and limitations. Most share an immunoglobulin G1 (IgG1) backbone, which is critical for activity, owing to the higher affinity of IgG1 to bind Fc receptors on macrophages and efficiently activate complement. Clinical data for anti-CD47–targeted drugs in PTCL are limited, but for TTI-621, there are robust data that have demonstrated marked responses in patients with cutaneous and PTCL via both intravenous and intralesional injections.[3,4]

By interrogating a host of factors historically demonstrated to influence the activity of macrophages, such as major histocompatibility class I,[4] SLAMF7,[5] and pyroglutamation,[6] the authors demonstrate that the latter 2 factors were not as important in PTCL. In their experimental systems, recruitment of effector cells through engagement of the drug Fc-macrophage-FcγRs was most critical. Other critical factors related to the elaboration of specific cytokines following anti-CD47 engagement included murine monocyte chemotactic protein-3 (MCP-3) and interleukin-18 (IL-18).[7] MCP-3 drives migration of monocytes into tissue, which leads to their differentiation into macrophages. IL-18 is a proinflammatory cytokine that induces MCP-1 through the PI3K/AKT and MEK/ERK1/2 pathways.[8]

Importantly, the authors also demonstrated that anti-CD47–directed therapy potently improved the activity of mogamulizumab, an anti-CCR4 IgG1 antibody approved for patients with adult T-cell leukemia or lymphoma. These types of fundamental observations lay the groundwork for future combination studies and provide an innovative strategy to target PTCL in a rational way.

As with any drug development pursuit, the devil is in the details. Jain et al have established some new principles regarding anti-CD47–based treatment and have challenged others. Their studies underscore the need for prodigious correlative studies as probably the best strategy to optimize these agents in PTCL. Quoting Paul Ehrlich himself, "The first rule of intelligent tinkering is to save all the parts."

Conflict-of-interest disclosure: O.A.O. has received research support from Trillium-Therapeutics, Affimed, Celgene, Mundipharma EDO, Bayer, Spectrum, Merck, Seattle Genetics, Astex, and TG THerapeutics; and is a consultant for Mundipharma and Celgene. ■

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DOI 10.1182/blood.2019002810

MYELOID NEOPLASIA

Comment on Sébert et al, page 1441

Lifting the veil on germline *DDX41* mutations

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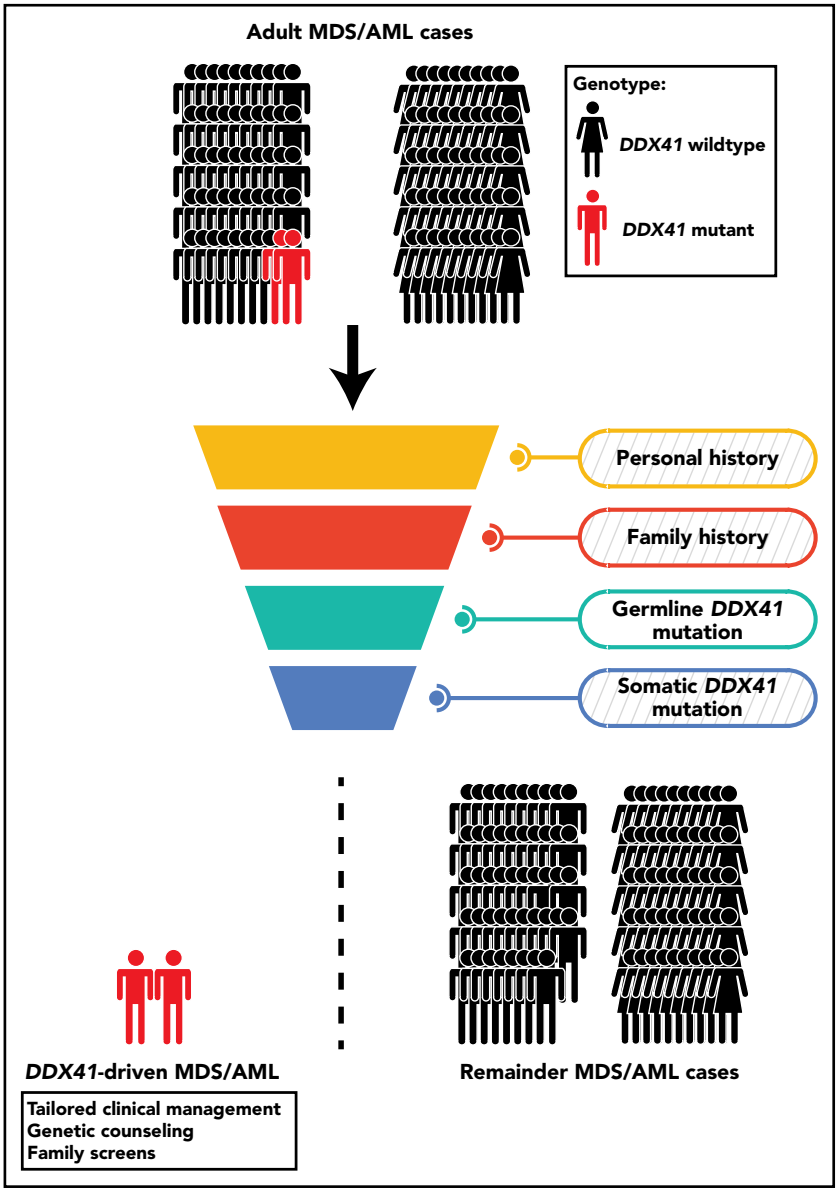
In this issue of *Blood*, Sébert et al made the intriguing observation that cases with germline DEAD-box helicase 41 (*DDX41*) mutations represent a unique entity among adult myeloid neoplasms (MNs), often with distinct clinical and molecular features.[1]

The advent of next-generation sequencing has profoundly improved our ability to define the genetic landscape of inherited hematological malignancies (HMs). Studies centered on familial HMs in combination with case studies of early-onset disease have been instrumental in identifying predisposing genetic variants. The list of genes with recognized predisposing variants is still growing.[2,3] To accommodate this disease entity, the World Health Organization 2016 classification defined MNs with germline predisposition as a new subgroup.[4] This distinction includes bone marrow failure syndromes (eg, Fanconi anemia), MNs with preceding cytopenias and platelet disorders (eg, inherited variants in *GATA2*, *RUNX1*, and *ETV6*) and a group of MNs lacking other preexisting dysfunctions (eg, inherited variants in *CEBPA*, and more recently, *DDX41*).

In this paper, the authors expand on the previous reports of germline *DDX41* mutations[5-8] by recognizing that cases carrying these germline mutations define a unique cluster within adult myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Germline *DDX41* mutations predispose to late-onset MDS/AML, often at an age where these malignancies commonly manifest sporadically and frequently without preexisting hematological disorders. These features render diagnosing this inherited disease challenging compared with other leukemia predisposition syndromes, which are often associated with early-onset disease and defining clinical features. In this context, careful review of personal or family history for hematological disorders or other clinical stigmata often yields insufficient support to suspect inherited cause.[6] Diagnostic assessment of germline *DDX41* mutations is a better approach, yet requires the capacity to make distinctions between causal mutations from those without predisposing effect, which is currently hindered



An unselected cohort of adult MDS/AML patients is screened to discover mutant *DDX41*-driven MDS/AML. Personal and family history of hematological disorders is recorded and reviewed for evidence of inherited cause, yet in the context of germline *DDX41* mutations, this approach might prove inconclusive (indicated by the diagonally-striped background). Diagnostic assessment for germline and somatic *DDX41* mutations could provide further indications, primarily when the germline *DDX41* mutation is known to be causal or is supplemented by a somatic *DDX41* mutation. Based on the results from Sébert et al, this approach would diagnose 2.4% of adult MDS/AML cases as being driven by causal germline *DDX41* mutations.

by the incomplete picture of the causal germline *DDX41* mutation landscape.

Sébert et al screened a large cohort (n = 1385) of unselected adult MNs to determine the prevalence and characteristics of germline *DDX41* mutations. Strict germline variant filtering yielded 21 causal variants detected in 33 patients, representing 2.4% of the total cohort. This frequency is remarkable, given the overall prevalence of inherited HMs within adult MNs, previously estimated at 5%, thereby rendering germline *DDX41* mutations the largest contributor to inherited myeloid disease. Fifteen cases (46%) experienced mild cytopenias in the years before diagnosis, contrasting with Lewinsohn and colleagues who reported that antecedent cytopenias were rare in mutant *DDX41*-driven HMs.[6] Only a limited number of cases had a family history of hematological disorders (n = 9, 27%). The previously unreported germline *DDX41* variant p.G173R was the most prevalent, outnumbering germline variants previously reported as prevalent.[5-8] This may indicate that the germline *DDX41* variant spectrum can differ considerably among patient cohorts, potentially reflecting population differences. This is supported by the finding that the p.M1I and p.D140Gfs *DDX41* germline variants are enriched in the Caucasian population, whereas the p.A500Cfs variant is exclusive to families of Asian descent.[8] One possibility is that these variants represent geographically or population-restricted founder mutations, causing a greater heterogeneity of germline *DDX41* mutations than previously appreciated.

Germline *DDX41* mutations strongly predispose to somatic *DDX41* lesions in the originally unaffected allele (79% of cases). Although concomitant germline and somatic *DDX41* mutations appear to be common, their functional impact on the disease biology remains unclear, warranting further investigation. Additional recurrent somatic mutations were detected in *ASXL1*, *EZH2*, *SRSF2*, *CUX1*, and *SETBP1*, which have previously been more strongly associated to secondary AML rather than de novo AML.[9] Quesada and colleagues[7] noted that 60% of mutant *DDX41*-driven AML arose from antecedent MDS. Multilineage dysplasia, enrichment of mutations associated with secondary AML and personal history of cytopenias are suggestive that a proportion of mutant *DDX41*-driven AML cases reported by Sébert et al also arose from antecedent MDS. The overall mutational repertoire deviated from observations made by Polprasert et al[5] and Quesada et al,[7] who respectively showed that splice factor mutations are mutually exclusive to *DDX41* mutations because of the role of DDX41 in precursor messenger RNA splicing, and that mutant *DDX41*-driven MNs are enriched for *TP53* mutations. In contrast, Sébert et al reported splice factor mutations present in 6 cases (18%), while *TP53* mutations were only present in 2 cases (6%). These discrepancies likely represent differences in patient population accrual as, for instance, Quesada et al[7] noted that their cohort is enriched for high-risk MDS/AML.

At a first glance, based on the reported survival curves by Sébert et al, it seems that mutant *DDX41*-driven MNs have a relative favorable outcome compared to other cases of MN, yet the difference in survival is not significant (*P* = .97). This may be more reflective of the small number

of included cases rather than the disease biology. In contrast, Polprasert et al[5] reported a significant association between *DDX41* lesions and poor survival. This divergence could be explained by the inclusion of MDS with 5q abnormalities spanning the *DDX41* locus by Polprasert et al.[5]

Collectively, the finding that germline *DDX41* mutations are common in a small fraction of MDS/AML warrants the integration of mutational analysis of this gene into routine diagnostics to inform long-term clinical management. Additionally, in the context of allogeneic stem cell transplantation, testing of related donors for the presence of these mutations is paramount to prevent donor-derived leukemia.[10] A few fundamental questions remain unanswered. Previous work postulated that germline *DDX41* mutations could predispose to lymphoid malignancies or, potentially, solid tumors.[6] Although a few lymphoid malignancies were uncovered in this study, larger studies are needed to gain sufficient support that germline *DDX41* mutations also predispose to lymphoid malignancies. On the other hand, questions concerning (1) the overall natural history of mutant *DDX41*-driven myeloid disease and (2) whether a complementing somatic *DDX41* mutation, which sometimes present at low variant allele frequencies, is required for developing myeloid disease still need to be addressed. Studies reporting on germline *DDX41* mutations have points of contention, such as, the presence or absence of cytopenia before disease or the enrichment or lack of certain classes of somatic mutations. Yet, all point out that reviewing the personal and family history for hematological disorders in combination with the screening for germline and somatic *DDX41* mutations is a viable approach to distinguish mutant *DDX41*-driven disease from all other cases of adult MDS/AML (see figure). Longitudinal studies with large patient cohorts are required to better define the landscape of causal germline *DDX41* mutations, establish the natural history of mutant *DDX41*-driven disease, and resolve the current points of contention, with the ultimate goal to improve diagnosis of this inherited hematological disease and further refine its clinical management.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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DOI 10.1182/blood.2019002982

THROMBOSIS AND HEMOSTASIS

Comment on Cherpokova et al, page 1458

Resolvin the clot: DVT resolution through RvD4

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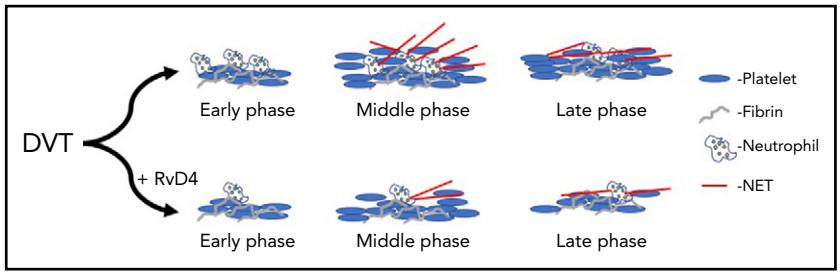
In this issue of *Blood*, Cherpokova et al have identified for the first time the important role lipid mediators play in both formation and resolution of clots in deep vein thrombosis (DVT). Their discovery, that Resolvin D4 (RvD4) is a critical specialized proresolving mediator that limits NETosis in the formation of the clot, as well as regulating the rate of clot resolution, identifies a new target for therapeutic intervention and reinforces the important role lipid metabolites play in regulation of blood clot formation under pathologic conditions.[1]

Although there is currently no national surveillance of DVT, it is known to be a common thrombotic disorder in the United States, with an annual incidence rate calculated to be at least 1 to 2 people per 1000 people in the population.[2] Much



RvD4 attenuates both clot formation and resolution. With treatment of RvD4, DVT clots show fewer neutrophils, reduced NETosis, and faster rate of resolution at late phase after induction of a DVT clot.