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TRANSFUSION MEDICINE

Comment on Karamatic Crew et al, page 135

PIEZO1: now also featuring blood group antigens

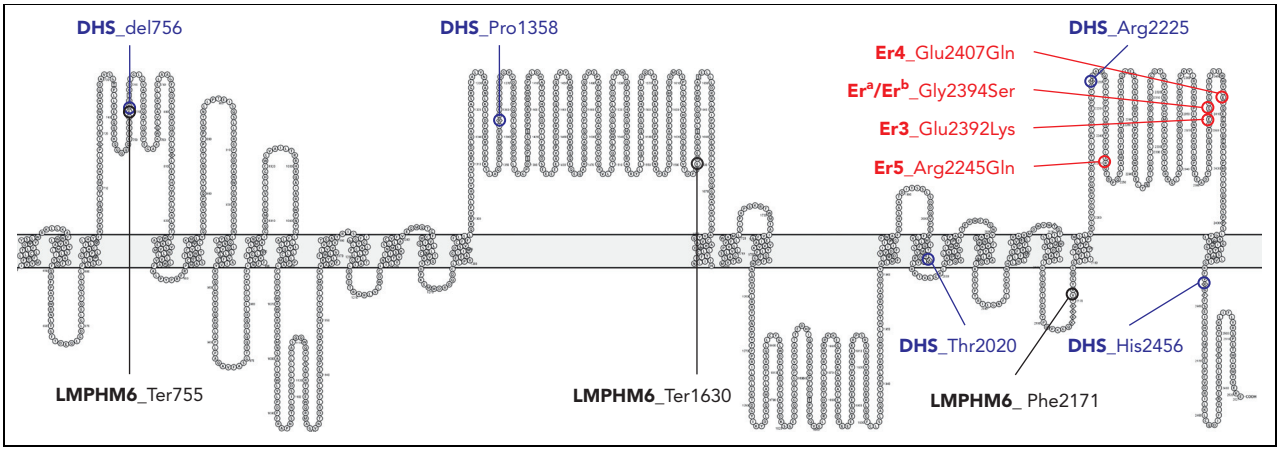
Christoph Gassner | Private University in the Principality of Liechtenstein

In this issue of *Blood*, Karamatic Crew et al examined alloantibody data from different patients with similar immunohematologic reaction patterns and identified *PIEZO1* as the common but previously unidentified genetic carrier of the corresponding antigens.[1] With the detection of at least one natural human alloantibody directed against an erythrocyte antigen and the description of the causative DNA polymorphism on a gene different from all other genes encoding antigens of existing blood group systems, the core criteria for the recognition of a candidate new blood group system have been fulfilled.

The discovery of such a "new" blood group system is preceded by years, often decades, of work, as in this case with the first Er antigen, named after the first propositus, reported in 1982.[2] During this period of time, comparative immunohematologic methods are used to meticulously collect individual samples, sometimes from all over the world, and the initial information is assembled into a first mosaic of what may then become a coherent picture of a new blood group system. Blood group experts with their deep-freeze archives had only been waiting for new methods, eg, whole-exome sequencing, to finally identify these cryptic blood groups. A total of 13 new blood group systems, from FORS (ISBT 031) in 2012 to ABCC1 (ISBT 043) in 2020 have been described and officially ratified by the International Society of Blood Transfusion (ISBT) Working Party for Red Cell Immunogenetics and Blood Group Terminology. the latest Working Party report is in revision and expected to be published in *Vox Sanguinis* in 2022.[3-5] Using immunoprecipitation, whole-exome sequencing, CRISPR/Cas9–mediated gene knockout and expression studies in an erythroblast cell line and pending the ratification of the ISBT Terminology Working Party, Karamatic Crew et al have once again[6] succeeded in the description of a candidate new blood group system, the Er system, proposed tentatively as ISBT 044, encoded by *PIEZO1*.[1]

The timing for the description of *PIEZO1* as the carrier of the genetic information for the blood group system Er could not have been better. On 4 October 2021, presumably just when the authors were compiling their data at the International Blood Group Reference Laboratory in Bristol, United Kingdom, in Stockholm, Ardem Patapoutian was announced as the 2021 Nobel Laureate in Medicine and Physiology for his discoveries involving the two mechanically activated ion channels Piezo1 and Piezo2. Similarly to Piezo crystals, in which electrical charges are generated under mechanical deformation, the transmembrane Piezo proteins translate mechanical forces into the flow of ions through cell membranes.[7] Such cellular mechanotransduction plays important physiologic roles in somatosensation (touch perception, proprioception, and pulmonary respiration), red blood cell volume regulation, vascular physiology, and various human genetic disorders.[8] It almost seems that whenever in the course of evolution mechanical pressure was needed to be measured physiologically, Piezo1 and Piezo2 were utilized. Accordingly, these proteins not only have a wide variety of biologic functions but also are linked to a number of hereditary diseases. The genetic *PIEZO1* disorders include dehydrated hereditary stomatocytosis (DHS1; 194380) and lymphatic malformation 6 (LMPHM6; 616843). DHS1 with and without pseudohyperkalemia is frequently observed to be caused by dominant gain-of-function mutations.[9] LMPHM6, on the other hand, appears to follow a recessive mode of inheritance caused by compound heterozygosity for alleles with absent protein expression.[10] At this point, the protein variants that cause known hereditary diseases and the blood group antigens newly localized to *PIEZO1* meet and may be considered from 2 different points of view: disease-associated genetic disorder or blood group (see figure). It would be worthwhile to study some of the patients affected by DHS1 or LMPHM6 to determine whether they express new Er antigens. Conversely, are different Er antigens associated with particular diseases? This idea was briefly, but certainly not conclusively, addressed within this article. Be that as it may, Piezo1 is a remarkable protein. This single protein teaches us to look beyond our respective horizons, to dive into foreign disciplines and learn new things.

Conflict-of-interest disclosure: C.G. acts as a consultant to inno-train Diagnostik, Kronberg im Taunus, Germany. Procedures for the molecular detection of GYPB *deletions for S-s-U- phenotype diagnostics have been granted as a European patent (EP 3 545 102 B1). Similar-content US patent application is pending.* ■



Piezo1 protein (Uniprot Q92508) amino acids 602 to 2521 and known mutations in *PIEZO1* encoding amino acid substitutions. Er blood group antigens encoded by *PIEZO1* are given in red and as detailed by Karamatic Crew et al.[1] Gly2394 is required for expression of the high-prevalence antigen Er^a, whereas Ser2394 encodes the antithetical low-prevalence antigen Er^b. Proposed novel high-prevalence antigens Er4 and Er5 are associated, respectively, with Gln2407 and Arg2245 in Piezo1. One Er3-negative allele encodes wild-type Gly2394 (Er^a) with a nearby Glu2392Lys mutation. Exemplary mutations of *PIEZO1* with resulting amino acid exchanges reported for patients with DHS are given in blue and are del756, Pro1358, Arg2225, Thr2020, and His2456. Exemplary mutations of *PIEZO1* with resulting amino acid exchanges reported for patients with LMPHM6 are given in black and are Ter755, Ter1630, and Phe2171. All Er blood group antigens cluster in the carboxy-terminal loop of Piezo1. Dominant mutations causing DHS and LMPHM6 mutations following a recessive mode of inheritance may be observed throughout all parts of Piezo1. The position of the *PIEZO1* mutations suggest coding of disease-associated alleles for blood group antigens and, vice versa, blood group antigens that may simultaneously represent disease-associated alleles. However, this hypothesis requires further research. Graphic generated in Protter.

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https://doi.org/10.1182/blood.2022018186

CLINICAL TRIALS AND OBSERVATIONS

Comment on de Botton et al, page 156

IDH2 inhibition in AML

Eytan M. Stein | Memorial Sloan Kettering Cancer Center

Donald's life was ending. As an 80-year old with relapsed IDH2-mutant acute myeloid leukemia (AML) the leukemia cutis erupting on his skin served as a visual reminder of his battered and blastic bone marrow. With limited standard treatment options he sought to enroll in a clinical trial with enasidenib, a potent inhibitor of mutant IDH2. Preclinically, enasidenib reliably led to the differentiation of malignant myeloblasts in vitro.[1] Would enasidenib be the first approved differentiation agent since the discovery of all-trans retinoic acid in the 1980s? After a long discussion Donald consented, screened and enrolled in the phase 1 trial of enasidenib for relapsed and refractory AML.

IDH2 mutations occur in 10% to 15% of patients with AML, increase in incidence as patients age, and exert their leukemogenic effect through the neomorphic production of β-hydroxyglutarate, an oncometabolite that poisons TET enzymes and leads to a subsequent block in myeloid differentiation.[2,3] Enasidenib, a potent and selective inhibitor of mutant *IDH2*, led to a reduction in β hydroxyglutarate, myeloid differentiation, and clinical responses in a phase 1/2 clinical study.[4,5] That study demonstrated a rate of complete remission (CR) and CR with partial hematologic recovery (CRh) of 23%, a median duration of remission of 8.2 months, and conversion of 34% of patients from transfusion dependent to independent. Based on these results,