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Molecular genetics of AML

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In the past decade, a series of technological advances have revolutionized our ability to interrogate cancer genomes, culminating in whole-genome sequencing, which provides genome-wide coverage at a single base-pair resolution. To date, the tumor genome has been sequenced in nearly 40 cases of acute myeloid leukemia (AML). On average, each AML genome contains approximately 400 mutations, including 6–26 coding mutations. The majority of these mutations are 'background' mutations that were acquired during normal aging of hematopoietic stem cells. Though comprehensively identifying 'driver' mutations remains a challenge, a number of novel driver mutations in AML have been identified through whole-genome sequencing. The digital nature of next-generation sequencing has revealed clonal heterogeneity in the majority of AML at diagnosis. Importantly, in some cases, a minor subclone contributed to relapse, suggesting the strategies to assess clonal heterogeneity are needed to optimize therapy. As sequencing technologies improve and costs decrease, it is likely that whole-genome sequencing of cancer cells will become commonplace in the diagnostic work-up of patients with AML and other cancers.

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Introduction

In the past, the size and complexity of the human genome (3 billion base-pairs) made sequencing of human cancer genomes impractical. Two major advances helped overcome these obstacles. First, the generation of the draft sequence of the human genome by the Human Genome Project in 2001

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provided a map of the human genome [1]. Second, technological advances in DNA sequencing dramatically reduced the cost and time required to sequence genomes (Fig. 1). Whereas the Human Genome Project took over 10 years and several billion dollars to sequence the first human genome, current estimates are 4–6 weeks and $10,000 per human genome ($20,000 for paired tumor/normal genomes). Thus, we are rapidly approaching the time when sequencing the genomes of patients with cancer will be practical in the clinical setting. This chapter will focus on the use of next-generation sequencing technologies to characterize AML genomes.

Next-generation sequencing of cancer

Massively parallel sequencing results in the generation of millions of short (50–100 nucleotide) DNA sequences simultaneously. These sequences are then mapped back to the human reference genome to generate a picture of the cancer genome. For studies of cancer, it is key to sequence both the tumor and non-malignant tissue from the individual. There are 3–4 million inherited sequence variants per human genome (and hundreds of copy number variants). Consequently, the great majority of sequence variants identified in a cancer genome are inherited polymorphisms and not acquired mutations. Thus, a comparison of a tumor genome to its paired normal genome is required to efficiently identify acquired (somatic) sequence variants.

Next-generation sequencing has been used in several different ways to interrogate cancer genomes. The goals, advantages, and limitations of each approach are summarized below. Ultimately, combinations of approaches (e.g., whole-genome and transcriptome sequencing) may be required to comprehensively study cancer cells.

Whole-genome sequencing

The goal of this approach is to sequence the entire genome. The advantages of whole-genome sequencing include: (1) the entire genome is surveyed, not just coding genes; and (2) structural variants, including deletions, amplifications, chromosomal translocations, and uniparenteral disomy are readily identified. The major limitations are cost and the complexity of the data analysis. As cost and bioinformatic approaches to analyze sequence data advance, whole-genome sequencing is likely to become the dominant platform for mutation discovery.

Exome sequencing

The goal of this approach is to selectively sequence the 1%–2% of the genome containing coding genes, microRNAs, and other non-coding RNAs. The major advantages of exome sequencing are reduced cost and relatively deep sequence coverage, since only 1%–2% of the genome is analyzed. However, exome sequencing will not detect mutations in regions outside of the exome (>98% of the

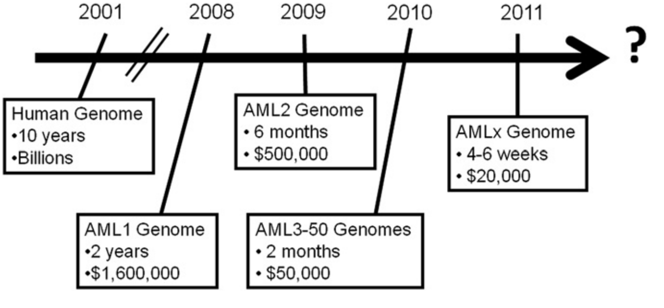

Fig. 1. *Timeline for sequencing of AML genomes*. Cost and time estimates are for paired leukemia/normal genomes and include data production, bioinformatic analysis, validation, and interpretation. Current cost and time estimates to sequence a human genome are based on data from the Genome Institute at Washington University.

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