Published in final edited form as:

Platelets. 2017 January ; 28(1): 2. doi:10.1080/09537104.2016.1262013.

SPECIAL REVIEW: GENETICS OF PLATELET BLEEDING DISORDERS:

Editorial: Platelet Genomics and Disorders of Platelet Number and Function

A. Koneti Rao

Sol Sherry Thrombosis Research Center and Department of Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA

These are exciting times in the world of disorders of platelets – anucleate megakaryocyte fragments that are remarkable in their complexity and essential for hemostasis and thrombus formation. Major advances have exploded on the scene and with the promise of more to come. A small part of these exciting advances are captured in four reviews in this issue of *Platelets*. They all relate to what underlies the altered platelet biology in health and disease. To some extent, they are built on the tremendous recent advances in platelet genomics, on the application of state of the art approaches, including the next generation sequencing (NGS), whole genome and exome sequencing, coupled to contemporaneous advances in bioinformatics. A common link is not that these four reviews venture into novel clinical areas in platelets – thrombocytopenias and platelet dysfunction are not new disorders – but that they capture the paradigm shifts in the era of genomics.

The first paper by Balduini, Melazzini and Pecci [1] addresses the issue of inherited thrombocytopenias. Richard May in 1909 and Robert Hegglin in 1945 independently described a clinical entity that bears their name, the May-Hegglin anomaly [2]. However, it was only at the turn of the century that the genetic basis of this entity was established to be mutation in *MYH9*, the gene encoding for the non-muscle myosin heavy chain IIA.2 In the last two decades there has been an explosion in our understanding of the genetic basis of inherited thrombocytopenias. Over two-dozen genes have been linked to inherited thrombocytopenias. Balduini et al. [1] describe the recent advances in the genetic basis of thrombocytopenias and relate it to megakaryocyte biology. The authors point out that despite the numerous gene variants identified recently, the genetic defects in nearly half of such patients still remain to be fully characterized. A better understanding of inherited thrombocytopenias is important in clinical practice, to avoid misdiagnosis and unnecessary therapy, and to recognize that some gene mutations (*RUNX1* and *ANKRD26*) have prognostic implications.

In the second review, MacLachlan, Watson and Morgan [3] provide evidence that the quest for DNA-based diagnoses is well under way in the remarkably heterogeneous group of patients with inherited defects in platelet function, as detected by routine platelet function testing. They capture the power of the newer technologies – NGS – to make important and

Declaration of Interest

The author reports no conflicts of interest.

rapid inroads into understanding the mechanisms, driven by collaborative studies in large numbers of patients. They appropriately provide caution about the potential complexities of NGS – arising from the voluminous genetic information delivered – in establishing with confidence the specific pathogenic variants underlying the platelet dysfunction.

The focus of the third review by Songdej and Rao [4] is on gene variants involving hematopoietic transcription factors as the basis for defects in platelet function and number in patients with bleeding disorders. Until recently, the focus of studies on the molecular mechanisms in such patients has been on postulated candidate proteins and pathways – a paradigm by which most platelet defects have been identified to date, but this comes with limitations. At the genetic level, the focus has largely been on delineating mutations in the coding sequence of genes that encode for candidate proteins. This review focuses attention on genetic defects in transcription factors that regulate megakaryocytic and platelet genes as a cause of platelet defects. It is becoming clear from various studies that transcription factor abnormalities may be far more common than currently considered in the pathogenesis of inherited platelet defects. Some of these variants come also with the additional baggage of predisposition to hematologic malignancies.

While studies on platelet dysfunction to a large extent have been driven by the impact of rare gene variants that portend major effects, the review by Nugent and Kunicki [5] focuses on the impact of common variants, such as single nucleotide polymorphisms, that regulate characteristics of platelet number, size, volume and function. These may in turn influence predisposition or risk for cardiovascular and inflammatory disease. These variants modify the clinical outcomes by interacting with other risk factors, including environmental factors and medical conditions. The review by Nugent and Kunicki summarizes the recent advances as they pertain to the genetic modulators of platelet size, volume, response to receptor activation and function.

Together these four reviews describe the remarkable advances in understanding the molecular and genetic basis of platelet defects. The recent progress is impressive – and the advances in genomics promise more to come in the near future.

References

1. Balduini CL, Melazzini F, Pecci A. Inherited thrombocytopenias - recent advances in clinical and molecular aspects. *Platelets*. 2017; 28(1)
2. Saito H, Kunishima S. Historical hematology: May-Hegglin anomaly. *Am J Hematol*. 2008; 83(4): 304–306. [PubMed: 17975807]
3. MacLachlan A, Watson SP, Morgan NV. Inherited platelet disorders: Insight from platelet genomics using next-generation sequencing. *Platelets*. 2017; 28(1)
4. Songdej N, Rao AK. Inherited platelet dysfunction and hematopoietic transcription factor mutations. *Platelets*. 2017; 28(1)
5. Nugent D, Kunicki T. Platelet Genomics: The Role of Platelet Size and Number in Health and Disease. *Platelets*. 2017; 28(1)