patients with CH and mutations in DDR genes at the time of cytotoxic therapy might represent a high-risk population. These findings suggest several conclusions to help guide treatment decisions. (1) Patients who are supposed to receive cytotoxic therapy should be screened for CH. Patients with mutations in DDR genes could be treated, if feasible, with alternative approaches (eg, immunotherapy or inhibitors). (2) In case cytotoxic therapy is unavoidable, patients should be closely monitored for the development of treatment-related hematologic neoplasms. (3) With the increasing availability of specific inhibitors, it might be interesting to target and eliminate the clonal HSC before the onset of disease. However, each treatment strategy will likely also cause side effects in otherwise asymptomatic individuals. For example, *Ppm1d* knockout mice display defects in B- and T-cell differentiation resulting in immunodeficiency, severe neutrophilia causing inflammatory disease phenotypes, and diminished self-renewal capacity of HSC.[12] The latter is specifically relevant in elderly patients, who may rely on oligoclonal hematopoiesis to ensure proper blood production.

In summary, the work by Kahn et al provides important mechanistic insights into the function of DDR genes in clonal hematopoiesis and the first experimental evidence for successful targeting driver mutations in CHIP. As a next step, prospective clinical trials are warranted to address the questions of whether early treatment of CHIP can reduce all-cause mortality and the risk of subsequent treatment-related hematologic neoplasms.

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PLATELETS AND THROMBOPOIESIS

Comment on Tsukiji et al, page 1167

The incomparable platelet: holy alveoli!

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In this issue of *Blood*, Tsukiji et al report on the consequences of platelet–lymphatic interactions in the lung, namely the influence of platelet activation with release of platelet transforming growth factor-β (TGF-β) on lung development.[1] The small but mighty platelet continues to amaze as functions beyond canonical roles in hemostasis and thrombosis are being discovered at a rapid rate. Key roles in inflammation, autoimmunity, and metastasis have recently been elucidated. One wonders how many more tricks the platelet has up its sleeve.

As with any biologic process, there is a balance of effects on the host system. With platelets, we have to consider the good (plugging holes, antimicrobial function) with the potentially harmful (thrombotic organ injury, exaggerating inflammation). There is a growing amount of literature on the role of platelets as biologic packages that deliver key signals to tissues, including the lung. For example, in a pneumonectomy model of lung regeneration, platelets deliver stromal cell–derived factor-1 to the lung endothelium, which drives alveolar epithelial cell expansion via membrane-type metalloproteinase MMP14.[2] Platelet-rich plasma, increasingly used in sports medicine to accelerate recovery, also accelerates lung regeneration after pneumonectomy through angiogenic factors such as angiopoietin-1.[3]

There is a well-established literature field on the role of platelet–lymphatic interactions in maintaining the separation of vascular and lymphatic channels. It may seem surprising that platelets and lymphatic channels would be in contact, and indeed, the exact sites of contact during organ development are unclear. C-type lectin-like receptor-2 (CLEC-2) on platelets, originally discovered as a receptor-mediating platelet aggregation in venomous snake bites,[4] and podoplanin in the lymphatic endothelium, constitute the major receptor–ligand pairs.[5] At the junction between the thoracic duct and the subclavian vein, the CLEC-2–podoplanin interaction amazingly is in continuous operation to prevent the entry of blood into the lymphatic system.[6] Other described interactions include platelet aggregation via CLEC-2 on metastatic

tumor cells that ectopically express podoplanin.[7]

Here, the authors studied CLEC-2 and podoplanin interactions during lung embryonic development. It has previously been observed that global deletion of CLEC-2 or podoplanin is lethal,[5,8] and the authors confirmed that these mice have defects in late embryonic lung development (primary septum formation). When CLEC-2 was completely deleted in platelets and megakaryocytes (using Cre-lox plus antibody-mediated deletion of residual CLEC-2), the fatal neonatal defects included lung developmental defects. Previous studies using mice with platelet-specific CLEC-2 deficiency have not reported lung developmental defects,[9] but the authors found mild defects that were worse when residual platelet CLEC-2 was completely deleted or if platelets in these mice were depleted by 90%. CLEC-2 signals through the spleen tyrosine kinase to activate platelets, and the authors determined that TGF-β released from activated platelets drives the development of alveolar duct myofibroblasts that are critical to primary septum formation and elastogenesis during late embryogenesis. Curiously, lung developmental defects have not been described in thrombocytopenic mouse models, but it appears that platelet counts must be severely decreased and combined with other defects in platelet activation, such as the absence of CLEC-2 signaling, to produce the lung phenotype.

Why would platelets be important in lung development and regeneration? The strong phenotypes observed in this study may derive from the large vascular surface area where platelets are in continuous circulation and where large numbers of megakaryocytes embolize to produce platelets.[10] Additionally, megakaryocytes may live in the lung interstitium, where they could theoretically interact with lymphatic channels to influence lung development. Future studies are needed to determine if the phenotypes observed in the lung are present in other tissues. Investigators in this field should also focus on the mediator(s) released from platelets that have biological influence on the developing lung. Platelet-derived TGF-β is unlikely to be the sole mediator involved because the TGF-β knockout mouse does not have apparent lung developmental defects. Platelets and megakaryocytes are rich sources of other mediators that could influence the tissue matrix during organogenesis and potentially also in disease states characterized by tissue fibrosis.

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PLATELETS AND THROMBOPOIESIS

Comment on Lepropre et al, page 1180

Platelet metabolism meets thrombosis

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Metabolic pathways intersect with many processes important in hematology, including thrombosis, innate and adaptive immunity, malignant transformation, and stem cell function. These pathways are increasingly recognized as potentially targetable for therapeutic intervention. In this issue of *Blood*, Lepropre et al identify the energy sensor AMP-activated protein kinase (AMPK) in platelets as a regulator of thrombosis.[1]

Platelet hyperreactivity is a key factor that promotes arterial thrombosis, and our laboratory and others have described how exogenous factors, including dyslipidemia and hyperglycemia, influence platelet activation. However, the impact of endogenous lipid metabolism on platelet function remains largely unexplored. Lepropre et al demonstrated that platelet AMPK, by phosphorylating acetyl coenzyme A (acetyl-CoA) carboxylase (ACC), regulates endogenous lipid synthesis, including the arachidonic acid–derived eicosanoid thromboxane A2 (TXA_2), thereby contributing to thrombus formation (see figure).

AMPK is a ubiquitously expressed serine/threonine kinase normally activated by low cellular energy state due to its unique ability to sense intracellular AMP levels; as ATP becomes depleted, AMP levels rise and AMPK is activated.[2] On activation, it has multiple targets, and the fundamental effect is to suppress metabolic processes that consume energy, such as lipogenesis, while stimulating pathways for energy production, such as fatty acid oxidation and mitochondrial oxidative phosphorylation. The major substrate for AMPK to achieve these effects is ACC, which converts acetyl-CoA to