partially characterized in early 1990s [8], and was re-discovered in an attempt to limit CAR-T therapy to only a subset of patient’s T-cells, ameliorating the immune suppression following such treatment. The diagnostic community quickly realized the importance of this discovery and followed with a massive effort to implement this antibody in indirect T-cell clonality testing [9–16]. Normal T-cells are a mixture of mutually ex-

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clusive TRBC-1 and TRBC-2 expressing cells, akin to kappa and lambda expression in normal B-cells. Even with a single anti-TRBC-1 antibody, it is possible to easily determine whether a certain T-cell population is likely clonal (if flow cytometry identifies the expression of TRBC1 present in less than 15% or more than 85% of the gated population) [15].

The inclusion of TRBC-1 (and, more recently, TRBC-2) [13] antibody in routine T-cell flow cytometry analysis enables rapid, accurate and cost-effective detection and quantification of T-cell clones, and it has dramatically changed the flow cytometry practice in the past several years. Of note, the increased sensitivity of this type of testing also results in detection of spurious small T-cell clones which may arise in reactive conditions (T-cell clones of undetermined significance – TCUS) [15], emphasizing the importance of clinical correlation, as is recommended for any laboratory test.

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