From helix to hematology: introduction to a collection of reviews on the emerging role of next-generation sequencing in hematology

The human genome contains more than 3 billion base pairs that encode the blueprint for all aspects of our health and well-being. The original draft and finished sequence of the human genome cost billions of dollars to complete, a cost that has been recovered many times over by providing the first fundamental understanding of the structure and biology of our genome and how it relates to disease. During the last decade, sequencing costs have dramatically declined (closed diamonds in figure), allowing studies of the structure and operation of the human genome to progress from an understanding of the consensus genome of a small number of individuals to an in-depth analysis of individual genomes. It is clear that in the not-too-distant future, an analysis of our sequenced genomes will be fully integrated into the practice of medicine. Although we may not be at the point of personalized genomes in 2013, genome-wide sequence analysis is already playing an important role in the hematology community. The Review Series on Genome Sequencing and Its Impact on Hematology is designed to present a state-of-the-art snapshot of this rapidly moving field.

The first review in the series, “Massively parallel sequencing: the new frontier of hematological genomics,” is an excellent overview of DNA sequencing technology and how it is used to assemble either complete genomes (whole-genome sequencing) or profiles of the 1% to 2% of the genome that contains the protein-coding sequence (whole-exome sequencing). Dr Jill Johnson, Dr Deborah Nickerson, and Dr Alex Reiner from the University of Washington (Seattle, WA) have done a thorough job of preparing the reader to appreciate the breadth of variations uncovered in the genome through sequencing, as well as the power of modern sequencing technology to detect these variations. The review concludes with a perspective on the effect of DNA sequencing on the field of human genetics, which defines the challenges that researchers, including hematologists, will face going forward. This review should be viewed as a prerequisite to the other 4 papers in the series.

Two reviews focus on the effect of genome-wide sequencing in benign hematologic disorders. The first review, “Genetic sequence analysis of inherited bleeding diseases,” was written by Dr Flora Peyvandi, Dr Tom Kunicki, and Dr David Lillicrap from the University of Milan, Italy; the Children’s Hospital of Orange County (Orange, CA); and Queen’s University in Kingston, ON, Canada, respectively. This review focuses on bleeding disorders and begins with a description of the enormous variation found in databases of mutations associated with hemophilia A and hemophilia B. The review goes on to describe targeted sequencing of clotting factor genes before culminating in a review of how whole-genome analysis has identified new mutations that cause bleeding disorders.

The effect of the new sequencing technologies on benign hematologic disorders that do not involve bleeding is the focus of the review written by Dr Vijay Sankaran from Harvard University in Boston, MA, and Dr Patrick Gallagher from Yale University in New Haven, CT: “Applications of high-throughput DNA sequencing to benign
This article begins with a historical review of how hematologists were the first to use molecular biology and DNA sequencing to identify disease-causing mutations. The review progresses into a series of vignettes demonstrating the power of the new sequencing technologies to provide molecular diagnoses to patients while at the same time expanding our understanding of their diseases. Readers will appreciate many examples of how genome-wide analysis has unlocked new avenues of research, diagnosis, and therapy for benign hematologic disorders.

Nowhere has the effect of the new sequencing technology been greater than in the area of hematologic malignancies. The ability to detect rare sequence variants in heterogeneous populations of tumor cells has had a profound effect on our understanding of hematologic malignancies. These findings have already improved diagnostic and prognostic criteria and may hold the potential to lead to new therapeutics. The broad field of myeloid malignancies is the subject of the review written by Dr R. Coleman Lindsley and Dr Benjamin Ebert, from Harvard University: “The biology and clinical impact of genetic lesions in myeloid malignancies.”

Dr Lindsley and Dr Ebert begin by emphasizing the process of naturally occurring mutations in human bone marrow stem cells and how complicated it can be to identify the malignant (driver) mutations among the background of benign passenger mutations. The authors then go into detail about mutations that affect specific biological pathways, describing their involvement in multiple myeloid malignancies, ranging from acute myeloid leukemia to myelodysplastic syndrome. The review concludes with a summary of the state of the field and a vision for what lies ahead.

The final review, “Genome sequencing of lymphoid malignancies,” written by Dr Charles Mullighan from St. Jude Children’s Research Hospital in Memphis, TN, includes 2 topics, copy number variation and analysis of mRNA sequence (transcriptome analysis), which are not covered in depth in the other reviews in the series.

The use of these methods in the analysis of lymphoid tumors demonstrates how integrating data from multiple sequencing studies can enhance the understanding of a wide range of tumors. The conclusion of this review provides a comprehensive appraisal of the field and its direction. Dr Mullighan makes the point that future advances in DNA sequencing technology will allow for an analysis of single tumor cells, which is the key to a complete understanding of lymphoid (and many other) malignancies.

All of the reviews discuss a future in which sequence-based analysis will play an integral role in hematology. To make this goal a reality, at least 2 further advances are necessary: first, sequencing costs must continue to decline to levels affordable for every individual, and second, analytical capacity must increase. The Moore’s Law curve in the figure, indicating a doubling of computing power every 2 years, demonstrates that analytical capacity has not kept pace with sequencing capacity. Computing power will need to improve to bring sequencing to the bedside. Concurrent with the increase in computing power will be the need to train hematologists to work with the data. However, if one looks back to where we were only a decade ago, it seems that these advances are right around the corner.
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