growth factor β inhibitors as a therapeutic option.

In 2013, and after all these descriptions, Gotlib et al. tried to recapitulate the different genotypes that an aCML sample could present in comparison with chronic neutrophilic leukemia, which gave us an overview of the disease’s complexity. These mutations are not mutually exclusive; for example, concomitant mutations of CSF3R and SETBP1 could be found in 14% of the patients.

However, a complete description of the somatic mutations involved in the onset of aCML was still lacking. Using a whole-exome analysis approach on 15 aCML cases, and after their own description of SETBP1 mutation in aCML, Gambacorti-Passerini et al described 2 point mutations of an ethanolamine kinase called ETNK1, an enzyme that is physiologically involved in the first step of the phosphatidylethanolamine biosynthesis pathway. In a large cohort of 515 hematologic clonal disorders, the authors described recurrent ETNK1 heterozygous mutations in 9% of atypical CML and 3% of CMML samples.

The described mutations are all restricted in the kinase domain, affecting 2 hot spot codons (H243Y and mainly N244S), as shown in the figure.

The authors also showed that these mutations are associated with impaired catalytic activity of the kinase, leading to an important decrease in the intracellular phosphoethanolamine/phosphocholine ratio. These results, obtained on patient samples, were confirmed on TF1 cell lines transduced with wild-type or mutated ETNK1, suggesting that ETNK1 mutations may inhibit the catalytic activity of the enzyme.

ETNK1 is responsible for the phosphorylation of ethanolamine to phosphoethanolamine, which is involved in many biochemical processes, mainly in the definition of the membrane architecture and participating in the respiratory complexes in the inner membrane of mitochondria. Given the pleiotropic role of phosphoethanolamine, the evaluation of biological effects of the ETNK1 mutations will be a challenging task.

All these studies clearly showed that aCML and CMML share not only clinical and morphologic features but also mutant genes, especially CSF3R, SETBP1 and ETNK1, which seems to be more specific than the other mutations that affect the TET2 and SRSF2 genes and frequently occur in CML.

In conclusion, this article by Gambacorti-Passerini et al shows for the first time evidence of recurrent somatic mutations of the ETNK1 gene in the context of myeloproliferative/myelodysplastic clonal disorders. Further studies will be required to clearly understand the functional effects of these mutations and to provide clues to define new therapeutic approaches.

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

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Comment on Zhang et al, page 562

Platelet GPIb: sensing force and responding

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In this issue of Blood, Zhang and colleagues identify a structural motif in the α-subunit of the membrane glycoprotein (GPIb)-IX-V complex that may explain how platelets sense mechanical force while responding to vascular injury.1

Translating mechanical stimuli into adaptive responses is a common process in plant and animal cells,2 with a fundamental role in determining the shapes and functionalities that have evolved to characterize living organisms as they exist today. In particular, mechanical force of varying intensity is important for vascular endothelial cells and cellular elements in the bloodstream, as well as for the function of lymphatic vessels.3 The endothelium responds to mechanical deformation from shear stress and from stretching of the vessel wall, and different levels of shear stress influence leukocyte and platelet responses to vascular injury.

Mechanosensing and mechanotransduction are the function of transmembrane receptors linked to intracellular effector systems typically organized on cytoskeletal scaffolds. The most common in animal cells are 2-chain integrin complexes, which signal bidirectionally on chemical as well as physical cues. Platelets possess integrins with diverse ligand specificities, including αIIbβ3 essential for hemostasis. In addition, platelets are endowed with a specialized receptor, the GPIbα-IX-V complex, which resists extreme shear stress when coupled to the polymeric ligand von Willebrand factor (VWF). Binding of the VWF A1 domain (VWF-A1) to the GPIbα amino-terminal domain in GPIbα-IX-V provides the pathway for platelet adhesion and aggregation at shear rate and stress levels encountered in normal arterioles and pathological arterial flow.
The VWF–GPIb interaction is independent of platelet activation. Rather, VWF senses mechanical force responding with elongation of multimers that expose A1 domain interaction sites initiating adhesion. Once formed, the VWF–GPIb bond is mechanically stabilized; the association of a rapid rate of bond formation with resistance to tensile stress supports the initial capturing of platelets that transition from rapid flow to low-velocity translocation on reactive surfaces. During this stop/go motion, GPIb-IX-V transduces tensile stress on the VWF bond into intracellular signals linked to platelet activation. Platelet adhesion at sites of vascular injury typically involves VWF immobilized onto adhesive substrates, such as collagen, which are capable of activating platelets on their own. Thus, discerning how signals induced by VWF–A1–GPIb binding contribute to thrombogenesis requires separating adhesion from transduction effects, which has not been possible to date.

On this background, the article by Zhang and colleagues is a decisive step toward understanding how GPIbα senses force. Noting that the mucin-like macroglycopeptide interposed between the ligand–binding and juxtamembrane regions of GPIbα argued against long-distance allosteric effects following VWF ligation, they devised an approach to document force-induced structural changes at the single-molecule level. Thus, they identified a mechanosensitive domain (MSD) that is structured but unstable and unfolds by pulling on VWF–A1 bound at the opposite end of the GPIbα extracytoplasmic portion (glycocalcin). They also documented that altering the MSD in GPIbα mutants abolished force-induced unfolding of the protein, indicating that no other region of the molecule can serve as an alternative mechanotransducer.

With the findings presented in this issue, new directions emerge for future studies. Developing models that can differentiate between GPIbα-mediated adhesive and signaling functions will illustrate how stimulation by force transmitted through the WFA1 bond is integrated with signals from other platelet receptors to promote thrombus growth and stability. This may lead to identifying new targets for antithrombotic intervention. Of note, the GPIbα cytoplasmic domain is linked to filamin–A, contributing to membrane stability. In a mouse model, mutated GPIbα with normal VWF binding (but lacking anchorage to filamin–A) causes membrane disruption when platelets translocate on VWF, signifying that force is transmitted to the cytoskeleton through the VWF bond under normal conditions. This could be one reason for the hitherto unexplained influence that gain-of-function type 2B VWF mutants with enhanced GPIbα binding have on thrombocytopoiesis, causing increased platelet size and altered structure as seen when GPIb-IX expression is defective.

Therefore, lack of GPIbα produces effects on thrombocytopoiesis similar to its enhanced stimulation. This is apparently paradoxical, but may indicate, in agreement with the proven role of shear stress in megakaryocyte biology, that fine-tuning of the response to mechanical stimuli is key for normal platelet production. Determining the possible role of GPIbα-mediated mechanotransduction in thrombocytopoiesis will be facilitated by the identification of the MSD in this receptor.

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

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**TRANSPLANTATION**

**Comment on Hechinger et al, page 570**

**Anti–common γ-chain antibody: one for all in GVHD**

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In this issue of *Blood*, Hechinger and colleagues investigate the efficacy of the blockade of the common γ-chain receptor (CD132) as a novel approach in the management of both acute and chronic graft-versus-host disease (GVHD).

The common cytokine receptor γ-chain family consists of interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21, and is so called because the receptors for these cytokines share the same γ chain. The gene encoding the γ chain (*IL2RG*) is mutated in humans with X-linked severe combined immunodeficiency (XSCID), and these patients lack T cells and natural killer (NK) cells, which indicates that the γ chain is crucial for the development of these cells.

Acute GVHD has been described as a “cytokine storm” involving a 3-step disease process: (1) conditioning regimen–associated inflammation,
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