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Unraveling the multiple myeloma genome in the next-generation sequencing era: challenges to translating knowledge into the clinic

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> "...advances in sequencing technology have started an unprecedented exploration of the cancer genome."

The origin and progression of human cancers is caused by the acquisition of genetic and epigenetic alterations. Over the last decades, significant efforts and technological advances were key in the characterization of the cancer genome in a wide range of tumors. In 1976, Peter Nowell, following the observation of karyotypic heterogeneity in multiple tumor genomes, proposed a multistep process to explain the molecular basis of tumorigenesis [1]. This model was not only the first comprehensive analysis of genetic heterogeneity and instability in the tumor clone, but also led for the first time to the concept of personalized medicine, where therapy should be individualized according to the genetic background observed in the tumor clone.

In the mid-1980s, at the time that the molecular techniques to search for oncogenes and tumor suppressor genes were developed, Renato Dulbecco pointed out in an influential article that sequencing the human genome was a critical priority, saying that the research community was faced with two options: either keep discovering the genes important in cancer individually, or use a massive approach and sequence the whole genome [2]. 4 years later, the Human Genome Project was started.

The Human Genome Project required several years of collaborative work from worldwide leading sequencing institutes and a budget of US$300 million to sequence the first single genome with seven-times coverage [3]. Now, 10 years after the completion of the first draft of the Human Genome Project, the incorporation of the massively parallel sequencing (also known as next-generation sequencing) technologies has revolutionized the search for genetic alterations in tumor genomes. The simultaneous catalog of all mutations, copy number aberrations and structural abnormalities in an entire cancer genome can be performed in one week using a single sequencer and for only US$5000. With the ultimate goal of offering the test for US$1000 in the near future, the implementation of next-generation sequencing in clinical practice will soon be a reality.

> "The Cancer Genome Atlas is running a 5-year program with a budget of US$275 million to analyze the genomic changes in more than 20 types of solid cancer."

These advances in sequencing technology have started an unprecedented exploration of the cancer genome. The complete genome of acute myeloid leukemia, breast cancer, glioblastoma, lung cancer, melanoma, ovarian and prostate cancer, among others, have already been described

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and it is anticipated that most of the common and clinically relevant human cancers will be analyzed in large scale in the coming years. In this context, The Cancer Genome Atlas is running a 5-year program with a budget of US$275 million to analyze the genomic changes in more than 20 types of solid cancer [101]. Furthermore, The International Catncer Genome Consortium seeks to catalog more than 50 clinically relevant cancers in the next 10 years and The Cancer Genome Project of the Wellcome Trust Sanger Institute has a comprehensive ongoing project aiming to sequence 4000 candidate cancer genes from a variety of cancer cell lines originated from solid tumors [102].

> "...the majority of tumors analyzed until now have a considerable intertumor heterogeneity, resulting in large numbers of genes mutated infrequently."

Significant advances have also been made in the study of hematological malignancies. In some malignancies, such as hairy cell leukemia, a common affected gene was found in all cases. Thus, *BRAF* V600E mutation and the subsequent activation of the RAF-MEK-ERK mitogen-activated protein kinase pathway is a widespread event in hairy cell leukemia, being found in all 48 patients recently analyzed, but absent in other hematological malignancies analyzed [4]. Conversely, the majority of tumors analyzed until now have a considerable intertumor heterogeneity, resulting in large numbers of genes mutated infrequently. The first acute myeloid leukemia patient sequenced showed ten nonsynonymous mutations in coding regions, eight of which have never been previously found in the disease [5]. More recently, the first whole-genome sequencing effort in chronic lymphocytic leukemia identified four genes that are recurrently mutated, but only one gene (*NOTCH1*) was affected in more than 3% of cases [6]. One of the biggest challenges is to reduce the complexity of the analysis by considering integration in molecular pathways affected, rather than single genes. In this context, two recent studies show a high prevalence of mutations affecting genes involved in histone modification and chromatin methylation in diffuse large B-cell lymphomas [7,8].

> "In some malignancies, such as hairy cell leukemia, a common affected gene was found in all cases."

Remarkably, one of the most significant efforts at this point has been focused on the characterization of the multiple myeloma (MM) genome. The first whole genome sequencing map was recently obtained from 38 MM patients [9], being currently one of the best-characterized tumors. The most remarkable findings obtained from initial analysis were mutations affecting genes involved in protein translation and in histone methylation, as well as activating mutations of the NF-κB pathway in a subset of patients. This study provides the first snapshot of the genomic landscape of MM at one single time point.

Recently, the Multiple Myeloma Research Foundation announced a 1000-patient study for an 8-year program. This integrated and collaborative effort will enroll at least 1000 newly-diagnosed MM patients who have not yet initiated therapy [103]. Interestingly, this study will be performed in sequential patient samples from initial diagnosis through the course of treatment, over a minimum of 5 years, in order to identify how the cancer genome background may affect the clinical progression and individual response to treatment. Moreover, multiple US centers will participate, thus potentially including patients enrolled in more than 30 clinical trials for MM treatment.

A key point facing the extraordinary amount of data being generated is the ability to differentiate the mutations that confer a selective growth advantage to the neoplastic clone (also called driver mutations) from the remaining mutations that do not confer growth advantage (also called passenger mutations)[10]. Another characteristic of the tumor genome to be highlighted comes from recent studies showing that the clonal architecture and evolution often resembles the multibranching rather than the linear evolution model [11,12]. From the standpoint of therapy strategy and novel drug discovery, the heterogeneous tumors present an obvious challenge.

> "Reducing the timeframe from the bench to the bedside is probably the biggest challenge that the research community will face in the post-genomic era."

Genetic studies have achieved a central role in the study of MM, as they become a critical component in the risk-based stratification of the disease [13–15]. Indeed, gene-expression profiling has been successfully implemented as a risk-stratification tool in MM [15]. Significant advances have also been made in recent years in MM drug development, essentially with the incorporation of proteasome inhibitors and thalidomide-related immunomodulatory drugs [16–18]. Although several mechanisms of action have been proposed to explain the antimyeloma effect of these molecules [19–21], the precise molecular mechanisms and targets through which these molecules exert their effects remains unclear. Moreover, MM patients still have an unmet medical need when it comes to those who have relapsed or whose disease is refractory to available drugs. We are expecting that the systematic and comprehensive analysis covering the MM genome, transcriptome and methylome will provide a paradigm shift in diagnosis, prognosis and treatment, initially with available therapies and with more personalized therapies in the long term.

The main challenge for the following years is to find potential 'Achilles' heels' to be exploited for drug discovery, and rapidly impel the translation of these insights into new clinical strategies and therapeutic options for MM patients. The paradigm from gene discovery to successful therapeutic intervention is the fusion gene *BCR-ABL*, found in almost all chronic myeloid leukemia (CML). The encoded protein is a constitutive active tyrosine kinase that has been successfully targeted with the development of the tyrosine kinase inhibitor imatinib [22]. However, from the initial discovery of the translocation t(9;22) in CML, it took another 41 years before imatinib was approved for use in CML patients. The paradigm has the potential to be rapidly extended to other cancers, including MM. Reducing the timeframe from the bench to the bedside

is probably the biggest challenge that the research community will face in the post-genomic era.

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